Analysis of Sequences of Events with Random Displacements Applied to Biological Systems

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ABSTRACT

A stationary and ergodic point process is considered, specified by the probability density function, expectation density function, and serial correlation coefficients of the intervals between the events. The same quantities are computed after the events have been subjected to random displacements. The model is applied to data on heartbeat irregularities indicated by the duration of R–R intervals on the electrocardiogram. From an analysis of the expectation density function of R–R intervals reported in the literature for one healthy subject and three patients with atrial fibrillation, an estimate is given of the degree of irregularity in the pacemaker period relative to the range of variations in conduction time through the heart tissue.

By means of an example concerning a thalamic neuron, it is shown how the theory may be used to investigate the relation between presynaptic and postsynaptic unitary nervous activity. Further applications relate to waiting-time problems in operations research where events are scheduled to take place according to a timetable but each event is influenced by factors that may retard or speed up its occurrence.

INTRODUCTION

Consider a regular series of stimuli each of which, after a delay, gives rise to a response of unitary nature. If the delay has a constant value, the sequence of responses will be regular, too. If the delay has a variable value, the intervals between successive responses will also be irregularly spaced in time. The larger the amount of variability in the delay, the more irregular the intervals will be. McGill [1] has listed some biological phenomena to which such a delay mechanism may apply, and he has

treated the case that variation in delay values obeys an exponential distribution with parameter λ. If the mean delay $1/\lambda$ is small relative to the period T of the stimuli, the response interval probability density function could be expressed approximately by $p(\tau) = (\lambda/2)\exp(-\lambda|\tau - T|)$. The starting-point of strictly regularly occurring stimuli seems to be an artificial one; it certainly is if these stimuli originate from a biological source. Stimuli distributed in time according to a more or less peaked function $\phi(\xi)$ seem more appropriate. Likewise, the variation in delay need not necessarily be restricted to an exponential distribution, but may be given by a function $\psi(\eta)$. In the following, the interval distribution of the responses is denoted by $p(\tau)$.

It is understood that it is the variation of the delay round its mean, and not the delay value itself, that determines the transformation of $\phi(\xi)$ into $p(\tau)$. Therefore, $\psi(\eta)$ is defined accordingly, leaving the mean value of the delay undecided. Finding $p(\tau)$ is, in general, difficult in view of the possibility that the response to a stimulus may occur later than the response to subsequent stimuli. Only if the total range in delay variation, governed by $\psi(\eta)$, and the total variation in the stimulus interval durations, determined by $\phi(\xi)$, are small in relation to the mean stimulus interval, can an exact solution be obtained rather easily. This situation explains the above-mentioned expression for $p(\tau)$, which, when $\phi(\xi) = \delta(\xi - T)$ and $\psi(\eta) = \lambda \exp(-\lambda\eta)$ for $\eta > 0$, is valid only if $1/\lambda \ll T$; $\delta(\xi)$ denotes the Dirac delta function. In the examples to be treated, the standard deviations of both functions $\phi(\xi)$ and $\psi(\eta)$ are small in comparison with the mean of $\phi(\xi)$; then the question of overlap in the explained sense is of no importance.

As has recently been emphasized (for instance, in an extensive review on the statistical analysis of neuronal spike data by Moore *et al.* [2]), the interval distribution of events only partly describes the properties of a time series, because an important feature, namely, an eventual sequential ordering of the intervals, is not taken into account. In other words, verifying theory and experiment solely by means of $p(\tau)$ leads to ambiguous interpretations. On the other hand, if this aspect is included in the analysis, the presence or absence of randomness or recurrency often constitutes a crucial test of the validity of a model; in addition, it provides extra information concerning fluctuations in the stimulus pattern and delay mechanism. To illustrate this point, we return to the example of the first paragraph. One can imagine that a response interval distribution of the form $p(\tau) = (\lambda/2)\exp(-\lambda|\tau - T|)$ might equally well be obtained

in quite a different way, namely, by means of stimuli that are distributed according to $\phi(\xi) = (\lambda/2)\exp(-\lambda|\xi - T|)$ and with a constant delay, characterized by $\psi(\eta) = \delta(\eta)$. Other combinations of $\phi(\xi)$ and $\psi(\eta)$ are also conceivable, all of which result in the mentioned output interval probability density function.

For $\phi(\xi) = \delta(\xi - T)$ the response time series possesses a first-order serial correlation coefficient equal to $r_1 = -0.5$, as noticed by McGill [1]. This property should therefore be present in the data that have been treated by McGill and in those suggested as treatable. But, conversely, if $\psi(\eta) = \delta(\eta)$, an eventually present correlation between response intervals is entirely due to correlation in the stimulus series, and may, consequently, have any value between -1 and $+1$. Thus, correlation analysis may lead to a choice between several alternatives and will therefore be dealt with rather extensively in the next section.

Another measure of nonrecurrency is the expectation density function $e(\tau)$. It is used herein especially because this quantity has been measured in the experiments we want to (re)analyze: intervals between heartbeats and between nerve cell action potentials.

Definition: $e(\tau)\,d\tau$ is the probability that an event occurs in $(\tau, \tau + d\tau)$, if an event has occurred at $\tau = 0$. Upon specifying the serial number of the event in relation to the event at $\tau = 0$, this probability can be resolved into corresponding components. The first term of $e(\tau)$ equals the interval probability density function $p(\tau)$. If the series of events is recurrent, the subsequent terms depend only on $p(\tau)$ and can be computed therefrom by successive convolution. If not, the other terms depend on $p(\tau)$ as well as on the nature and degree of interdependence between the interval durations.

Cox and Lewis [3] have derived an expression for $e(\tau)$ for the delay process at issue, if the sequence of delays is a recurrent process. They did not comment on the interval distribution. We will derive $e(\tau)$ of the response process for the general case of two nonrecurrent ϕ and ψ processes.

The properties of time series in which the events are subjected to random displacements would seem to be of wider interest, stretching beyond the field of theoretical biology. Beutler and Leneman [4] have provided the following application. In engineering it is often necessary to deal with periodic signals whose timing is perturbed by random phenomena. In particular, communication systems often sample a random signal at supposedly equal intervals, only to incur errors due to the perturbations that are called time jitter.

Cox and Lewis [3] have mentioned a practical situation, referring to queuing and inventory systems, where arrival processes occur in which events are scheduled at regular intervals but for various reasons are displaced from these scheduled times. Govier and Lewis [5] have compared the delay model with the arrivals of oil tankers at an oil terminal. The tankers are scheduled to arrive at regular intervals to ensure a proper stock of oil, but each tanker is independently influenced by many factors that may retard or speed up its progress.

DEFINITIONS AND FORMULAS

Let the ϕ process be a stationary and ergodic sequence of events given by the joint probability density function of k successive intervals $\phi_k(\xi_1, \xi_2, \ldots, \xi_k)$ where k runs from 1 to infinity. Let the ψ process be a stationary and ergodic sequence of delays given by the joint probability density function of k successive delays $\psi_k(\eta_1, \eta_2, \ldots, \eta_k)$ where k runs from 1 to infinity. Thus, $\phi_1(\xi)$ and $\psi_1(\eta)$ denote $\phi(\xi)$ and $\psi(\eta)$, respectively, the probability density function of the intervals between successive events of the ϕ process and the ψ process. The probability density function of the intervals between successive events of the response or the p process is denoted by $p(\tau)$. The ϕ and ψ processes are independent of each other.

The corresponding variances are designated σ_ϕ^2, σ_ψ^2, and σ^2. For order-preserving delay, assumed in the following, and because of the independence of the ϕ and ψ processes, it follows that

$$p(\tau) = \int_0^\infty \phi(\xi) \cdot g_1(\tau - \xi)\, d\xi$$

where $g_1(\eta)$ denotes the probability density function of the difference between two successive delays or, in symbols,

$$g_1(\eta) = \int_{-\infty}^{\infty} \psi_2(\eta_0, \eta + \eta_0)\, d\eta_0.$$

$p(\tau)$ is symmetric if $\phi(\xi)$ and $g_1(\eta)$ are both symmetric. Therefore, $\phi(\xi)$ or $g_1(\eta)$ is asymmetric if $p(\tau)$ is asymmetric. In case of a symmetric $\psi_2(\eta_1, \eta_2)$, $g_1(\eta)$ is symmetric, so that an asymmetric $p(\tau)$ implies asymmetric $\phi(\xi)$. Since a symmetric $\psi_2(\eta_1, \eta_2)$ may yield a symmetric as well as an

asymmetric $\psi(\eta)$, but always a symmetric $g_1(\eta)$, an asymmetric $\psi(\eta)$ is not reflected in the shape of $p(\tau)$.

To derive an expression for $e(\tau)$ we use the functions $g_k(\eta)$ and $\phi_k(\xi)$. Let $g_k(\eta)$ denote the probability density function of the difference between the delay of the kth ϕ event and the delay of the response at $\tau = 0$. Let $\phi_k(\xi)$ denote the probability density function of the kth ϕ event after, or before, the ϕ event corresponding to the response at $\tau = 0$ that occurs at $\xi = 0$. The signs of k and ξ indicate the position after, or before, a zero ϕ event. Then, the kth contribution to $e(\tau)$ is given by

$$\int_{-\infty}^{\infty} \phi_k(\xi) g_k(\tau - \xi)\, d\xi,$$

where for $k \geqslant 2$

$$\phi_k(\xi) = \int_0^{\infty} \cdots \int_0^{\infty} \phi_k\left(\xi_1, \xi_2, \ldots, \xi_{k-1}, \xi - \sum_{i=1}^{k-1} \xi_i\right) d\xi_1\, d\xi_2 \cdots d\xi_{k-1},$$

$$g_k(\eta) = \int_{-\infty}^{\infty} \cdots \int_{-\infty}^{\infty} \psi_{k+1}(\eta_0, \eta_1, \ldots, \eta_{k-1}, \eta + \eta_0)\, d\eta_0 \cdots d\eta_{k-1},$$

and for $k \leqslant -1$

$$\phi_k(\xi) = \phi_{-k}(-\xi) \quad \text{and} \quad g_k(\eta) = g_{-k}(\eta).$$

$e(\tau)$ is found by summing the expression over k from $-\infty$ to $+\infty$, except $k = 0$. In symbols

$$e(\tau) = \sum_{-\infty}^{\infty} \int_{-\infty}^{\infty} \phi_k(\xi) g_k(\tau - \xi)\, d\xi.$$

Note that for the computation of $e(\tau)$ it is, as an exception, not necessary to make the condition of order-preserving delay.

For recurrent ψ when

$$g_k(\eta) = g_1(\eta) = \int_{-\infty}^{\infty} \psi(\eta_0) \cdot \psi(\eta + \eta_0)\, d\eta_0$$

we arrive at an expression given by Cox and Lewis [3]:

$$e(\tau) = \int_{-\infty}^{\infty} e_\phi(\xi) \cdot g_1(\tau - \xi)\, d\xi$$

where $e_\phi(\xi)$ denotes the expectation density function of the ϕ process.

For the kth-order serial correlation coefficient of the p process r_k, we find (see the Appendix):

$$(\sigma_\phi^2 + 2\sigma_\psi^2 - 2\sigma_\psi^2 \cdot r_1^\psi) r_k = \sigma_\phi^2 r_k^\phi - \sigma_\psi^2 (r_{k-1}^\psi - 2r_k^\psi + r_{k+1}^\psi)$$

where r_k^ϕ and r_k^ψ denote the corresponding quantities of the ϕ and ψ processes with $r_0^\psi = 1$.

If the ϕ and ψ processes are both recurrent, we have $r_1 = -0.5 + 0.5\sigma_\phi^2(\sigma_\phi^2 + 2\sigma_\psi^2)^{-1}$. The higher-order coefficients are zero.

As an exercise we give the results for the ϕ and ψ processes when both are Gaussian Markov processes with parameters m_ϕ; σ_ϕ, ρ_ϕ; and σ_ψ, ρ_ψ, respectively; m_ϕ denotes the mean interval duration of the ϕ process. After elaboration one finds for $p(\tau)$ a Gaussian distribution with mean m_ϕ and variance $\sigma_\phi^2 + 2\sigma_\psi^2(1 - \rho_\psi)$.

$e(\tau)$ is equal to the sum of Gaussian functions with means $k \cdot m_\phi$ and variances

$$\sigma_\phi^2\{|k| + 2\rho_\phi(\rho_\phi^{|k|} - |k|\rho_\phi + |k| - 1)(1 - \rho_\phi)^{-2}\} + 2\sigma_\psi^2(1 - \rho_\psi^{|k|}).$$

The serial correlation coefficient r_k amounts to

$$r_k(\sigma_\phi^2 + 2\sigma_\psi^2 - 2\sigma_\psi^2\rho_\psi) = \sigma_\phi^2\rho_\phi^k - \sigma_\psi^2(\rho_\psi^{k-1} - 2\rho_\psi^k + \rho_\psi^{k+1}).$$

SUPERPOSITION OF DELAYS

Two delays ψ' and ψ'' operating in cascade and independently of each other can be dealt with by means of the foregoing formulas by treating them as one delay ψ with properties that can be deduced from the component delay processes. If ψ' and ψ'' represent recurrent processes, $p(\tau)$ and $e(\tau)$ can be derived from

$$g_1(\eta) = \int_{-\infty}^{\infty} g_1'(\eta - \bar{\eta}) g_1''(\bar{\eta})\, d\bar{\eta}.$$

The expressions for the serial correlation coefficients also remain valid if allowance is made for the variance of the resulting delay, which is equal to the sum of the variances of the two contributing delays. If ψ' and ψ'' are nonrecurrent, we have, for the computation of $p(\tau)$, to deal with

$$\psi_2(\eta_1, \eta_2) = \int_{-\infty}^{\infty}\int \psi_2'(\bar{\eta}_1, \bar{\eta}_2) \cdot \psi_2''(\eta_1 - \bar{\eta}_1, \eta_2 - \bar{\eta}_2)\, d\bar{\eta}_1\, d\bar{\eta}_2.$$

For instance, if both delays are Gaussian Markov processes, the equivalent process is Gaussian with a variance σ_ψ^2 equal to the sum of the two variances; r_k^ψ is such that $\sigma_\psi^2 r_k^\psi$ equals the sum of the corresponding quantities of the delays.

In general, the joint probability density function of the cascaded delay $\psi_k(\eta_1, \eta_2, \ldots, \eta_k)$ can be computed by convolution, in the same way as was just done for $\psi_2(\eta_1, \eta_2)$.

An alternative approach is to take the ϕ and ψ' processes together as a new (nonrecurrent) stimulation process delayed by a one-stage delay ψ''. One may check that the solution for the p process is the same. The number of delays can be extended to more than two.

ESTIMATION OF σ_ϕ/σ_ψ FOR A SIMPLE CASE

If $\phi(\xi)$ and $\psi(\eta)$ are both Gaussian, with standard deviations σ_ϕ and σ_ψ, $p(\tau)$ is also Gaussian, with standard deviation $\sigma = (\sigma_\phi^2 + 2\sigma_\psi^2)^{0.5}$, in case of a recurrent ψ process. If the condition of a recurrent ψ process is dropped, $p(\tau)$ need not be Gaussian.* Conversely, if $p(\tau)$ is Gaussian, $\phi(\xi)$ and $\psi(\eta)$ are also likely to be Gaussian (although they need not be).** A Gaussian distribution of output intervals $p(\tau)$ can be effected by a recurrent Gaussian ϕ and ψ process in a variety of combinations of values of σ_ϕ and σ_ψ, as follows from the expression for σ.

The ambiguity strengthens the remarks made in the Introduction, namely, that from inspection of an interval distribution, especially if

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* Counterexample: Let $\psi_2(\eta_1, \eta_2)$ be symmetric Gaussian for $\eta_1 > 0$, $\eta_2 < 0$ and $\eta_1 < 0$, $\eta_2 > 0$, and zero otherwise; then $\psi(\eta)$ is Gaussian, but $g_1(\eta)$ is not.

** Counterexample: Let $\psi_2(\eta_1, \eta_2)$ be symmetric Gaussian for $\eta_1 + \eta_2$ greater than an arbitrary constant, and zero otherwise; then $\psi(\eta)$ is non-Gaussian, but $g_1(\eta)$ is Gaussian.

it is the rather often encountered Gaussian function, not much can be said about the degree of irregularity in the stimulus presentation relative to the amount of variation in conduction or delay time. In contrast, matching $e(\tau)$ gives a better indication as to whether the proposed kind of delay mechanism is present and, if so, which is the value of σ_ϕ/σ_ψ.

If the ϕ process (with mean m_ϕ) and the ψ process are recurrent Gaussian, $e(\tau)$ equals the sum of Gaussian functions with means $m_k = k \cdot m_\phi$ and variances $\sigma_k^2 = |k|\sigma_\phi^2 + 2\sigma_\psi^2$. If $\sigma_\psi = 0$ or $\sigma = \sigma_\phi$, the p process is recurrent. The maxima of $e(\tau)$ decrease with their order k, as $\sqrt{k}$ and $e(\tau)$ will ultimately become flat. If $\sigma_\phi = 0$ or $\sigma = \sigma_\psi\sqrt{2}$, the functions contributing to $e(\tau)$ will all have the same spread, and $e(\tau)$ will remain absolutely periodic.

HEARTBEAT INTERVAL PATTERNS

A rhythm-generating source that seems very suitable to be treated by the model is presented by the more or less regularly beating heart. The impulse originating in the sinoatrial node in the right atrium during each cycle we identify, in our terminology, with the stimulus. The delay consists of the time it takes for the impulse to be conducted from the two atria, via the atrioventricular node, through the Purkinje fibers to the ventricular musculature. The response, the contracting ventricular heart tissue, manifests itself by the QRS complex in the electrocardiogram (EKG), and is usually measured by means of the R wave. The distribution of R–R intervals is set equal to $p(\tau)$.

The example is convenient because the distribution of R–R intervals often obeys a Gaussian or a Gaussian-like law [6–8] so that the relatively simple expressions for $p(\tau)$ and $e(\tau)$ apply. Consequently, both the pacemaker period variability and the conduction time variability are considered to be Gaussian distributed with standard deviations σ_ϕ and σ_ψ, respectively. Moreover, the fluctuation in constancy is, under normal conditions, small in relation to the mean interval duration, and the trouble of crossover, which is rather critical for the applicability of the formulas for some of the expressions derived, does not arise.

For a thorough analysis of experimental records, it has been emphasized that, in addition to $p(\tau)$, a quantity like $e(\tau)$ must also be incorporated. As far as heart signals are concerned, to our knowledge only Braunstein and Franke [9] have published data on $e(\tau)$ (or, more precisely, on the autocorrelation function, which equals $e(\tau)$ except for a factor). We will

use their results, which concern data from one normal subject and from three patients with atrial fibrillation. These authors did not give the interval distribution, but thanks to the property that the first component

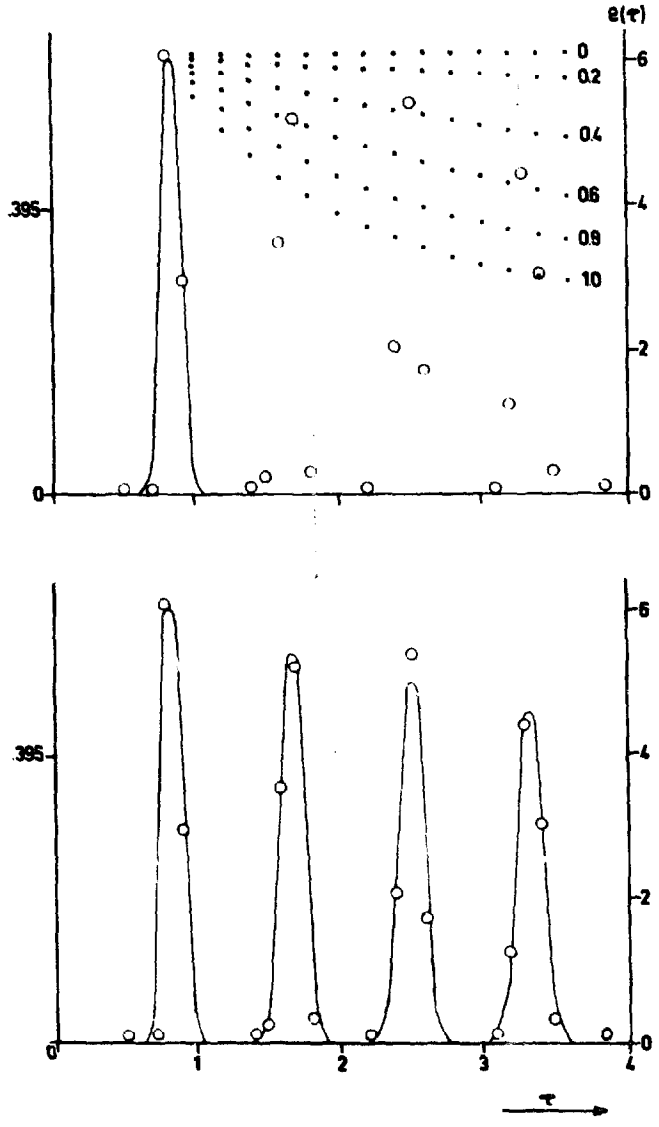

FIG. 1. Expectation density function $e(\tau)$ of R–R intervals of healthy person (circles), adapted from Braunstein and Franke [9]. Top: Curve represents a Gaussian function, presumed to fit the R–R interval distribution. Theoretically expected maxima of $e(\tau)$ are, at multiples of 0.83 sec, on one of the dotted curves computed for different values of σ_ϕ/σ, indicated by numbers. Bottom: Curve for model with $\sigma_\phi/\sigma = 0.5$. Abscissas in sec; left-hand ordinate in arbitrary units, right-hand ordinate in sec^{-1}.

of $e(\tau)$ is equal to $p(\tau)$, the latter function can be deduced from the former in the case of a fairly regular pattern. In this way, for three of the four

cases reported, $p(\tau)$ could be estimated with sufficient accuracy; it was found to be consistent with a Gaussian distribution. We have further assumed that the ϕ and ψ processes are recurrent, first, because it is the simplest possible supposition, since no extra parameters are involved; and second, because we have no data at our disposal that give quantitative information about the nature and degree of an eventual nonrecurrency. The cases $\sigma_\phi = 0$ and $\sigma_\psi = 0$ represent two extremes that in actual practice do not occur, since neither a strictly regular stimulation nor an absolutely constant conduction time will be present.

In Fig. 1 (top), $e(\tau)$ for the healthy person is given by circles, adapted from [9]. The left-hand side of the ordinate is copied from Braunstein and Franke [9], according to whom it is expressed in arbitrary units. From their computational procedure we were able to reconstruct a quantitative measure per second, given in the right-hand ordinate in Fig. 1. The first cluster of points, from 0.5 to 0.9 sec and well separated from those at higher values of τ, would seem to fit a Gaussian $p(\tau)$ (curve) with $m = 0.830$ sec and $\sigma = 0.066$ sec, although the resolution time of 0.1 sec is too small to permit us to be sure on this point. If the model holds, the local maxima of $e(\tau)$ for $\tau = m$, $2m$, $3m$, and $4m$ should be on one of the family of dotted curves computed for different values of σ_ϕ/σ. The course of the curves depends on the numerical value of σ_ϕ and σ_ψ, chosen such that $\sigma = 0.066$ sec. A value of σ_ϕ/σ between 0.4 and 0.6 seems to be appropriate, corresponding with $0.026 \text{ sec} < \sigma_\phi < 0.040$ sec and $0.043 \text{ sec} > \sigma_\psi > 0.037$ sec. A reasonably good agreement between theory and experiments is obtained for $\sigma_\phi/\sigma = 0.5$ as can be seen from Fig. 1 (bottom). It would follow that $\sigma_\phi = 0.033$ sec and $\sigma_\psi = 0.040$ sec. In addition, we predict $r_1 = -0.375$.

Figure 2 represents $e(\tau)$ of one of the patients; it is adapted from Fig. 2 of Braunstein and Franke [9]. Although the first component of $e(\tau)$ is not completely separated from the subsequent contributions, a Gaussian $p(\tau)$ with $m = 0.706$ sec and $\sigma = 0.095$ sec seems to satisfy the conditions. In comparison with the previous case, m has changed slightly, but in the present context it is of more interest to note a considerably larger value for σ found in this way. If we suppose that the increase is due, entirely or mainly, to an increase of σ_ψ (that is, of irregularity in conduction time), then the negative correlation would have been enhanced. On the other hand, if the increase of σ is brought about chiefly by an increase in irregularity of the nervous steering process σ_ϕ, the R–R interval series would be more recurrent. Judging the mode of decrease of the max-

ima of $e(\tau)$, which proves to be consistent with the supposition $0.8 < \sigma_\phi/\sigma < 1$, we must conclude that the latter possibility has occurred. More precisely, given $\sigma = 0.095$ sec, we have $0.076 \text{ sec} < \sigma_\phi < 0.095$ sec and $0.040 \text{ sec} > \sigma_\psi > 0$ sec. The curve in Fig. 2 is from the theory and holds for $\sigma_\phi/\sigma = 1$.

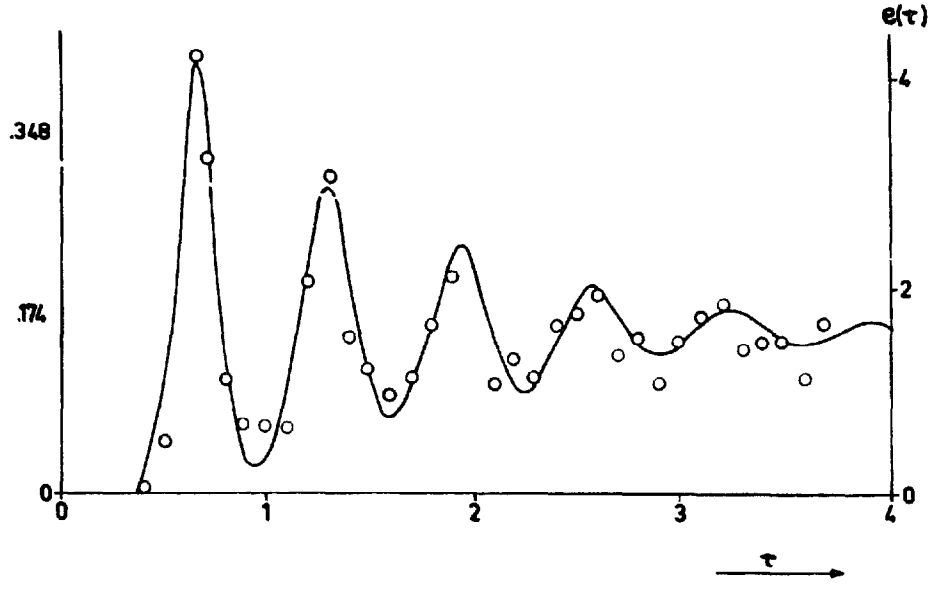

FIG. 2. Expectation density function $e(\tau)$ of R–R intervals of patient with atrial fibrillation (circles), adapted from Braunstein and Franke [9]. Curve for theory with $\sigma_\phi/\sigma = 1$. Coordinates as in Fig. 1.

For another patient, we have also used a Gaussian function for $p(\tau)$ with $m = 0.652$ sec and $\sigma = 0.125$ sec, and found good agreement between experimental and theoretical $e(\tau)$ if $0.9 < \sigma_\phi/\sigma < 1$. This implies that $0.113 \text{ sec} < \sigma_\phi < 0.125$ sec and $0.039 \text{ sec} > \sigma_\psi > 0$.

NEURONAL SPIKE TRAINS

The model under discussion can be considered as an input-output system and may be used to study the relation between presynaptic and postsynaptic unitary nervous activity. Analogous to the preceding example, it can be stated that the very common irregularity of central nerve cell discharge is caused in part by an irregular primary input and in part by fluctuations in the duration of synaptic delays. If both sorts of variation are of a recurrent nature, as we will assume, a distinct feature

is that the first-order serial correlation coefficient has a value between 0 and -0.5, the actual value depending on the ratio of the two contributing sources of irregularity. In fact, a search through the literature reveals that negative correlation occurs rather frequently in neuronal spike trains. In the Discussion at the end of this article we will touch on these

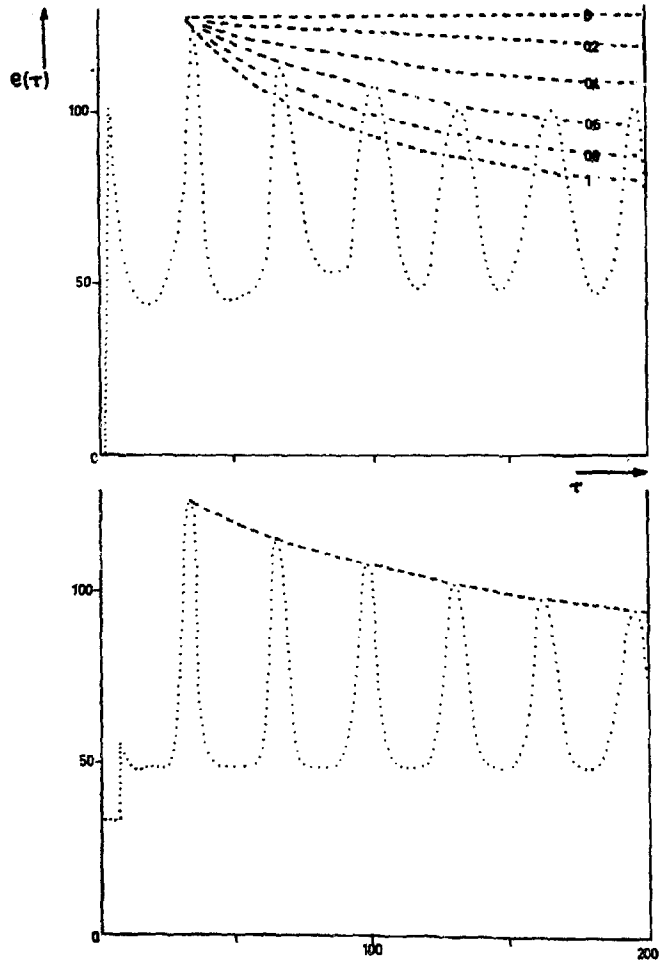

FIG. 3. Expectation density function $e(\tau)$. Top: Dotted curve (from smoothed data) for thalamic neuron, adapted from Poggio and Viernstein (1964). Theoretically expected maxima of $e(\tau)$ are, at multiples of 32.5 msec, on one of the dashed curves computed for different values of σ_ϕ/σ, indicated by numbers. Bottom: Curve for theory with $\sigma_\phi/\sigma = 0.6$. Abscissas in msec; ordinates in sec^{-1}.

findings again. For a recent survey on this subject, see Moore *et al.* [2]. In the subsequent paragraphs we will infer the presence of negative correlation by detailed inspection of the expectation density function of a thalamic nerve cell.

Figure 3 (top) represents $e(\tau)$ of the discharges of a thalamic neuron during sensory stimulation, redrawn from the smoothed data published by Poggio and Viernstein [10] as their Fig. 12. The interval distribution of this cell and of several other specimens of the same population were characterized, among other things, by an excess of counts in the short-interval region as well as by one or more peaks at a longer interval. Elsewhere [11] we have shown that these types of distributions can be described fairly accurately by supposing that a more or less regular train of impulses (e.g., with intervals that are Gaussian distributed) is intermingled with irregularly occurring impulses with intervals that are distributed exponentially or in an exponential-like manner.

It was found [12] that in this case a reasonably good agreement between theoretical and experimental interval distributions was obtained, if the two pooled impulse series consisted of a Gaussian-distributed series with a mean interval $m_\phi = 32.5$ msec and a standard deviation $\sigma = 2.5$ msec, and a series with intervals distributed according to an exponential function with time constant $1/\nu' = 25$ msec and a dead time $\delta = 6$ msec. The mean interval $1/\nu$ of the latter series equals $1/\nu' + \delta$.

The expectation density function $e(\tau)$ of two superimposed time series of events with corresponding functions $e_1(\tau)$ and $e_2(\tau)$ can, in general, be computed from [13]:

$$e(\tau) = \frac{2}{(m_1 + m_2)} + m_2 \cdot \frac{e_1(\tau)}{(m_1 + m_2)} + m_1 \cdot \frac{e_2(\tau)}{(m_1 + m_2)},$$

where m_1 and m_2 denote the mean interval duration. The subscripts 1 and 2 relate to the exponential and Gaussian distributions, respectively.

If a series of impulses with this $e(\tau)$, to be identified with the ϕ process, is subjected to a delay, given by the ψ process, we obtain a series of impulses, the ϕ process, that has an $e(\tau)$ containing similar components. The first term proves to be unaffected by the delay mechanism and amounts, in the considered case, to $2\nu/(1 + \nu m_\phi)$. The second term is hardly altered, at least for delay variation of a magnitude that will be arrived at in the following paragraphs. It is about 0 for $0 < \tau < \delta$ and for larger τ converges quickly to $m(\nu)^2/(1 + \nu m_\phi)$. The third term is equal to a sum of Gaussian distributions, for ψ Gaussian and recurrent, weighted by a factor of $(1 + \nu m_\phi)^{-1}$ and with means that are multiples of m_ϕ. The variances will be calculated later.

The sum of the first two terms amounts to an approximately constant value $(31.5 + 16.5)$ sec$^{-1} = 48$ sec^{-1}. The third term has its first maximum

at $\tau = 32.5$ msec equal to $(1 + \nu m_\phi)^{-1}$. $(\sigma\sqrt{2\pi})^{-1} = 78$ sec^{-1}. Therefore, the first maximum of $e(\tau)$ equals 126 sec^{-1}. The values of the subsequent maxima depend on the degree of nonrecurrency of the delayed Gaussian series, which factor, in turn, is determined by the ratio σ_ϕ/σ_ψ.

In analogy with latency distributions of nerve fibers, the range of variation in synaptic delay will be assumed Gaussian with standard deviation σ_ψ. As the total variation has been taken to be Gaussian with standard deviation σ, the variation in presynaptic impulse interval duration is also Gaussian, with standard deviation σ_ϕ such that $\sigma^2 = \sigma_\phi^2 + 2\sigma_\psi^2$.

In Fig. 3 (top) the dashed curves relate to points of expected maxima for different values of σ_ϕ/σ, all starting at the same point, with coordinates 32.5 msec and 126 sec^{-1}. In comparison with the experimental data, a value of $\sigma_\phi/\sigma = 0.6$ seems appropriate. The corresponding theoretical $e(\tau)$ for the said parameter values is pictured at the bottom in Fig. 3 and gives a good overall fit to the dotted curve at the top in this figure.

The delay process we have taken to occur after pooling the two cooperating impulse series. It is recognized that the total delay caused by a nerve cell is determined by the synaptic delay (the finite time needed for the transmitter substance to cross the synaptic cleft); by a delay due to decremental conduction in the dendritic branches; and by the time needed to invade the cell body up to the axon-hillock. Consequently, the delay may be thought of as being split up into corresponding components, some of which may occur before the two impulse series are mixed. Formally, this extension is equivalent to the procedure followed, as long as the delays are independent of each other. The negative correlation present in the two contributing series after delay can, after pooling, change into a positive correlation; this change depends on the values of the various parameters. Poggio and Viernstein [10] also found both signs for the correlation in their material.

DISCUSSION

A stimulus response system with delay governed by probabilistic laws has been described and applied to data on neuronal spike statistics and to heartbeat interval irregularities.

An interesting side issue of the mechanism considered is that even if the stimulus interval durations are independent of each other as well

as of the delay times, the response interval durations do possess interdependency. This property provides, in addition to the distribution of interresponse times, a useful criterion for testing the adequacy of the present model and of other models that are believed to simulate probabilistic properties of time series of biological signals of binary nature. The two classes of examples treated in detail were, in part, also of a nonrecurrent nature, as revealed by an analysis of the expectation density function. Taking this into consideration, it turns out that in both cases neither the stimulus interval nor the delay, or conduction time, was absolutely constant in duration. Moreover, an estimate of the degree of inconstancy could be inferred. The analysis was facilitated by the assumption that the ϕ and ψ processes were recurrent. As to the computation of $p(\tau)$ and r_k, an additional favorable circumstance was that the fluctuations in stimulus intervals and delay times were small relative to the mean stimulus interval. A third point that made the evaluation of the formulas rather easy, without detracting from their essential features, was that the ϕ and ψ processes could be assumed to be Gaussian.

To fit $e(\tau)$ of a thalamic neuron, reported by Poggio and Viernstein [10], we have supposed, in accordance with earlier studies, that a Gaussian series of impulses has been superimposed on a Poisson series with dead time. If each impulse is delayed according to a Gaussian distribution, it follows that the standard deviation of the synaptic delay is equal to 1.45 msec. This value seems to be of the right order, judging from information on monosynaptic latency variations, although these measurements, in most instances, incorporate variations due to peripheral nerve fiber conduction time.

A quantity less cumbersome to compare than the expectation density function, and equally critical, is given by the serial correlation coefficient. Within the scope of the simplified assumptions adopted so far, it is predicted that the value of r_1 ranges from 0 to -0.5, whereas the higher-order coefficients are 0. In this respect several reports that incorporate values of the serial correlation coefficients are of interest. Kuffler *et al.* [14] have studied the durations of successive intervals of maintained discharge of ganglion cells in the cat's retina. In the five cells listed all r_1 values were negative between the extremes of -0.10 and -0.24, and these values were found to be significantly different from 0. The mean values of r_2 and r_3, however, were not significantly different from 0. Both conclusions are in harmony with the properties of the model. The experiments were repeated recently by Gestri *et al.* [15], who used the same

preparation. The previous results were confirmed. For the twenty units investigated, r_1 ranged from 0 to -0.3.

A study on the discharge of human motor units by Hagiwara [16] cited by Kuffler *et al.* [14] points in the same direction. The values of r_1 were found to be about -0.5, the maximum possible value permitted by the theory, while the higher-order correlation coefficients were nearly 0. We should add that, in the frog muscle spindle afferent discharge, Hagiwara [17] found no significant serial correlation.

Goldberg *et al.* [18] studied the response of neurons of the superior olivary complex when stimulated by acoustic stimuli of long duration. Those units that exhibited extremely irregular discharge patterns were characterized by the fact that the values of the interspike intervals occurring during sustained discharge were linearly independent. In other neurons there was a small but statistically significant degree of negative correlation between the values of the intervals occurring next to each other in a record. As the variation in synaptic delay time, characterized by σ_ψ, probably does not differ greatly from neuron to neuron and for different stimulation intensities, the regularity or irregularity in discharge should be attributed primarily to differences in afferent input variability, denoted by σ_ϕ. From the expressions $r_1 = -\sigma_\psi^2/\sigma^2$ and $\sigma^2 = \sigma_\phi^2 + 2\sigma_\psi^2$, it follows that for a given value of σ_ψ, r_1 is the more negative the smaller σ_ϕ or the more regular the input. Conversely, r_1 approaches 0, the larger σ_ϕ or the more irregular the afferent inflow, as found for the very irregularly discharging cells. Moreover, insertion for σ_ψ of a value of about 1 msec gives, for the range of standard deviations σ of the interval distribution, values for r_1 that are of the same order of magnitude as the values listed by Goldberg *et al.* [18].

A similar interpretation applies to the data on sustained response of neurons of the dorsal and posteroventral cochlear nuclei to acoustic stimuli of long duration that were published by Goldberg and Greenwood [19]. For one half of the neurons r_1 did not differ significantly from 0. For the other half, r_1 was approximately equal to -0.3 at high rates of the discharge and diminished as the discharge rate fell. Because the inverse of the discharge rate, the mean interval duration, was monotonically related to the spread σ of the interval distributions, this means that r_1 diminished for larger σ. If again the synaptic delay characteristics do not change much under different physiological conditions, the decrease of r_1 with larger overall spread of the distributions is also quantitatively compatible with the theory.

A differently nuanced application of the model was concerned with the pacemaker aspects of the human heart action. A time series analysis of heartbeat interval sequences starts conveniently from the EKG, in particular from the moments of occurrence of the R waves; R–R interval histograms have been given by several authors, mostly for pathological arrhythmias. For an approach against the background of the delayed response concept, however, interval distributions do not give enough information about sources of irregularities. We have therefore gratefully made use of data published by Braunstein and Franke [9] on the autocorrelation function of the times of occurrence of R waves. Unfortunately, that report was concerned with only few records. Our comments and conclusions must be weighed accordingly.

It is tempting to make a comparison between the normal subject and the one patient analyzed with regard to the time course of the experimentally obtained autocorrelation function or the parameter values that underly the theoretical curves pictured in Fig. 2 and Fig. 3, respectively. First, the irregularity in beating, as quantified by the standard deviation of the interval distributions, is larger for the two patients than for the healthy subject. Second, the intervals of the normal subject must have been negatively correlated, as can be deduced from the autocorrelation function. In contrast, the other autocorrelation functions could be explained well if the successive interval durations were independent of each other or nearly so.

According to the implications of the model, these findings indicate that variations in conduction time (from the sinoatrial node to the ventricles) is the same or shorter for the patients than for the normal referee. A smaller variation for the pathological cases would seem unlikely in the first instance. In order to settle this point, additional information should be extracted from the EKG, for instance, by measuring the position of the P wave relative to the R wave. With regard to variation in pacemaker period, that parameter was found to be definitely two to three times larger during atrial fibrillation than under the normal conditions.

Negative correlation between successive intervals means that short intervals are more likely to be followed by long ones and vice versa. It may be argued, particularly with regard to heartbeat interval sequences, that such a process resembles, or at least possesses the properties of, a homeostatic mechanism in that a deviation of interval durations from the mean is more or less counteracted by a deviation in the opposite direction. Although this is true, it is equally possible to regard negative correlation

as a mere epiphenomenon of a stochastically delayed response, leaving teleologically tinged interpretations aside. A similar observation applies to the comments of Kuffler *et al.* [14], who state, regarding their data on unitary nervous activity, that the measured sign of the first serial correlation coefficient may be relevant to the problem of analysis of the afferent nerve fiber message by the central nervous system. Again, according to the model presented herein, negative correlation does not, a priori, call for a raison d'être.

APPENDIX: DERIVATION OF r_k

In case of order-preserving delay, the correspondence between the intervals of ϕ, ψ, and p processes is given by

$$\tau_1 = \xi_1 + \eta_1 - \eta_0, \qquad \tau_2 = \xi_2 + \eta_2 - \eta_1, \ldots, \tau_k = \xi_k + \eta_k - \eta_{k-1}, \ldots .$$

Let E denote the expectation operator. Then, E being a linear operator and the ϕ and ψ processes being independent and stationary, it follows that

$$\begin{aligned} E[\tau_1 \cdot \tau_k] &= E[(\xi_1 + \eta_1 - \eta_0) \cdot (\xi_k + \eta_k - \eta_{k-1})] \\ &= E[\xi_1 \cdot \xi_k] + 2E[\eta_1 \cdot \eta_k] - E[\eta_1 \cdot \eta_{k+1}] - E[\eta_1 \cdot \eta_{k-1}]. \\ E[\tau_k^2] &= E[\xi^2] + 2E[\eta^2] - 2E[\eta_1 \cdot \eta_2]. \\ E[\tau_k] &= E[\xi_k]. \end{aligned}$$

It is observed that the indices of τ, ξ, and η enclosed in the same square brackets of an E operator may be varied by adding an integer, or can eventually be omitted while the p, ϕ and ψ processes are stationary.

Given the sequence of random variables $x_1, x_2, \ldots, x_k$ the kth-order serial correlation coefficient is defined as

$$r_k = \mathrm{Cov}[x_1, x_{k+1}]\{\mathrm{Var}[x_1] \cdot \mathrm{Var}[x_{k+1}]\}^{-0.5},$$

where

$$\mathrm{Cov}[x_1, x_k] = E[x_1 \cdot x_k] - E[x_1] \cdot E[x_k]$$

and

$$\mathrm{Var}[x_k] = E[x_k^2] - E^2[x_k].$$

In our case $r_k = \mathrm{Cov}[\tau_1, \tau_{k+1}]/\sigma^2$, where

$$\begin{aligned}\sigma^2 &= E[\tau^2] - E^2[\tau] \\ &= E[\xi^2] - E^2[\xi] + 2E[\eta^2] - 2E^2[\eta] - 2E[\eta_1 \cdot \eta_2] + 2E^2[\eta] \\ &= \sigma_\phi^2 + 2\sigma_\psi^2 - \mathrm{Cov}[\eta_1, \eta_2].\end{aligned}$$

Further

$$\begin{aligned}\mathrm{Cov}[\tau_1, \tau_{k+1}] &= E[\tau_1 \cdot \tau_{k+1}] - E^2[\tau] \\ &= E[\xi_1 \cdot \xi_{k+1}] - E^2[\xi] + 2E[\eta_1 \cdot \eta_{k+1}] - 2E^2[\eta] \\ &\quad - E[\eta_1 \cdot \eta_{k+2}] + E^2[\eta] - E[\eta_1 \cdot \eta_k] + E^2[\eta] \\ &= \mathrm{Cov}[\xi_1, \xi_{k+1}] + 2\,\mathrm{Cov}[\eta_1, \eta_{k+1}] - \mathrm{Cov}[\eta_1, \eta_{k+2}] \\ &\quad - \mathrm{Cov}[\eta_1, \eta_k].\end{aligned}$$

The expression for r_k given in the text immediately follows.

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