NEURONAL SPIKE TRAINS AND STOCHASTIC POINT PROCESSES

I. The Single Spike Train

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ABSTRACT In a growing class of neurophysiological experiments, the train of impulses ("spikes") produced by a nerve cell is subjected to statistical treatment involving the time intervals between spikes. The statistical techniques available for the analysis of single spike trains are described and related to the underlying mathematical theory, that of stochastic point processes, i.e., of stochastic processes whose realizations may be described as series of point events occurring in time, separated by random intervals. For single stationary spike trains, several orders of complexity of statistical treatment are described; the major distinction is that between statistical measures that depend in an essential way on the serial order of interspike intervals and those that are order-independent. The interrelations among the several types of calculations are shown, and an attempt is made to ameliorate the current nomenclatural confusion in this field. Applications, interpretations, and potential difficulties of the statistical techniques are discussed, with special reference to types of spike trains encountered experimentally. Next, the related types of analysis are described for experiments which involve repeated presentations of a brief, isolated stimulus. Finally, the effects of nonstationarity, e.g. long-term changes in firing rate, on the various statistical measures are discussed. Several commonly observed patterns of spike activity are shown to be differentially sensitive to such changes. A companion paper covers the analysis of simultaneously observed spike trains.

INTRODUCTION

Motivation

A neuronal spike train is the sequence of nerve impulses, or action potentials, produced by a neuron, typically observed over a relatively long period of time. The analysis of spike trains has been of increasing interest to neurophysiologists in recent years, stimulated, no doubt, by wide availability of automatic data-processing equipment. Spike-train analysis differs from "classical" electrophysiological methods

in that the raw data of interest are not precise voltage measurements, but rather precise measurements of times of occurrence of events. From these essentially temporal data, statistical descriptions are obtained of the output behavior of neurons, from which inferences may be made, in turn, with regard to certain specific types of basic neurophysiological questions. It is not our intention to pursue the questions of interpretation and inference in the present paper (for a recent review, see Moore, Perkel, and Segundo, 1966), but rather to present in systematic fashion the statistical techniques of spike-train analysis, and in particular to point out some of the relevant mathematical assumptions and relationships underlying the computational techniques.

Methodological considerations, however, must not be isolated from inferential and interpretational questions; we have tried to discuss the computational techniques within the larger context of neurophysiological investigation. Our principal working assumptions, as stated in the study mentioned above (Moore, Perkel, and Segundo, 1966), are "(*a*) that there is an enormous wealth of information about the structure and function of the nervous system which can be derived from careful study of the detailed timings of spike events; (*b*) that analysis of these signals can shed light on mechanisms of spike production within the observed cell, on the presynaptic input to the cell, and on the mechanisms by which the latter is transformed into a postsynaptic output; and (*c*) that observation of multiple units can reveal details of interconnections and functional interactions . . . [and] the appreciation that neuronal processes at all levels involve a probabilistic element which must be adequately incorporated if quantitative hypotheses or models of neuronal functions are to be valid. Finally, it is held that only the more detailed analyses of spike timings are appropriate to any quantitative theory of information processing by the nervous system."

Spike-train analysis is applied at several different levels of interpretation, and it is the level of interpretation that largely dictates the choice and depth of statistical techniques for processing of the data. At one level, the statistical measures of the spike train provide a relatively concise characterization of the output of the neuron, which may be used for description, comparison, and classification of nerve cells. At another level, spike-train statistics of a neuron may afford insight into the internal mechanisms underlying spike production; of particular importance here is the comparison of models of spike-production mechanisms, which is typically effected through comparison of the corresponding spike-train statistics. In *inter*neuronal analysis, simultaneously recorded spike trains are compared statistically to reveal information concerning possible connections between neurons, shared sources of activity, responses to stimuli, and synaptic input-output relations. It is in the comparison of neuronal spike trains, however, that we believe the greatest promise of these techniques to lie, despite the greater incursion of mathematical difficulties when compared with single-train analysis.

In summarizing currently used techniques of spike-train analysis, we are further

prompted by our feeling that these computational techniques have lacked adequate theoretical underpinning, which has resulted in (*a*) inconsistency of nomenclature and notation in this field, (*b*) difficulties, not always well enough appreciated, in assigning measures of statistical significance to experimental findings, (*c*) presentations of experimental data in several forms that are in fact mathematically derivable from each other, and (*d*) the risk of attributing particular physiological significance to results that illustrate purely mathematical theorems or that are more plausibly attributable to chance effects. With the advent of the high-speed electronic digital computer, it has become feasible to perform on a routine basis the lengthy computations required for spike-train analysis; it is our feeling that in relating these computations to the underlying mathematical, i.e. probabilistic and statistical, theory, the potential usefulness of these techniques will be enhanced.

Basic Terminology and Scope

In every instance in which a detailed examination is made of the timing of neuronal events, we are forced to realize that a certain degree of unpredictability or randomness is present in the underlying process. For some purposes we can afford to overlook this aspect of the record, but for other purposes, and in particular those we focus on here, the question of interest, and indeed the source of greatest information about the process being observed, is the variability and randomness of the spike train.

This very property forces us to describe the spike train in statistical terms and to view the processes underlying it either as inherently probabilistic or as sufficiently complex that we can best and most simply treat them in probabilistic terms. Processes of this type are commonly referred to as *stochastic processes*. Indeed, the transfer and processing of information in nervous systems may be viewed as a repeated alternation, in time and space, of two different types of stochastic processes. The first type is characteristic of the continuous *intraneuronal* fluctuations in significant state variables of each neuron. Typically, a state variable might be the membrane potential as observed at the primary spike-initiating locus, and a model of the underlying process might be described as a complicated type of *random walk*, with continuous time and "displacement" variables. The second type of stochastic process, which is the primary concern of this paper, arises in the study of the times of occurrence of *interneuronally* transmitted action potentials, i.e. the spike train, as commonly observed with either extracellular or intracellular microelectrodes. Because of our "all-or-none" conception of the nerve impulse, each spike is regarded as indistinguishable from the others produced by the same neuron. Furthermore, with each spike can be associated a unique instant of time, e.g. the time of maximum excursion of electrical potential, which can be measured with a high degree of precision. By virtue of the assumed indistinguishability[1] and instantaneity of the

[1] I.e., they are distinguishable only by where they occur in time.

individual spike events, the stochastic process characterizing the spike train can be considered an example of a *stochastic point process*. This process occurs in one dimension, corresponding to the time axis.

In any point process, in which all "events" (spikes, for example) are indistinguishable except for their times of occurrence, it is the elapsed times between events, e.g. the interspike intervals, that exhibit the properties of random variables. These intervals are regarded as being drawn (not necessarily independently) from an underlying probability distribution; if that distribution, together with its parameters, does not vary with time of observation, the stochastic point process is *stationary*.[2] A sample from a stationary point process might be approximated, for example, by a spike train from a spontaneously firing neuron, or from a neuron well adapted to a steady stimulus. A monotonic trend in the firing rate or other parameter is one of the many features of a spike train that may preclude its characterization as stationary.

In most of this paper, spike trains will be considered as realizations of stationary point processes (except for local effects due to stimulation). We cover first the analysis of the spike train produced by a single neuron exhibiting spontaneous or "steady-state" activity. After a presentation of basic concepts and nomenclature, we describe the statistical measures that are independent of the serial order of intervals. We then describe order-dependent statistical measures. Then we discuss some problems of description and interpretation encountered with single spike trains. Next we consider the effects on a spike train of isolated, repeated presentations of a stimulus. Finally, we describe the effects of nonstationarity on the statistical measures described for stationary processes. The presentation is illustrated with examples drawn largely from digital computer simulations (Perkel, 1965).

A companion paper covers the analysis of simultaneously observed spike trains (Perkel, Gerstein, and Moore, 1967).

THE SINGLE SPIKE TRAIN

Stochastic Point Processes: Basic Nomenclature

A stochastic point process, as mentioned above, is a stochastic process "whose realizations consist of a series of point events" (Cox and Miller, 1965). The point events are considered to be instantaneous and indistinguishable (except for position in time); for neuronal spikes, therefore, we consider, for example, the time corresponding to the maximum of the observed action potential to be the time of occurrence, and we ignore all other characteristics of the spike, such as duration, amplitude, undershoot, etc.

[2] Strictly speaking, stationarity is defined in terms of the invariance under translation in time of the joint distribution of numbers of events in fixed intervals of time (Cox and Miller, 1965, pp. 339–340; Cox and Lewis, 1966, p. 59). An equivalent definition in terms of interval distributions is difficult to formulate rigorously, mainly because of the complications introduced by the choice of the starting point for describing the process.

In a *stationary* point process, the underlying probability distributions governing the times of occurrence of the point events do not vary with respect to an arbitrary translation of the time axis.[3] Therefore, accelerations and decelerations in firing rates and effects such as fatigue and adaptation disqualify spike trains from acceptance as realizations of stationary point processes. We consider the detection of nonstationarity and its effects, if present, in the final section of this paper. For a spike train observed in the absence of repetitive stimulation, the assumption of stationarity means, in a practical sense, a neuron that does not display any apparent trend in firing rate and whose "mode" of firing does not exhibit any significant shift from one portion of the record to another.

One important class of stationary point processes, known as *renewal processes*, has the property that the lengths of intervals between events are statistically independent.[4] Neuronal spike trains rarely satisfy this requirement completely; even those spike trains that can adequately be described as stationary often exhibit serial dependence among interspike intervals.

Many results first established in renewal theory have subsequently been generalized to nonrenewal stationary point processes (McFadden, 1962), and in some cases even to nonstationary processes. The terminology of renewal theory, however, has been retained because of its intuitive appeal, and we use it here. Another set of metaphors more appropriate to neuron firings could easily be substituted.

The Poisson, the Erlang, and the Weibull processes are some of the most commonly encountered renewal processes with particularly simple properties. These are discussed amply in the literature (Cox, 1962) and have been applied to the description of certain classes of neuronal spike trains. Most spike trains with independent interval lengths, however, do not fall into any of these mathematically attractive classes.

In the following sections we describe some of the most important and useful statistical measures of spike-train properties.

Order-Independent Statistical Measures

For both renewal and nonrenewal stationary point processes, the (marginal) distribution of intervals between successive events is of paramount importance in characterizing the process. For a renewal process, in fact, the distribution of intervals completely characterizes the process. For finite samples of data, such as an observed neuronal spike train, the interspike-interval histogram serves as an estimator of the "actual" probability density function (pdf).

To construct it, the range of observed interval lengths is customarily divided into

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[3] A more explicit definition is given by Cox and Lewis (1966), p. 59.

[4] A renewal process is stationary only if observation begins at a random instant in time, in which case the interval from that instant to the first event has a different distribution from that of subsequent interevent intervals (Cox, 1962). We will assume this condition when discussing renewal processes.

bins of equal width δ; if the ith observed interspike interval T_i satisfies the inequalities

$$(j - 1)\delta < T_i \leq j\delta, \tag{1}$$

then that interval is placed in bin j of the histogram. The bins are thus numbered 1, 2, $\cdots$, J. Letting N_j designate the number of intervals placed in bin j in an observation of N intervals, i.e., $N + 1$ spikes, then the ratios N_j/N are a smoothed estimate of the pdf $f(\tau)$; i.e., they estimate the corresponding integrals

$$\frac{N_j}{N} \approx \int_{(j-1)\delta}^{j\delta} f(\tau)\, d\tau. \tag{2}$$

This quantity is the probability that the duration of a randomly chosen interval lies between $(j - 1)\delta$ and $j\delta$. The estimator for the average value of the pdf within the bin is given by

$$f_j \equiv N_j/(N\delta). \tag{3}$$

Although N interval measurements are used in estimating the usual population parameters such as mean, variance, etc., it is only for a renewal process that the N observations are independent. Measures of precision assigned to these estimates by the standard formulas may be misleading if the process is not a renewal.

For both renewal and nonrenewal processes, there are several functions completely equivalent mathematically to the pdf $f(\tau)$ or its estimator f_j (Cox, 1962, pp. 2–7). These are illustrated in Fig. 1. One of these, the (cumulative) *distribution function*,

$$F(\tau) = \int_0^\tau f(t)\, dt = \text{prob } (T \leq \tau), \tag{4 a}$$

is estimated by

$$F_j = \sum_{k=1}^{j} f_k \tag{4 b}$$

and, in neurophysiological terms, measures the probability that a neuron will have fired by time τ from the last firing.

The *survivor function*, the complement of $F(\tau)$, or

$$\mathfrak{F}(\tau) = 1 - F(\tau) = \text{prob } (T < \tau), \tag{5}$$

is the probability that the neuron will not have fired by time τ.

A third function, the *hazard function*, measures (in the terminology of renewals)

the instantaneous risk of failure of a component known to be of age τ. It is given by

$$\varphi(\tau) = f(\tau)/\mathfrak{F}(\tau) = f(\tau)/[1 - F(\tau)]. \tag{6}$$

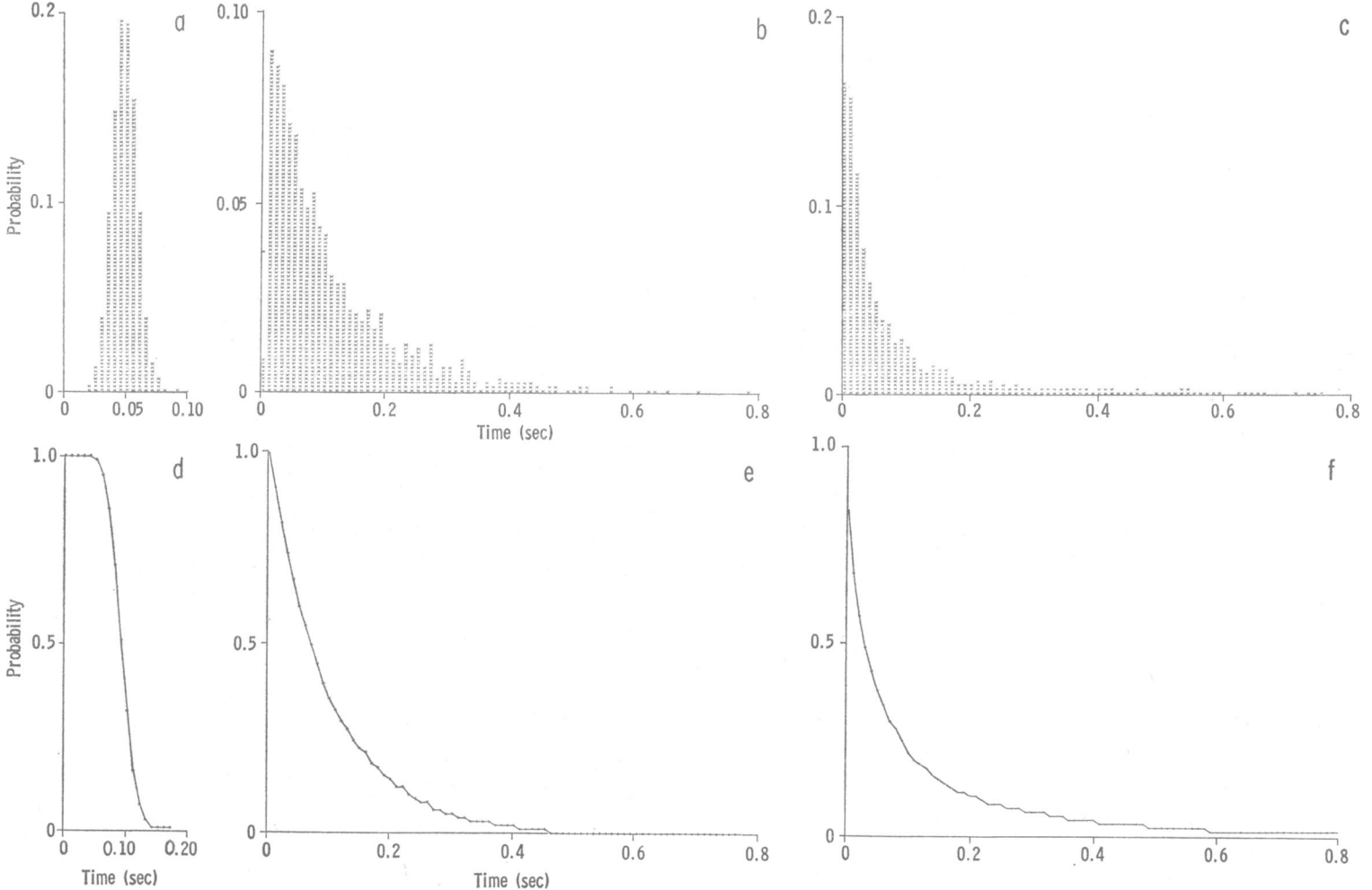
In the neurophysiological context, the quantity $\varphi(\tau)\Delta\tau$ is the probability that a neuron will fire during the time interval $\Delta\tau$, given that it has not fired prior to the time τ. This function is called the "age-specific failure rate" by Cox (1962). In the neurophysiological literature, it is denoted as c(x) by Poggio and Viernstein (1964) and called by them the "postimpulse probability;" the same function is called "conditional probability" by Goldberg et al. (1964). It is also denoted as $\lambda(x)$ by McGill (1963), who points out some earlier synonyms for the same function: "IRT/OPS," "conditional density function," and "hazard function."

For a Poisson process the hazard function is a constant (Fig. 1 b, bottom). Other processes display positive or negative "ageing" accordingly as $\varphi(\tau)$ increases or decreases with τ. Interspike-interval distributions from pacemaker neurons, for example, characteristically display positive ageing, i.e. an increased "hazard" of firing as a function of time since the last spike (Fig. 1 a, bottom), whereas long-tailed distributions, such as those obtained for some neurons in the auditory system (Gerstein and Mandelbrot, 1964), display negative ageing (Fig. 1 c, bottom). Note that the estimate of the hazard function loses precision for long intervals (Watson and Leadbetter, 1964 *a*, 1964 *b*).

Summaries of the interspike-interval distribution are furnished by various scalar quantities; estimation of these scalars from finite samples of spike-interval data does not differ in any essential respect from estimation using sample data from any other source. Useful quantities are the mean interval μ, the interval variance σ^2, the standard deviation σ, and the coefficient of variation σ/μ. The mean firing rate ρ is defined as the reciprocal of the mean interval. Standard measures of skewness and kurtosis are often useful for describing and classifying interval distributions.

Order-Dependent Statistical Measures

It is of considerable neurophysiological interest to determine whether or not successive interspike intervals are independent in the statistical sense, i.e., whether or not the spike train can be described as a realization of a renewal process. Cox and Lewis (1966, pp. 164–171) discuss two classes of tests for independence of intervals, one based on sample serial correlation coefficients, and the other based on the spectrum of intervals. These authors state that "this is a difficult problem because the null hypothesis is very broad and the alternatives usually not at all clearly specified, and also because the associated distribution problems are hard." Moreover, if the intervals are not independent, such tests offer little information about the type of dependence, and they have so far found little application in spike-train analysis.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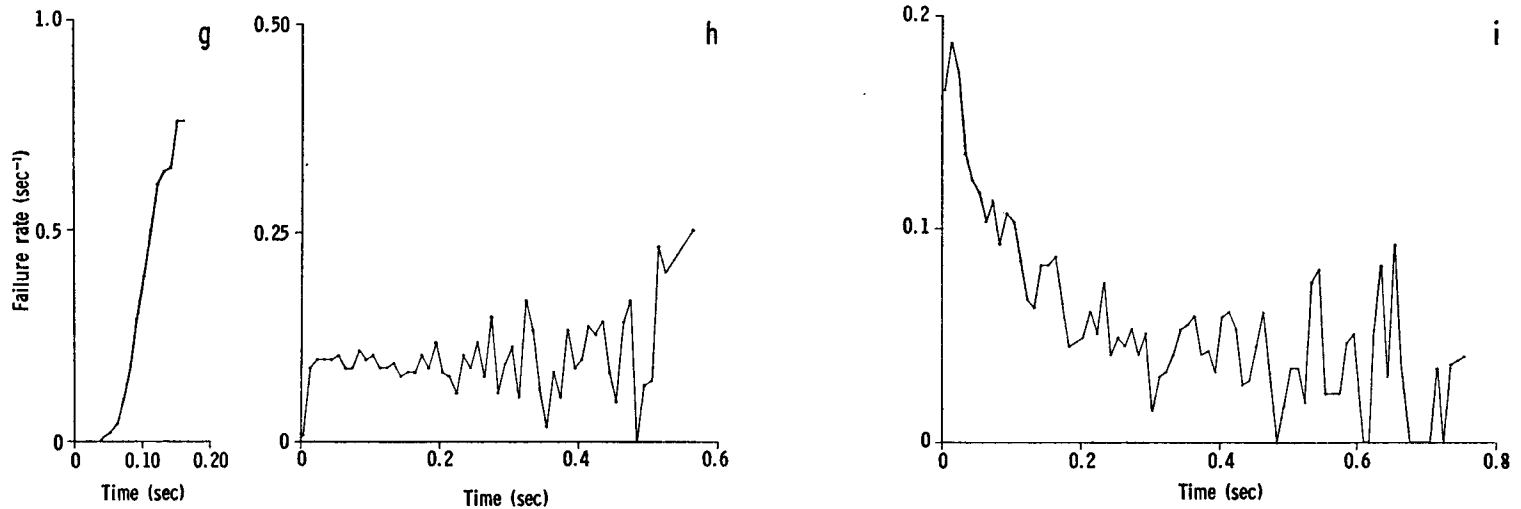

FIGURE 1 Equivalent forms of the interspike-interval distribution. a–c, interspike-interval histogram (estimate of the pdf); d–f, survivor function; g–i, hazard function; a, d, and g drawn from a "pacemaker neuron": independently normally distributed intervals with mean 100 msec and standard deviation 5 msec. b, e, and h from a Poisson process with mean interval 10 msec, conditioned by a normally distributed dead time (refractory period) with mean 10 msec, standard deviation 2 msec. c, f, and i from a log-normal distribution, with pdf $x^{-1}(2\pi\alpha)^{-1/2}\exp\{-[\log(\rho x)]^2/(2\alpha)\}$, with $\rho = 27.2\ \text{sec}^{-1}$ and $\alpha = 2$. Each sample contains approximately 2000 intervals.

Aside from their use in hypothesis testing, certain statistical measures have been used to describe and quantify serial dependence among interspike intervals. We call these measures *order-dependent*, in order to distinguish them from those based solely on the interspike-interval distribution, discussed above. The methods of spectral analysis, recommended by Cox and Lewis (1966; see also Bartlett, 1963), have not been used for analyzing spike-interval data, but their potential utility deserves extensive investigation. Serial correlation coefficients are statistics based on joint distributions of intervals, and another set of measures is based on intervals between nonadjacent spikes. We describe here the latter two classes of techniques.

Use of the *joint interval density* for spike-train analysis was introduced by Rodieck, Kiang and Gerstein (1962). The data are displayed in the form of a scatter diagram, in which the length of an interspike interval is represented by the abscissa, and the length of the next interval in the record by the ordinate. Each point on the diagram then represents a pair of adjacent intervals. An alternate form is the matrix equivalent of Smith and Smith (1965). If successive intervals are independently distributed, then the normalized frequency distribution along the ordinate is the same for each abscissa value, and vice versa. This implies that the corresponding row and column means in the corresponding joint interval histogram have a constant expected value. An observed constancy of row and column means, which is a necessary condition for independence of adjacent intervals, has in practice been used as a sufficient test. Departures from independence are reflected not only in these means but also in the symmetries of the scatter diagram itself. For example, an over-all "upward" trend in the joint-interval scatter diagram (as illustrated in Fig. 7 of Rodieck et al., 1962, units 261-1, R-4-10, and 240-1) indicates positive correlations between successive intervals. This means, loosely, that short intervals tend to be followed by short ones, and long intervals by long ones. A "downward" trend would imply negative serial correlation. The uncorrelated case is illustrated by unit 259-2 in the same figure. The corresponding row and column means are shown in Fig. 8 of the same work.

A quantitative measure of such correlation is furnished by the *serial correlation coefficient* of interval lengths, which is defined as follows: We define the covariance of interval lengths, of lag j, by

$$C_j = E[(T_i - \mu)(T_{i+j} - \mu)](j = \cdots, -1, 0, 1, \cdots), \tag{7}$$

where T_i is the ith interspike interval in an (infinite) stationary train of spikes, with mean interval μ and variance σ^2. Then the serial correlation coefficient ρ_j of order j is the ratio of the corresponding covariance to the interval variance:

$$\rho_j = C_j/\sigma^2. \tag{8}$$

In a finite sample, the mean μ and the variance σ^2 must be estimated from the

sample data. To avoid the slight bias introduced by use of sample mean and variance to estimate the corresponding population parameters, more complicated formulas are suggested by Cox and Lewis (1966, pp. 89–92).

The serial correlation coefficient of lag 1 furnishes a single scalar quantity as a summary of the entire diagram of the joint interval distribution of lag 1. Joint interval distributions of larger lags, i.e., for nonadjacent intervals, have not been used in the analysis of spike trains; the corresponding serial correlation coefficients, however, have been used extensively. The set of serial correlation coefficients is usually called the *serial correlogram*; it has sometimes (Hagiwara, 1954) been called the "autocorrelogram" or "autocorrelation," terms that we reserve for a different function (see below).

The expected value of the serial correlation coefficients of all orders (lags) is approximately zero if the intervals arise from a (stationary) renewal process, i.e., if the intervals are drawn independently from a common distribution. For large N, for a renewal process, the quantity $\rho_i/(N-1)^{1/2}$ has a unit normal distribution. However, the distribution of the sample serial correlation coefficient is not known for small samples, and the sample coefficients of various lags are correlated for moderately sized samples (Cox and Lewis, 1966, p. 165). No test of independence of intervals is known which is based jointly on several serial correlation coefficients (P. A. W. Lewis, private communication).

One useful expedient, however, is to subject the sample of interspike intervals to random shuffling, which destroys serial dependence but preserves the order-independent statistics of the sample. Shuffling thus converts the sample to one from the corresponding renewal process. The recomputed serial correlogram for the shuffled train provides a control case, in which the departures from 0 of the serial correlation coefficients are in fact those due to random fluctuations. The net departure may be measured, for example, by the sum of squares of the coefficients. In principle, the shuffling and recomputation can be repeated at length to provide an empirical sampling distribution of the sum of squares under the null hypothesis of serial independence. From this distribution, tests of the independence hypothesis for the unshuffled data can readily be constructed. This kind of procedure is discussed by Cox and Lewis (1966, p. 165) as a permutation test of serial correlation. A refinement discussed there is to replace the observed interval values by ranks or exponential scores. In this way the sampling distribution can be computed once and for all for a given sample size.

The most frequently encountered source of positive contributions to the serial correlation coefficients is a long-term trend in the data; a sufficiently great monotonic increase or decrease in the firing rate over the time of observation will contribute a positive component to each serial correlation coefficient, out to lags of arbitrarily high order. Monotonic trends, of course, are a form of nonstationarity; they are discussed further in a subsequent section.

In a stationary point process that is not a renewal process, the serial correlogram

furnishes indications as to the nature of departure from independence among intervals. Local trends in firing rate will introduce positive contributions to the serial correlation coefficients, primarily to the lower lag values (Hagiwara, 1949; Junge and Moore, 1966). Cyclic variations in firing rate, for example, produce a damped oscillation in the serial correlogram, which starts at positive values. Somewhat similar oscillations are produced by fairly regular occurring bursts of spikes, as exemplified by medullary respiratory neurons. Irregular bursts of spikes, such as have been described by Smith and Smith (1965), are characterized by negative serial correlations for low lags, followed by slightly positive and then 0 correlation coefficients. Alternation between long and short intervals, as commonly seen in certain cells in the dorsal column nuclei (Amassian et al., 1962) or in locust wing-muscle motor neurons (Wilson, 1964), gives a strongly negative first serial correlation coefficient with subsequent alternation in sign of the coefficients of higher order. Other types of patterned activity have corresponding signatures in the serial correlogram. Some examples, from computer simulations, are illustrated in Fig. 2.

It must be emphasized that both the joint interval histogram and the serial correlogram must be interpreted with caution and in conjunction with other statistical measures. The positive contribution to low-order correlation coefficients due to local or global trends in firing rate may mask any negative correlation between adjacent intervals that would otherwise be apparent. Segmentation of the data may clarify this situation, but at the expense, of course, of statistical reliability. A gap in the record, which introduces an exceptionally long interval, may grossly affect the interval variance and seriously distort the serial correlogram; this effect is most pronounced in pacemaker neurons (small coefficient of variation of intervals). On the other hand, effects of trends and gaps on the serial correlogram are much less pronounced in data with a large inherent variability (large coefficient of variation), such as a Poisson process with a time-varying rate parameter or neurons with highly irregular firing times. It is important to measure and correct for these distorting effects since significant information about the physiology of the neuron, such as refractory effects, persistence of synaptic effects, etc., may be uncovered through correlational analysis of successive intervals (Firth, 1966; Junge and Moore, 1966; Geisler and Goldberg, 1966).

The use of ranks or exponential scores greatly alleviates the effects of gaps in the record. The use of the estimated spectrum of intervals overcomes some of the effects of trends. The tests for independence of intervals based upon the spectrum of intervals, as described by Cox and Lewis (1966, pp. 67 et seq.), appear to have been neglected by investigators of spike trains. The estimated spectrum gives a single test for independence based on all of the data and thereby overcomes the obstacles mentioned above to the interpretation of the serial correlogram. Computation of the spectrum has been greatly facilitated by a recently devised algorithm (Cooley and Tukey, 1965), which has been incorporated in a set of computer programs by P. A. W. Lewis (1966) for the statistical analysis of series of events.

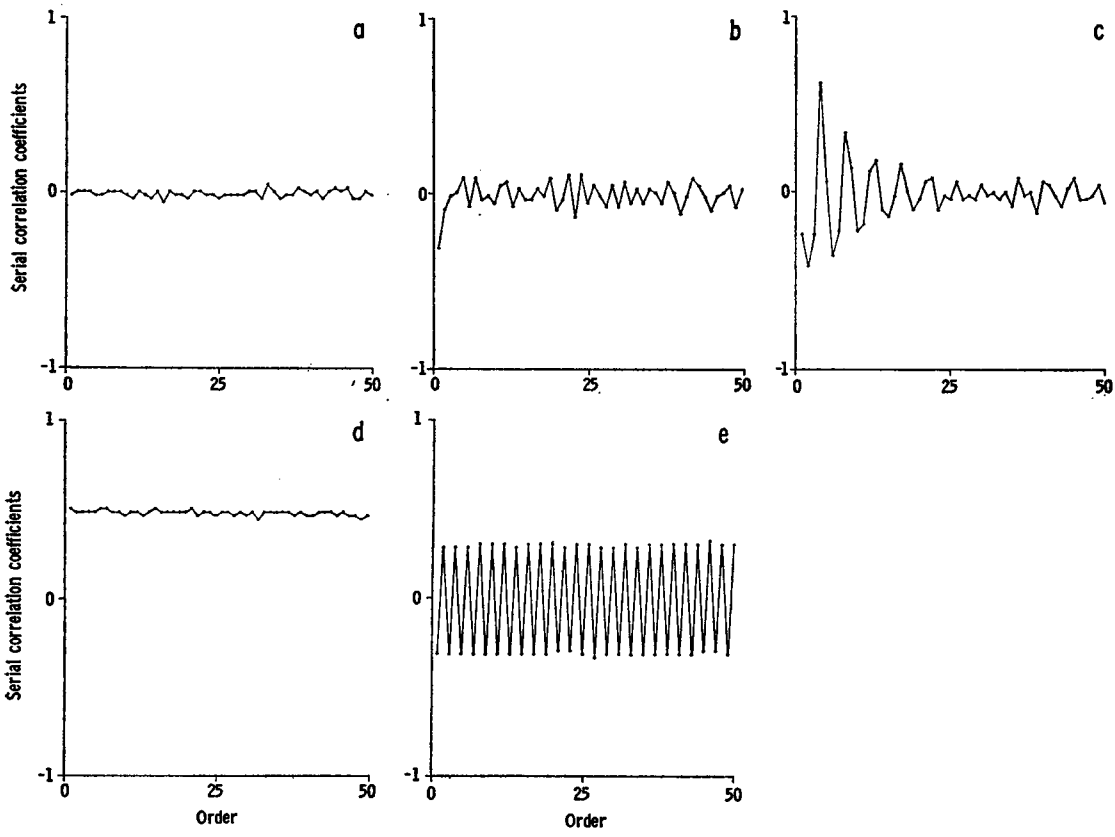

FIGURE 2 Typical serial correlograms. a, independent intervals drawn from a Weibull distribution, with pdf $\alpha\rho(\rho x)^{\alpha-1} \exp -(\rho x)^{\alpha}$; $\rho = 15$ sec^{-1}, $\alpha = 0.6$, 2161 spikes. b, simulated neuron producing irregular bursts. Resting level of membrane potential -70 mv, reset to -100 mv after a spike; exponential recovery with decay constant of 6.93 sec^{-1}. Asymptotic threshold -40 mv, reset to -20 mv after a spike; exponential recovery with decay constant 3.47 sec^{-1}. Two input channels producing 18.5-mv EPSP's: one channel with mean firing rate 2.0/sec, the other with mean firing rate 2.1/sec; standard deviation of intervals 3% of mean. Cell fires with mean interval 2.6 sec, standard deviation 2.9 sec, with sample of 389 spikes. c, simulated neuron producing more regular bursts. Similar to case b, but with standard deviation of intervals in input channels 0.6% of respective means. Cell fires in bursts of four or five spikes; interspike intervals within bursts 0.5–1.0 sec; bursts start at intervals of approximately 10 sec. Sample of 424 spikes has mean interval 2.4 sec, standard deviation 2.8 sec. d, decelerating train. Intervals drawn from a time-dependent normal distribution with $\mu(t) = 0.1 - 0.02e^{-.01t}$ sec, $\sigma = 0.01$ sec. Sample of 2447 spikes. e, alternation between long and short interval lengths. Intervals drawn alternately from distribution with mean 0.11 sec and from distribution with mean 0.09 sec, each with standard deviation 0.015 sec. 5000 spikes.

Joint interval distributions and the corresponding serial correlation coefficients involve time intervals that are defined by two successive spikes. The second class of order-dependent statistical measures that we discuss involves time intervals between nonsuccessive events. Denoting as a first-order interval the elapsed time from

an event to the next following event, we may define a second-order interval as the elapsed time between an event and the second following event, etc. An nth-order interval is the sum of n consecutive first-order intervals and is spanned by $(n + 1)$ consecutive spikes (see Fig. 3).

The probability density of the nth-order interval is designated $f_n(\tau)$. The interval density for successive events is thus the first-order density: $f_1(\tau) = f(\tau)$.

In the special case of a renewal process, the higher-order densities may be obtained by successive convolutions of the first-order density because the intervals are independent. Thus, the second-order interval density is given by the convolution integral

$$f_2(\tau) = \int_0^\infty f(t)f(\tau - t)\, dt, \tag{9 a}$$

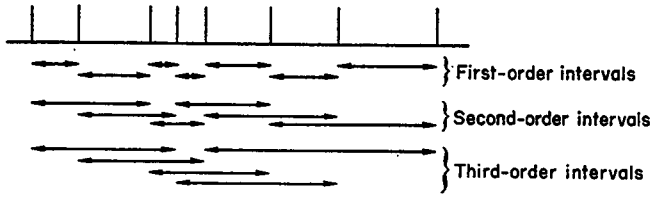

FIGURE 3 Higher-order interspike intervals. A first-order interval is the time difference between adjacent spikes. A second-order interval lies between a spike and the second spike following, etc. Note that an interval of order n spans $n + 1$ spikes. See text.

and in general we have the recursion

$$f_{n+1}(\tau) = \int_0^\infty f_n(t)f(\tau - t)\, dt. \tag{9 b}$$

These equations do not apply when successive interval durations are not independent.

A related function is the *renewal density*, $h(\tau)$, which specifies the probability of encountering any event as a function of time after a given event; i.e.,

$$h(\tau) = \lim_{\Delta\tau \to 0} \text{prob } \{\text{an event in } (\tau, \tau + \Delta\tau) \mid \text{an event at } 0\}/\Delta\tau. \tag{10}$$

Since any event encountered must be either the first, second, . . . , etc., event after the event at time 0, it is evident that the renewal density is the sum of the interval densities of all orders:

$$h(\tau) = \sum_{k=1}^{\infty} f_k(\tau). \tag{11}$$

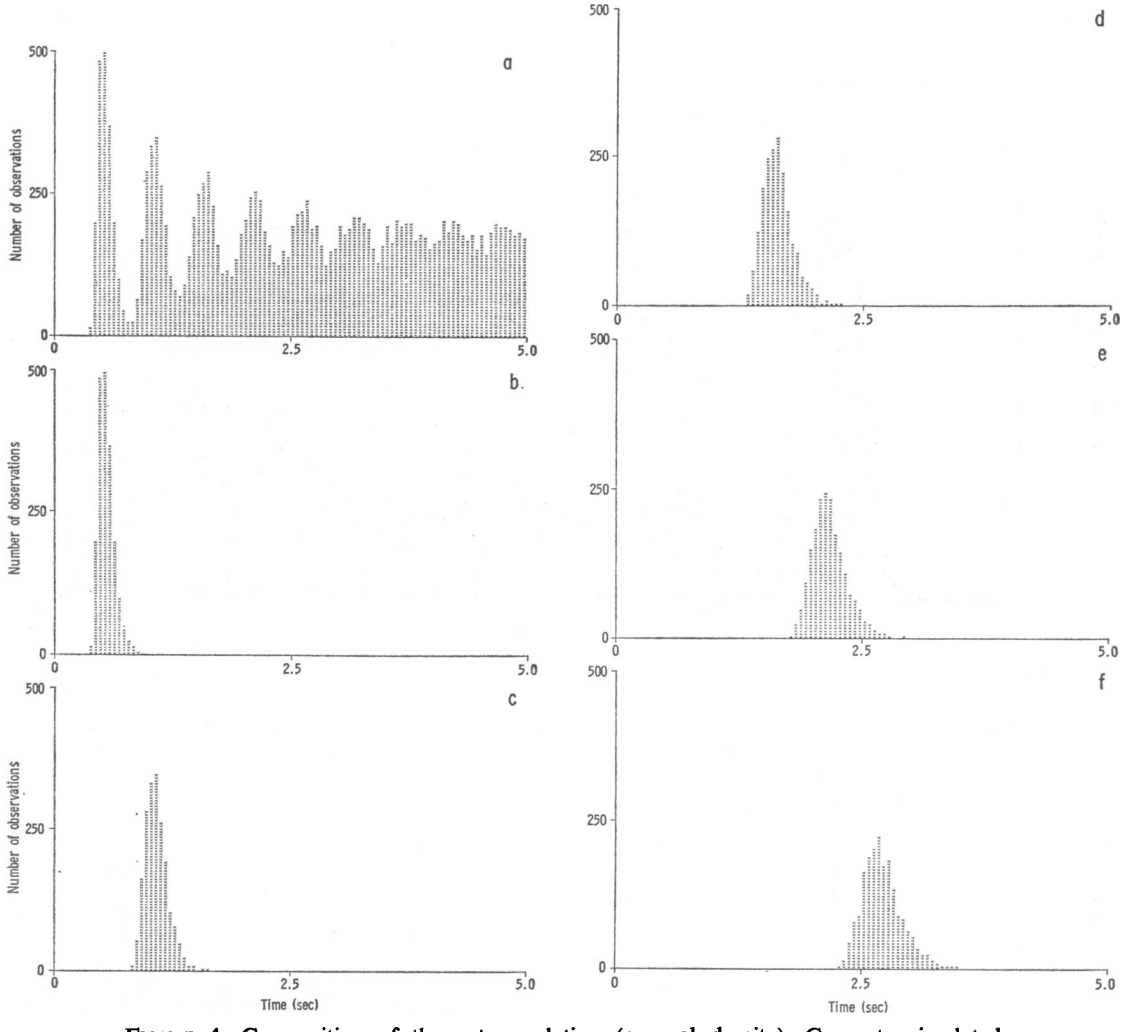

FIGURE 4 Composition of the autocorrelation (renewal density). Computer-simulated noisy pacemaker with inhibitory synaptic input. Mean interspike interval without inhibition 0.47 sec; Poisson arrivals of IPSP's at mean rate of 4/sec; maximum hyperpolarization of IPSP's normally distributed with mean 5 mv, standard deviation 1 mv. Mean interspike interval 0.54 sec, standard deviation 0.09 sec, 2000 spikes. a, autocorrelation histogram. b, interspike-interval histogram. c–f, second- through fifth-order interval histograms. See text.

This is illustrated in Fig. 4, in which is shown the renewal density (as estimated by a histogram) from a sample of spike activity of a computer-simulated neuron; together with it are displayed the corresponding interval densities of the first four orders.

In spike-train analysis, the renewal density is often called the *autocorrelation* (Gerstein and Kiang, 1960), since if the spike train is regarded as a signal of 0 am-

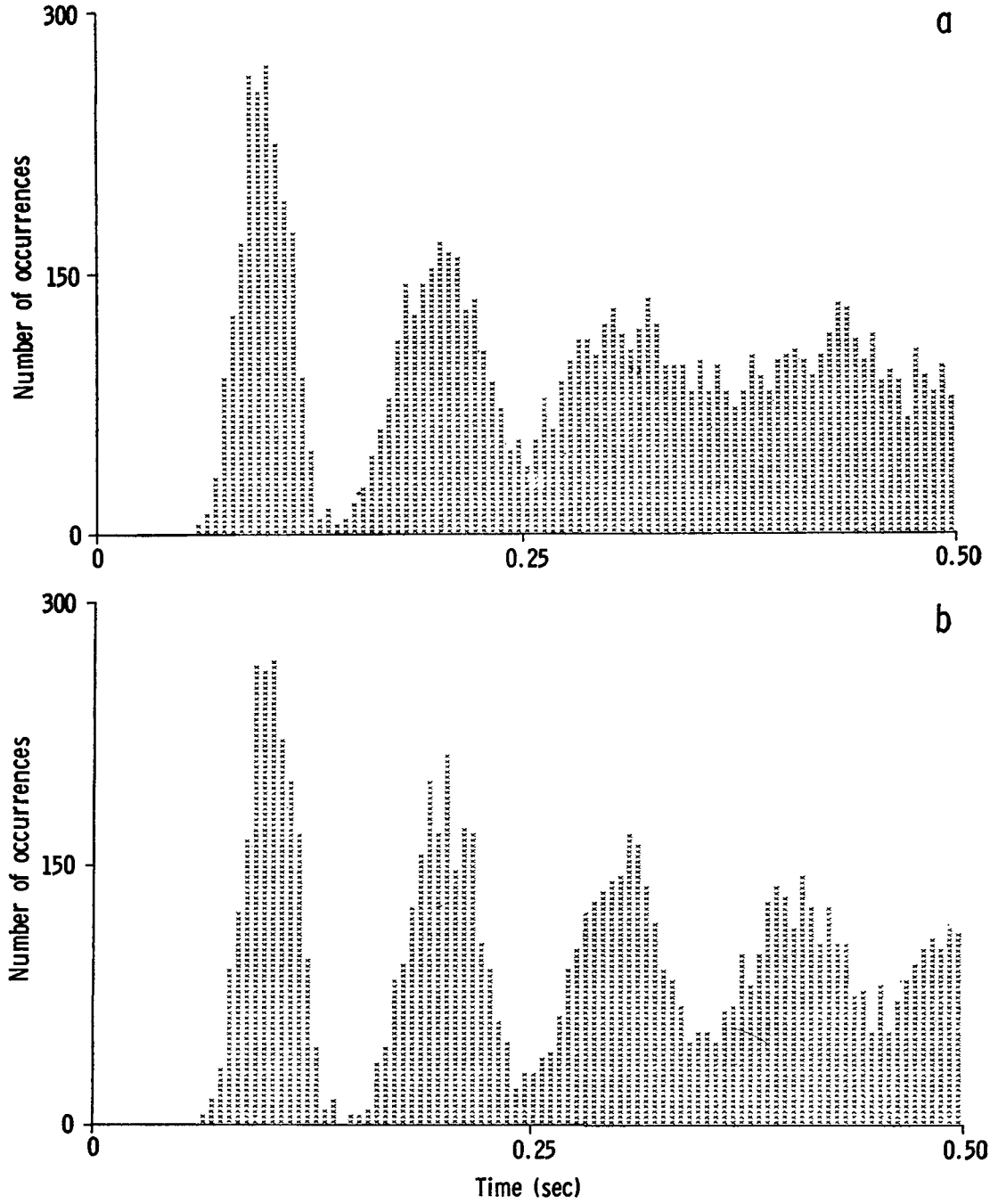

FIGURE 5 Effect of shuffling on peaks in the autocorrelation. Intervals generated by a semi-Markov process with three states with mean intervals as follows: state 1 (short), 0.09 sec;

plitude everywhere except where a spike is present, and if each spike is represented as a Dirac delta function, then the renewal density corresponds to the autocorrelation as ordinarily defined for continuous signals. In the usage of Cox and Lewis (1966), the renewal density is one of a class of "intensity functions." Another synonym that has gained some currency is "expectation density;" it is used by Poggio and Viernstein (1964) and others, following a usage introduced by Huggins (1957). Yet another synonym is "post-firing interval distribution," introduced by Lamarre and Raynauld (1965).

Another property of the autocorrelation is that it "flattens out" to a constant value; i.e.,

$$\lim_{\tau \to \infty} h(\tau) = 1/\mu. \tag{12}$$

In general, this limit is approached slowly for pacemaker neurons (narrow interspike-interval densities), and more rapidly for spike trains with greater variation in interval length. The limiting value is attained for all values of τ for a Poisson process; it can be shown, in fact, that a Poisson process is the renewal process having a constant renewal density.

The representation of higher-order interval densities as corresponding convolutions of the first-order density (Equation 9) holds only for independent intervals. If there is serial dependence (as measured by the serial correlogram), more complicated expressions are required, as given by McFadden (1962). Thus, the sum of the interval densities of various orders (the autocorrelation) for two spike-train sequences having identical interval distributions will be different if in one train the intervals are independent, i.e. a renewal process, and in the other they are dependent. Hence, it is possible to compare the observed autocorrelation with that predicted under the independence hypothesis as a test of that hypothesis. One convenient computer method is that of prolonged random shuffling of the intervals, as discussed above. The autocorrelation of the shuffled train then represents a control case of serial independence. Discrepancies between the unshuffled and shuffled autocorrelation not only furnish a test of serial dependence, but may also indicate the nature of that dependence.

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state 2 (medium), 0.10 sec; state 3 (long), 0.11 sec. All intervals normally distributed with standard deviation 0.01 sec. Transition matrix

$$\begin{pmatrix} 0.70 & 0.20 & 0.10 \\ 0.45 & 0.10 & 0.45 \\ 0.10 & 0.20 & 0.70 \end{pmatrix}$$

is such that a long interval is most likely to be followed by a long interval, and a short by a short. Mean interval 0.10 sec, standard deviation 0.014 sec, in sample of 2000 spikes; first five serial correlation coefficients: 0.251, 0.184, 0.085, 0.071, 0.040. After shuffling of intervals, first five serial correlation coefficients were −0.018, 0.017, 0.021, −0.041, −0.004. a, autocorrelation histogram, unshuffled data. b, autocorrelation histogram of reconstructed spike train after shuffling of interspike intervals. Note sharpening of peaks. See text.

Shuffling may either enhance or flatten peaks in the autocorrelation. For example, if interspike-interval lengths exhibit negative serial correlation, peaks in the autocorrelation are generally broadened by shuffling. On the other hand, if interval lengths are positively correlated, shuffling of intervals may sharpen peaks in the autocorrelation. An example of the latter effect is shown in Fig. 5, in which the original interval sequence was generated by a three-stage semi-Markov process (Cox and Lewis, 1966, p. 82), according to which relatively long intervals were more likely to be followed by long intervals than by short ones, and vice versa.

To avoid confusion it should be emphasized that the autocorrelation is a function of time; the serial correlogram [Hagiwara's (1954) "autocorrelation"] is a function of the serial position of the interval, an integer. The two functions need not correspond at all. For example, a pacemaker cell that fires at nearly uniform intervals will have a strongly oscillating autocorrelation, whereas the serial correlogram may be positive, negative, oscillatory, or zero.

Long-term trends or slow oscillations in firing rates are ordinarily not obvious in the autocorrelation, but are more typically revealed in the serial correlogram. These and other effects of relatively long-term rate variations are discussed below, in the section dealing with the effects of nonstationarity.

Description, Prediction, and Information

Having presented certain statistical measures that can be applied to individual spike trains, we now introduce briefly some considerations about the adequacy and utility of statistical descriptions of the train. These considerations bear on the use of statistical descriptions both in characterizing and classifying neurons and in comparing observed spike data with those predicted by models.

The simplicity of statistical description of a spike train differs widely from case to case. A single parameter suffices to describe a Poisson process, whereas two are required for an Erlang or Weibull process. If a spike train fits into one of these categories, not only is the characterization of the particular spike train extremely simple, but also the pdf of the interval distribution (and therefore the hazard function, autocorrelation, etc.) may be written as an explicit equation. For less easily described renewal processes, the entire interspike-interval histogram is required to characterize its properties. When successive intervals are not independent, then much more complicated descriptions are needed, except in special cases of highly patterned spike configurations. When higher-order joint interval densities or similarly elaborate statistical measures are required to effect a reasonably complete description, the statistical description itself is unmanageable, and its practical utility is highly questionable. The limit is reached, of course, when the number of parameters in the statistical model equals (or exceeds!) the number of spikes in the sample, at which point statistical analysis loses all justification.

The relationship between the statistical properties of a spike train and the in-

formation-handling capability of the neuron is generally complex. Estimates of channel capacity depend strongly upon the particular choice of encoding scheme imputed to the neural structure. Once a choice of encoding scheme has been made, then estimates of channel capacity can be obtained on the basis of interval statistics. For example, if a parameter is thought to be encoded in terms of mean firing rate, then a smaller coefficient of variation of intervals gives rise to a higher channel capacity, etc. Interval statistics, however, cannot of themselves provide a choice of coding scheme. Facile "derivations" of information-handling characteristics of neurons based solely or primarily on spike-interval statistics are usually misleading or worse. For a more extended discussion of these problems, the reader is referred to Moore et al. (1966) and to Segundo et al. (1966).

SINGLE SPIKE TRAINS IN THE PRESENCE OF STIMULATION

In many neurophysiological experiments a controlled series of changes in the physical environment is introduced. We consider here the case of a repeated, relatively short stimulus. In order to detect and evaluate the effect of such a *stimulus train* on the train of spikes, it is now common to compute a post-stimulus-time (PST) histogram (Gerstein and Kiang, 1960). Specifically, the PST histogram shows the probability of firing as a function of time after the stimulus onset. As shown below, this measure is equivalent to a cross correlation between the train of stimulus presentations and the train of spikes. If the stimulus has no effect on the pattern of the spike train, the PST histogram will be flat (subject to the usual statistical fluctuations). On the other hand, if the stimulus does produce a timelocked "evoked response" in the spike-train pattern, the PST histogram will show deviations from flatness. A peak in a PST histogram indicates a higher probability of firing at that particular time after stimulation and can presumably be associated with an excitatory process. Dips in a PST histogram indicate a lower timelocked probability of firing and often are associated with inhibitory or refractory processes.

In interpreting a PST histogram it is obviously necessary to decide on the statistical significance of the observed deviations from flatness. A simple method that has been used (Weiss, 1964) is to compute the mean square deviation of all bins from the mean level of the histogram. Some criterion value for this number can be chosen to distinguish a "flat" PST histogram from one that shows a weak timelocked response pattern.

There is some difficulty in this type of significance test, however, since successive bins in the histogram may not represent independent quantities. For example, since each firing of the neuron is followed by a refractory period, there is always a tendency toward a negative correlation between adjacent bins in the histogram. An empirical control case can be constructed by randomly shuffling the intervals of the spike train and computing the corresponding "flat" PST histogram. The distribution of mean square deviations from mean bin level can be obtained from a

set of replications of this procedure, and the criterion value can then be chosen as usual to satisfy a specified error probability. A control case can also be constructed using fictitious times of stimulus presentation in a portion of record where no actual stimulations were presented (Gerstein, 1960; Burns and Smith, 1962).

Because of such correlation effects, it is necessary to verify that features in a PST (or similar) histogram that are suspected of having significance are not simply artifacts of the choice of bin width. Two techniques that may be helpful are (*a*) recomputing the histogram with a different bin width that is not a simple fraction of the original bin width and (*b*) calculating the autocorrelation of the PST histogram. Meaningful features should have a width of several bins. The existence of "wide" features in the PST histogram will be shown by large values near the origin of its autocorrelation function.

Another way of analyzing stimulus effects on a single spike train is to measure the elapsed times or "latencies" between stimulus presentations and the earliest encountered subsequent spikes. Latency and PST studies are discussed in the review paper by Moore et al. (1966).

THE PROBLEM OF NONSTATIONARITY

Basic Concepts

All the statistical measures discussed above, with and without stimulation, carry the implicit assumption that the data are stationary. Specifically, this means that in the absence of stimulation, the spike trains represent realizations of stationary point processes. In the presence of stimulation, it is assumed that the point processes are time dependent, but that the time variation is the same after each stimulus presentation, i.e., that each stimulus presentation represents a new, independent trial. Thus the stimulated cases are "stationary" in a larger sense.

It should be kept in mind that the phrases "stationary data" and "nonstationary data" are, strictly speaking, misnomers. The experimental data are samples, i.e., realizations over finite durations of stochastic point processes; only the (hypothetical) underlying point processes possess the properties of being stationary or nonstationary. In testing data for "stationarity," we are in fact testing whether the assumption of a stationary underlying process is a reasonable one for the body of data in question.

One of the difficulties commonly encountered in neurophysiological investigation is the fact that the behavior of a neuron under study may change significantly during the course of observation, and therefore cannot validly be assumed to arise from a stationary process. Such changes may be exhibited in a gross way, or may be subtle and difficult to detect. The problems of detecting nonstationarity and assessing its effects are vexatious. The very meaning of stationarity depends on the context of the experiment. If, for example, a neuron undergoes a diurnal cycle of activity, a sample of a few minutes' activity may well be accepted as "stationary," whereas a

sample of a few hours' activity may show marked trends, and hence be classified as nonstationary. In operational terms, therefore, it may be impossible to distinguish nonstationarity from inadequate sampling.

The most direct, straightforward, and recommended way of dealing with suspected nonstationarity is to segment the data, analyze each segment separately, and apply standard techniques for testing that the several samples were drawn from the same population. In practice, this is often impossible because of an insufficiently long sample.[5] A related technique, which is useful when data processing is accomplished "on line," is to observe the temporal order in which a histogram is built up. For a stationary process, the fractional mean rate of accumulation should be uniform for all portions of the histogram (over a time period that is long with respect to any known periodic variation); any conspicuous systematic departures from this uniformity strongly suggest nonstationarity in the data.

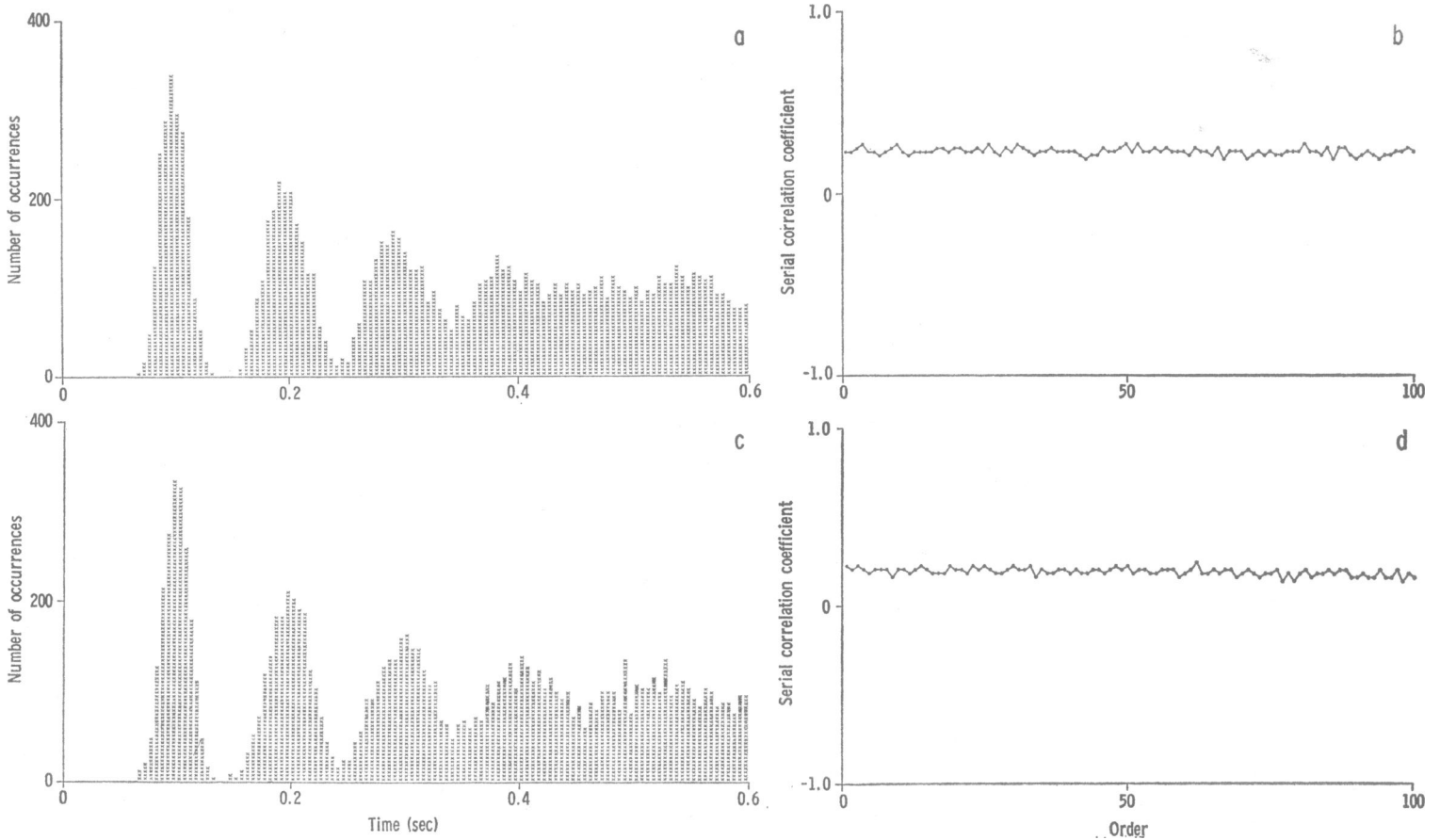
Although the strict definition of stationarity implies that all parameters of the stochastic process are invariant with respect to a random displacement in time, detection and measurement of nonstationarity in spike trains has centered almost exclusively upon one parameter, the firing rate. In the following discussion we restrict ourselves to nonstationarities in firing rates, after pointing out the utility of statistical techniques for investigating nonstationarities in, for example, the variance of intervals, such as Bartlett's test for homogeneity of variance (see Kendall and Stuart, 1961).

There are three principal aspects to the analysis of rate nonstationarities in spike data. The first is the detection of nonstationarity. "We may wish to test the reality of any apparent trends and this is done by testing the hypothesis of no trend" (Cox and Lewis, 1966, p. 37); to this end the reader is referred to a chapter by Cox and Lewis (1966, chapter 3) devoted to the analysis of trends. The second aspect deals with the characterization and measurement of the variations in rate when they have been found to occur. The third aspect refers to the assessment of the effects of rate variations on other statistical measures; we consider below the effects of rate variations on the autocorrelation and the serial correlogram.

Measurement of Rate Variations

In spike trains exhibiting rate variation together with a relatively high degree of variability in interspike intervals, special techniques are necessary to observe the rate variations themselves, unobscured by the "local" fluctuations in interval length. One

[5] Some classes of spike trains, which arise from certain random-walk models of neurons, correspond to renewal processes which do not have finite moments (Gerstein and Mandelbrot, 1964). A renewal process with an infinite mean would correspond to a nerve cell which has a finite probability of remaining silent indefinitely long after a spike. A nonpacemaker cell with wholly inhibitory synaptic input would remain permanently silent; some mixture of inhibitory and excitatory input could result in the cell's firing sporadically, with a long-tailed distribution of interspike intervals, which might not have a finite mean. Finite samples of such a process cannot adequately establish this possibility.


a
b
c
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Number of occurrences
Serial correlation coefficient
Time (sec)
Order
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200
0
1.0
-1.0
0.2
0.4
0.6
50
100

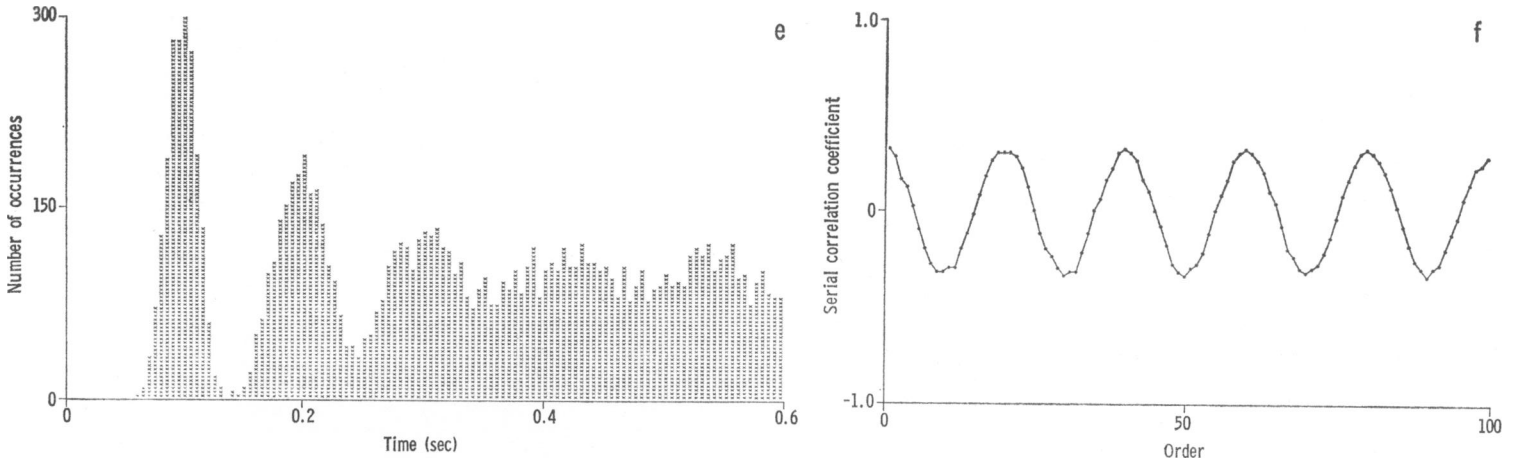
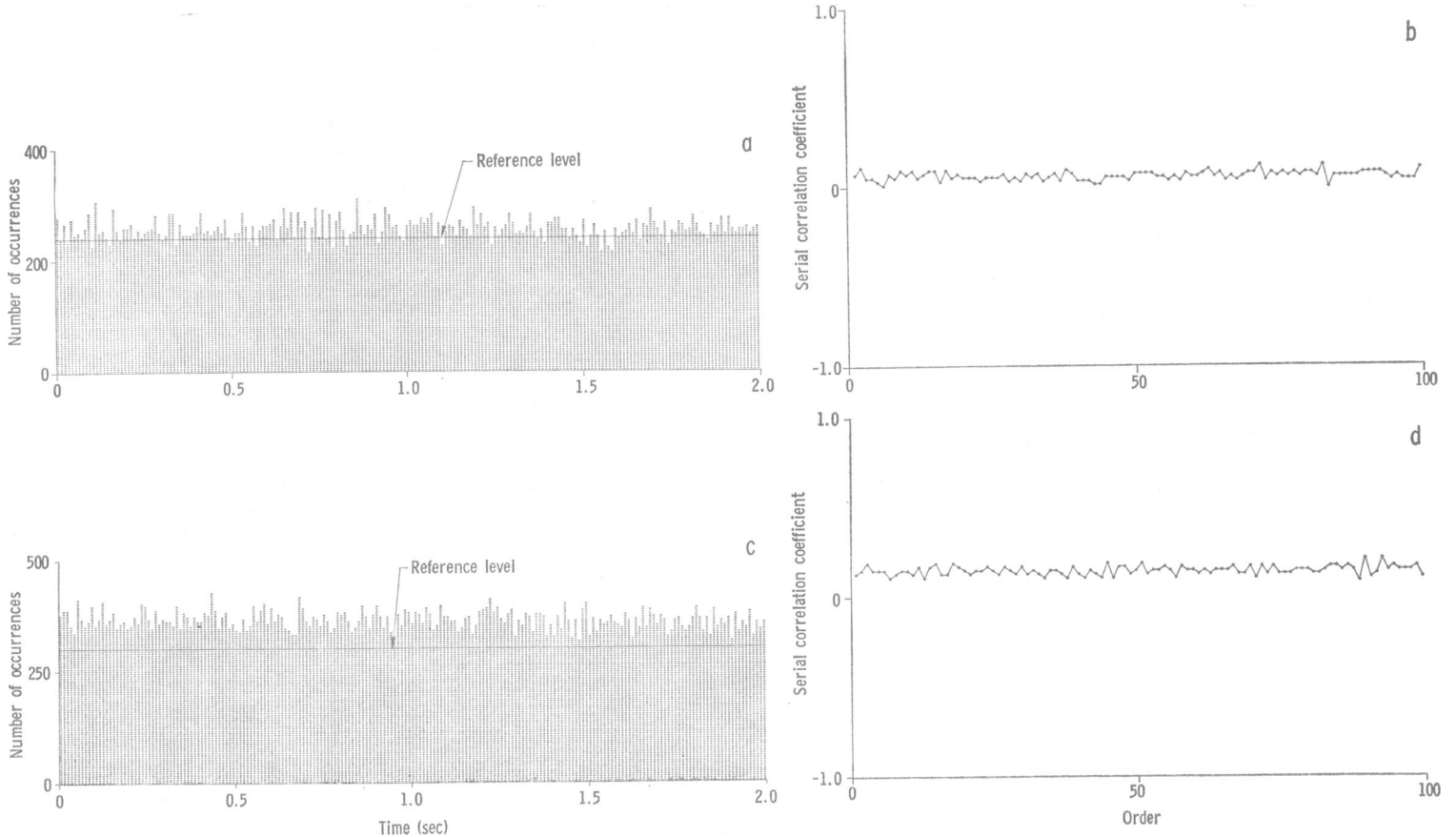


FIGURE 6 Effects of slow rate changes in a pacemaker neuron. On the left, autocorrelation histograms; on the right, serial correlograms of interspike intervals. Intervals are independently normally distributed with time-varying mean, over-all mean interval in sample of 100 msec, and constant standard deviation of 10 msec. All samples are 200 sec long, approximately 2000 spikes each. a–b: *accelerating pacemaker*. Mean interval decreases linearly from 110 msec to 90 msec during observation period. c–d: *decelerating pacemaker*. Mean interval increases linearly from 90 msec to 110 msec during observation period. e–f: *oscillating pacemaker*. Mean interval varies sinusoidally with time, from maximum of 110 msec to minimum of 90 msec, with a 2 sec period.


a
Reference level
Number of occurrences
400
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2.0
b
Serial correlation coefficient
1.0
0
-1.0
0
50
100
c
Reference level
Number of occurrences
500
250
0
0
0.5
1.0
1.5
2.0
Time (sec)
d
Serial correlation coefficient
1.0
0
-1.0
0
50
100
Order

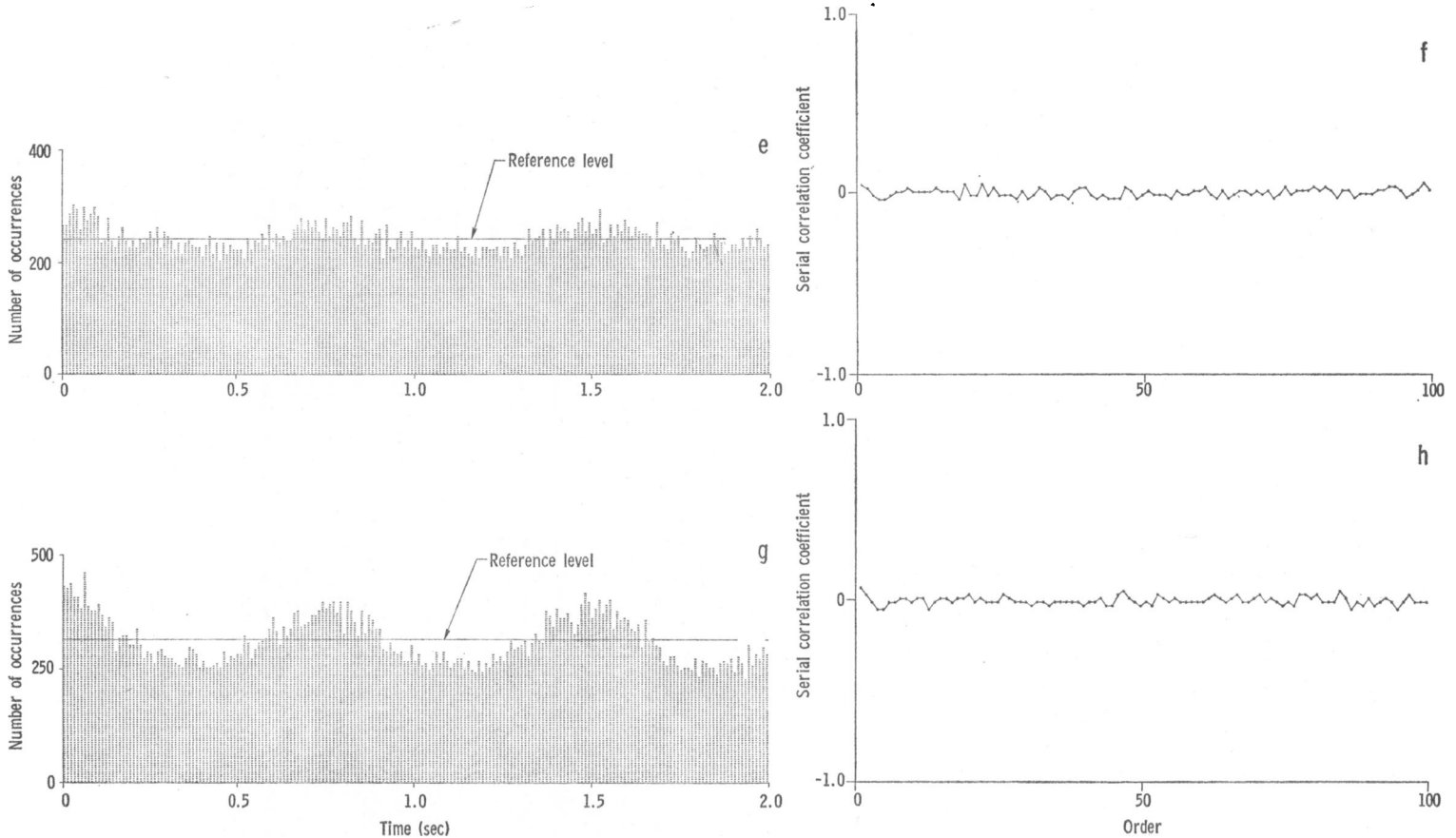

FIGURE 7 Effects of slow rate changes in a nonpacemaker neuron. On the left, autocorrelation histograms; on the right, serial correlograms of interspike intervals. Intervals are generated by a Poisson process with time-varying rate parameter; period of observation is 200 sec, with approximately 2000 spikes each sample. Reference level in autocorrelation is predicted asymptotic value (see text, Eq. 12). a–b: *deceleration*, ±*50%*. Mean interval increases linearly with time from 50 msec to 150 msec. c–d: *deceleration*, ±*70%*. Mean interval increases linearly with time from 30 msec to 170 msec. e–f: *oscillation*, ±*50%*. Mean interval varies sinusoidally from minimum of 50 msec to maximum of 150 msec, with period of 0.75 msec. g–h: *oscillation*, ±70%. Mean interval varies sinusoidally from minimum of 30 msec to maximum of 170 msec, 0.75 sec period.

common technique for examining rate variations in a spike train is to plot each interval length as a function of time (usually taken to be the time of the second spike determining the interval) or of serial number of the interval. If the cell fires fairly regularly, such a plot will clearly reveal the structure of rate variations. If, on the other hand, the interval variance is large, trends are hidden in the "noise."

Moving-average techniques have often been used for smoothing purposes. They are typically based on either a fixed number of intervals or a fixed length of time over which an average rate is computed. A more meaningful type of moving average would be one in which the contribution of each spike to the rate estimate is a decreasing exponential function of the time interval between the occurrence of the spike and the time referred to by the estimate. A "ratemeter" approach of this sort corresponds more closely to the response of an integrating neuron than do the more rigid moving-average techniques. The time constant for the exponential function can be chosen to correspond to the integration period of a neuron known or postulated to receive the output from the observed neuron (Segundo et al., 1966).

If trends are monotonic, estimation methods based on regression analysis are useful; these are described by Cox and Lewis (1966, chapter 3).

Effects of Trends

One important effect of rate changes on a spike train is to increase the variation of the interspike intervals. This effect will be conspicuous, and therefore detectable in the statistics, only if this additional variability of intervals is significantly large as compared with the "intrinsic" variability of the intervals. We illustrate this with two classes of examples: a "noisy pacemaker," with an intrinsic coefficient of variation of 10%, and a Poisson process (intrinsic coefficient of variation 100%), in each of which the mean interval is a function of time.

The pacemaker results are shown in Fig. 6, in which the autocorrelation and serial correlograms are shown for a linearly accelerating train, a linearly decelerating train, and a train with sinusoidally varying mean intervals. In each of these examples, the maximum deviation of mean interval, due to rate changes, was $\pm 10\%$ of the mean interval. The effects on the autocorrelation and on the interval histograms (not shown) are not conspicuous; there is some broadening of the peaks, but this effect is apparent only upon detailed comparison with the exactly corresponding null case of no trend. Given the autocorrelations as observed experimentally, there is no reason for suspecting a trend in the data. The serial correlograms, on the other hand, clearly indicate the rate variations. An elevated serial correlogram, extending more or less uniformly out to high orders, is a specific indicator of monotonic trend. It is to be noted that the effects of monotonic acceleration are indistinguishable from those of monotonic deceleration. The undamped oscillatory nature of the third serial correlogram shown is due to the imposed constancy of period of rate variation; if that period had varied during the observation, the oscillations in the serial

correlogram would have exhibited damping. An ingenious method is described by Firth (1966) for separating the effects of trend on the serial correlogram from its "inherent" features. His technique, involving successive differences, is in essence a form of analysis of variance and is applied to cells that fire at extremely regular intervals.

The time-varying Poisson process, on the other hand, requires a rate variation of $\pm 50\%$ before some effects are noticeable, and only at $\pm 70\%$ rate variation do the effects become conspicuous (Fig. 7). The only effect on the autocorrelation of a monotonic trend is to increase its level; the shape remains flat, as in the absence of trend. The predicted asymptotic level for the autocorrelation depends only on the mean observed interval (Equation 12); therefore, the observed autocorrelation histogram, together with this predicted level, can indicate a trend. For the monotonically time-varying Poisson processes illustrated (Fig. 7), this is the only conspicuous effect of the large rate variations, since the corresponding serial correlograms depart only slightly from 0. At these intensities of cyclic rate variation, oscillations are visible in the autocorrelation, but not in the serial correlogram; this is in contrast to the opposite situation observed in the case of a pacemaker with weak oscillations in rate. A monotonically declining autocorrelation histogram, such as the early portions of Figs. 7 c and 7 d, is strongly suggestive of rather severe rate changes in the data, and some detailed statistical features of the spike train may be masked or distorted thereby.

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