STOCHASTIC MODELS OF NEURAL NETWORKS INVOLVED IN LEARNING AND MEMORY

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Stochastic models of some aspects of the electrical activity in the nervous system at both the cellular and multicellular levels are developed. In particular, models of the subthreshold behavior of the membrane potential of neurons are considered along with the problem of estimation of physiologically meaningful parameters of the developed models. Applications to data generated in experimental studies of plasticity in the nervous system are discussed. In addition, non-stationary point-process models of trains of action potentials are developed as well as measures of association such as cross-correlation surfaces of simultaneously recorded spike trains from two or more neurons. Applications of these methods to studies of connectivity and synaptic plasticity in small neural networks are explored.

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1. INTRODUCTION

The purpose of this paper is to present an in-depth exposition of recent developments in applications of stochastic modeling and inference in stochastic processes to neurophysiology with emphasis on studies of higher brain functions such as learning and memory. The focus here is on the development and application of stochastic models and methods of statistical inference to studies of the electrical activity in the nervous system at the cellular as well as multicellular levels, and to apply these methods to studies of neuronal plasticity.

More specifically, the objective of the methods developed in this paper is to provide neuroscientists and experimental psychologists with quantitative means to estimate reliably physiologically meaningful parameters of appropriate stochastic models that describe certain aspects of the electrical activity of nerve cells or neurons using experimentally generated data. Careful analysis of the estimated parameters obtained under different experimental conditions should enable the experimentalist to draw inference concerning the ways these parameters change in response to experience. This may shed light on some of the mechanisms involved in neuronal plasticity in response to natural and experimentally controlled experience.

For instance, a detailed knowledge of the mechanisms of development of the ways neurons integrate input is an important step toward identifying the crucial mechanisms underlying neuronal plasticity and in particular synaptic plasticity, which is an important aspect of neural learning. Therefore, stochastic models of the subthreshold somal transmembrane potential of single neurons in the nervous system are developed in order
to describe some aspects of neuronal integration of synaptic input as well as generation of action potentials. These models are Ito-type stochastic differential equations that include parameters which reflect important neurophysiological properties such as effective somal-membrane time constant, amplitudes of excitatory and inhibitory post-synaptic potentials, the excess of excitation over inhibition in general, and variability of synaptic input. Theoretical and applied problems concerning the estimation of some of these parameters are addressed in more detail in Habib (1985). The applications of these models and estimation methods to studies of synaptic plasticity and in particular to studies of development of orientation specificity in the visual cortex is considered in Habib and McKenna (1985).

In Section 2 the somal membrane potential of a neuron is modeled as a solution of a stochastic differential equation (SDE) driven by point-processes. In this model, it is assumed that the post-synaptic potentials (PSPs) arriving within a small interval of time are linearly integrated near the initial segment (or the axon hillock). In between synaptic input the membrane potential decays exponentially. For this reason, this neuronal model is known as the leaky integrator, and the membrane potential is modeled as a stationary Markov process with discontinuous sample paths. The discontinuities occur at the moments of arrival of the PSPs. Under the appropriate conditions, i.e. if amplitudes of the PSPs are very small and their rate of occurrence is very high, the discontinuous model may be approximated by a diffusion model. That is, the membrane potential is modeled as a solution of a stochastic differential equation driven by a
Wiener process. This model is most appropriate for describing the sub-threshold behavior of the membrane potential of spontaneously active neurons or neurons which receive extensive synaptic input with small PSP amplitudes and no dominating PSPs with relatively large amplitudes. Problems of estimation of the parameters of the diffusion models are also discussed.

The stochastic models of the somal membrane potential of nerve cells, along with the methods of inference in stochastic processes developed here, should allow the experimental physiologist to estimate neuropathologically interpretable parameters for the first time with experimentally generated data. This development should be of importance for studies of intracellular recording conducted to study changes in neurophysiological parameters in response to experience or experimental manipulation, as well as to pharmacological experiments.

Furthermore, in order to analyze quantitatively the relationship of temporal firing patterns of assemblies of neurons, non-stationary stochastic point-process models for the study of spike discharge activity of neurons are developed in Section 3. In this report, trains of action potentials are modeled as realizations of stochastic point-processes with random intensity. In order to study the joint behavior of networks of neurons, measures of association such as cross-correlation surfaces of simultaneously recorded spike trains of two or more neurons have been derived. Such measures of association may be used to study functional connectivity of neurons in the nervous system. Some aspects of this work are reported in Habib and Sen (1985). Maximum likelihood estimates of the cross-correlation surfaces are derived and their asymptotic properties, such
as consistency and asymptotic normality, are studied. Use is made of the theory of stochastic integrals as developed by the Strasbourg school of probabilists (see Meyer, 1976) together with the theory of counting processes developed by such workers as Brémaud (1975), Jacod (1975), and Boel, Varaiya and Wong (1975a, 1975b). An excellent treatment of the modern theory of counting processes using martingales is given by Brémaud (1981).

Quantitative neurophysiological studies of two or more simultaneously recorded spike trains using measures of cross-correlation and related statistical techniques have proven to be effective in indicating the existence and type of synaptic connections and other sources of functional interaction among observed neurons. (See, for example, Bryant, Ruiz-Marcos and Segundo (1973), Toyama, Kimura and Tanaka (1981), Michalski et al. (1983)). It must be noted, though, that all these studies assume that the recorded spike trains are individually as well as jointly weakly stationary. This stringent assumption is not likely to hold in reality, in particular for stimulus driven neurons. The incorporation of non-stationary processes is crucial for studies of discharge activity of neurons driven by external stimuli. See Johnson and Swami (1983) for a discussion of certain classes of neurons which fire in a non-stationary fashion. Non-stationary models are then in particular suitable for studies of neuronal aspects which change due to experience, and in general for studies of the neural basis of learning and memory. Thus, the developed models appear to have both mathematical generality and experimental validity. In addition, the three-dimensional shape of our newly developed cross-correlation surfaces enables the observer to draw conclusions concerning neuronal processes taking place during the time
period of stimulus presentation. In other words, assume that the cross-
correlation surface indicates that there is a positive (excitatory)
correlation between the cells at lag 2 (say). If the amplitude of this
correlation is constant, it means that the two spike trains are jointly
stationary. The classic methods of cross-correlation analysis are then
applicable with the associated interpretations. On the other hand, if
the amplitude of the cross-correlation changes, then the two spike
trains are jointly non-stationary and the classic methods are invalid.
Now assume that the amplitude of the correlation at lag 2 increases
during the stimulus presentation. This means that the correlation
between the temporal firing patterns of the observed neurons in strengthening,
and may be indicative of synaptic facilitation. A decrease of the
amplitude, however, may indicate anti-facilitation or depletion of the
neural transmitter at the synaptic junction between the observed neurons
or any of a multitude of physiological interpretations. It should be
clear, then, that our methods will enable the experimental neurophysiologist
to study subtle neural properties. In the past, such studies have only
been possible in simple preparations (e.g. experiments conducted on
*Aplysia* or in vitro). Using these methods, the experimental scientist
should be able to study these delicate properties in advanced neural
centers like the auditory, visual and somatosensory cortices.
2. STOCHASTIC MODELS FOR SUBTHRESHOLD NEURONAL ACTIVITIES

The purpose of this section is to develop continuous-time stochastic models of the subthreshold somal transmembrane potential of neurons. These models are Ito-type stochastic differential equations that include parameters which reflect synaptic potency as well as variability of synaptic input. Problems concerning the estimation of these parameters from real data are considered. The application of these methods are then discussed. That is, the somal membrane potential of a neuron is modeled as a solution of (non-stationary) stochastic differential equations (SDE) driven by Wiener as well as generalized point-processes. After developing models appropriate for describing the behavior of the membrane potential during spontaneous as well as stimulus driven activity, maximum likelihood estimators for the parameters of these models are derived. These methods are then applied to study neuronal plasticity. As a result of affording the neuron a certain type of experience, changes in the values of the parameters then reflect the impact of this type of neural learning.

Furthermore, in Section 2.2 conditions for absolute continuity of probability measures induced by solutions of SDEs and the corresponding Radon-Nikodym derivatives and the maximum likelihood estimators of the parameters of the models are discussed. Using Grenander's (1981) method of sieves, maximum likelihood estimation of infinite dimensional parameters of randomly stopped diffusion processes is considered (Habib and McKeague, 1985). This is presented in Section 2.3. Stochastic models for the subthreshold behavior of neuronal membrane potential for spontaneous as well as stimulus driven activity are developed in the following
section. For a detailed discussion of this aspect of neuronal modeling and its applications see Habib and McKenna (1985). Extensions of these models which take into account important neurophysiological properties such as the dependence of the amplitude of the PSPs on reversal potentials and role played by the spatial aspects of synaptic input in spike generation are also briefly considered.
2.1 A Temporal Stochastic Neuronal Model.

The state of the neuron is assumed to be characterized by the difference in potential across its membrane (membrane potential, for short) near a spatially restricted area of the soma in which the sodium conductance, per unit area, is high relative to that of the remaining somal membrane. This spatially restricted area is called the trigger zone (also initial segment of axon hillock). The membrane potential at any point of time \( t \) is subject to instantaneous changes due to the occurrence of post-synaptic potentials (PSPs) which are assumed to arrive at the initial segment according to Poisson processes. This assumption is justified by the well-known fact that if a large number of sparse point-processes are superposed, the result is approximately a Poisson process. The first proof of this result is by Khintchine (1960). It is limited to stationary point-processes and gives only sufficient conditions. Griglionis (1963) extended these results by considering arbitrary point-processes as components and gave necessary and sufficient conditions for convergence to a (possibly non-stationary) Poisson process. Indeed, assume that the number of post-synaptic potentials generated at the synapse at location \((n,j)\) on the neuronal surface is denoted by \( N_{nj} \), and that \( j=1,2,\ldots,k_n \), and \( n=1,2,\ldots \).

Next are lump groups of synapses which belong to the same spatial area together. Consider the behavior of the resulting process

\[
N_n = N_{n1} + N_{n2} + \ldots + N_{nk_n}, \quad n=1,2,\ldots
\]
Griglionis (1963) showed that if

$$\lim_{n \to \infty} \sup_{1 \leq j < k} P\{N_{n j}(B) > 1\} = 0$$

for bounded intervals $B$ of the real line, then the superposition process $N_n$ converges weakly to a Poisson process. With mean measure $\lambda$ if and only if

$$\lim_{n \to \infty} \sum_{j=1}^{k} P\{N_{n j}(B) = 1\} = \lambda(B)$$

and

$$\lim_{n \to \infty} \sum_{j=1}^{k} P\{N_{n j}(B) > 2\} = 0$$

for every finite interval $B$ of the real line. On this basis the PSPs are assumed to arrive at the initial segment according to Poisson processes. See Cinlar (1972) for a review of such results.

Now assume that the membrane potential, $V(t)$, at any point of time $t$ is a random variable which is subject to instantaneous changes due to the occurrence of PSPs of two different types:

(1) Excitatory post-synaptic potentials (EPSPs) which occur according to mutually independent Poisson processes $P(\lambda_k^{e}, t)$ with rates $\lambda_k^{e}$, $(k=1,2,\ldots,n_{L})$, each accompanied by instantaneous displacement of $V(t)$ by a constant amount $\alpha_k^{e} > 0$ $(k=1,2,\ldots,n_{L})$. That is, the dependence on reversal potential is ignored at the moment.

(2) Inhibitory post-synaptic potentials (IPSPs) which occur according
to mutually independent Poisson processes $P(\lambda_k^i, t)$, with rates $\lambda_k^i$
and amplitudes $\alpha_k^i > 0$ (k=1,2,\ldots,n_2).

Between PSPs, $V(t)$ decays exponentially to a resting potential $V_0$ with
a membrane time constant $\tau$.

The PSPs are assumed to be summed linearly at the trigger zone, and
when $V(t)$ reaches a certain constant level $S$, called the neuron's
threshold, an action potential is generated or elicited. Following the
action potential the neuron is reset to a resting potential.

Based on this physical model, which takes into account only
temporal aspects of synaptic inputs, a stochastic model of $V(t)$ is
formally built as follows: in the absence of synaptic input, $V(t)$
decays exponentially, i.e., in a small period of time $(t, t + \Delta t)$,
$V(t)$ changes by $-\rho V(t) \Delta t$, where $\rho = \tau^{-1}$. On the other hand, the
displacement in $V(t)$ due to the arrival of an EPSP during $(t, t + \Delta t)$
is equal to

$$\alpha^e[P(\lambda^e; t + \Delta t) - P(\lambda^e; t)].$$

Similarly, the displacement in $V(t)$ due to the arrival of an IPSP in
$(t, t + \Delta t)$ is given by

$$-\alpha^i[P(\lambda^i; t + \Delta t) - P(\lambda^i; t)].$$

Then an increment $\Delta V(t) = V(t + \Delta t) - V(t)$ may be modeled as
\[ \Delta V(t) = -\rho V(t)\Delta t + \sum_{k=1}^{n_1} \alpha_k^e [P(\lambda_k^e; t + \Delta t) - P(\lambda_k^e, t)] \]
\[ - \sum_{k=1}^{n_2} \alpha_k^i [P(\lambda_k^i; t + \Delta t) - P(\lambda_k^i, t)]. \]

As the time increment becomes small, the above model takes the form

\[ dV(t) = -\rho(V(t))dt + \sum_{k=1}^{n_1} \alpha_k^e dP(\lambda_k^e; t) - \sum_{k=1}^{n_2} \alpha_k^i dP(\lambda_k^i; t), \]

\[ V(0) = V_0. \] The solution of (2.1) is a homogeneous Markov process with discontinuous sample paths.

In this model it is assumed that the tens of thousands of synapses are replaced or approximated by just a few thousand ideal synapses with PSPs occurring according to independent Poisson processes. It may be constructive in certain cases, though, to approximate model (2.1) by a model which contains only a few identifiable, physiologically meaningful parameters for the purpose of parameter estimation using experimentally generated data.

Models in which the discontinuities of the membrane potential, \( V(t) \), are smoothed out have been sought where the discontinuous model (2.1) is approximated by a diffusion model (Ricciardi and Sacerdote (1979); Hanson and Tuckwell (1983)). These approximations are particularly suited for neurons with extensive synaptic input with no dominating synaptic events with large amplitudes. The approximation to a diffusion model is accomplished by allowing the amplitudes \( \alpha^e, \alpha^i \) of the EPSPs and IPSPs to become small and the rates \( \lambda^e \) and \( \lambda^i \) to become large.
in a certain manner. Kallianpur (1983) established this approximation using the functional central limit theorem of Liptser and Shiryayev (1980, 1981). Indeed, as $a^e, a^i \rightarrow 0$ and $\lambda^e, \lambda^i \rightarrow \infty$, the following linear sum of independent Poisson processes

$$\sum_{k=1}^{n_1} a^e_k P(\lambda^e_k, t) - \sum_{k=1}^{n_2} a^i_k P(\lambda^i_k, t)$$

is replaced by a Wiener process with mean $\mu$ and drift $\sigma$. That is, model (2.1) is approximated by the diffusion model

$$dV(t) = -\rho V(t) \, dt + \mu \, dt + \sigma \, dW(t)$$

where $W(t)$ is a standard Wiener process (or Brownian motion), i.e. $W(0) = 0$, the sample paths of $W$ are continuous, and for $0 < t_1 < t_2 < \ldots < t_{n-1} < t_n$, the increments

$$W(t_1), W(t_2) - W(t_1), \ldots, W(t_n) - W(t_{n-1})$$

are independent and normally distributed random variables, with mean zero and variances $t_1, t_2 - t_1, \ldots, t_n - t_{n-1}$ respectively.

An Ito-Markov Neuronal Model. The diffusion model (2.2) describes the subthreshold behavior of the membrane potential of neurons with extensive synaptic input and post-synaptic potential (PSP) with relatively small amplitudes. It is also assumed that there are no PSPs with large dominating amplitudes. The diffusion models are thus appropriate for
describing the subthreshold activity of the membrane potential of the neuron under study only when it is experiencing spontaneous activity (see e.g. Favella et al., 1982, and Lánský, 1983). It is therefore not suitable for describing the membrane potential while the neuron is driven by an external stimulus, since the synaptic input is represented by a Wiener process which in this context is considered as a limit of the sum of a large number of independent point-process type synaptic inputs. The Wiener driven diffusion model thus does not lend itself to studying important neurophysiological properties such as neuronal coding of external stimuli and feature detection in the cerebral cortical sensory areas in the nervous system (e.g., the auditory and visual areas).

Now consider stochastic neuronal models which take into account the influence of extensive low amplitude synaptic input as well as PSPs with large amplitudes, which may be reflecting the influence of a number of dominating synapses. These synapses may be electrotonically close to the initial segment. The activity of these synapses will be modeled by a linear combination of independent point-processes. This mixed model is a special case of a well-known class of stochastic processes called Itô-Markov processes (see Ikeda and Watanabe, 1981).

Now assume that in addition to the extensive synaptic input leading to the diffusion model (2.2), there are $n_1$ EPSPs arriving according to independent point-processes $N(\lambda^e_k(t), t)$ with random intensities $\lambda^e_k(t)$, and EPSP amplitudes $\alpha^e_k$, $k=1,2,\ldots,n_1$. In addition, IPSPs are arriving according to the independent processes $N(\lambda^i_k(t), t)$, with the corresponding parameters $\lambda^i_k(t)$ and $\alpha^i_k$, $k=1,2,\ldots,n_2$. We propose the following extended mixed model to describe the membrane potential of
A stimulus driven neuron:

\[ dV(t) = (-\rho V(t) + \mu) \, dt + \sigma \, dW(t) \]

\[ + \sum_{k=1}^{n_1} \alpha_k^e \, dN(\lambda_k^e(t), t) - \sum_{k=1}^{n_2} \alpha_k^i \, dN(\lambda_k^i(t), t). \]

A possible physiological interpretation of this model may be as follows. A relatively small number of pre-synaptic neurons are activated as a result of the presentation of a certain stimulus to the receptive field of the post-synaptic neurons. The rest of the pre-synaptic neurons, projecting to the neuron under study, are spontaneously active. On the other hand, in the absence of stimulation the post-synaptic neuron receives synaptic input from a large number of spontaneously active pre-synaptic neurons. The input in this case is in the form of impulses of small magnitude (relative to the difference between the threshold and the neuron's resting potential) arriving at a large number of synaptic sites according to independent Poisson processes. In this case the diffusion approximation is valid, and the membrane potential, \( V(t) \), can be adequately modeled by a diffusion process satisfying (2.2). In the presence of an effective stimulus, a limited number of pre-synaptic neurons will fire in response to the stimulus, while the rest of the pre-synaptic neurons are firing spontaneously. Assume that there are \( n_1 \) excitatory and \( n_2 \) inhibitory stimulus activated synapses. The input at the excitatory (inhibitory) synapses arrives according to independent Poisson processes with amplitudes \( \alpha^e(\lambda^e) \) and rates \( \lambda^e(\lambda^i) \). The subthreshold potential, \( V(t) \), of the post-synaptic neuron is modeled in this case by
the stochastic differential equation (2.3). In the absence of an effective stimulus, the rates of the Poisson processes will be small, and hence the terms representing the Poisson input will drop from the model. In this case, model (2.3) reduces to (2.2).

Reversal Potentials. A feature which undoubtedly plays an important role in information processing in the nervous system is the dependence of the amplitudes of post-synaptic potentials on the pre-existing value of the membrane potential. It is well established that arrival of an action potential at a pre-synaptic terminal causes a release of a transmitter substance (for the cerebral cortex this could be a variety of substances including acetylcholine, glutamate, or glycine). In any case, a transmitter's action on the neuronal membrane at a given synaptic junction can be characterized by means of the experimentally observable reversal potential. This is the membrane potential at which the observed change in membrane potential caused by transmitter induced conductance change is zero. Reversal potentials have been utilized in deterministic modeling of neuronal membranes (Rall, 1964).

The neuronal model (2.3) is then extended to take the form

\[ dV(t) = (-\rho V(t) + \mu) \, dt + \sigma \, dW(t) \]

\[ + \sum_{n=1}^{N} \alpha_n^{e} [V(t) - V_n] \, dN_n^{e}(t), t) \]

\[ - \sum_{k=1}^{N} \alpha_k^{i} [V(t) - V_k] \, dN_k^{i}(t), t), \]
where it is assumed that the neuron has excitatory synapses which, when activated, result in displacing $V(t)$ toward the reversal potential $V^e_m$ ($m=1,2,\ldots,n_1$), and inhibitory synapses, which when activated, result in displacing $V(t)$ away from the reversal potential $V^i_k$ ($k=1,2,\ldots,n_2$).

Another important characteristic of central nervous system (CNS) information processing is the dependence of both the magnitude and time course of the post-synaptic potential, evoked by a given synapse, on the spatial location of the active synaptic junction. This important feature is not considered in most existing stochastic models of single neurons, which have concerned themselves only with the influences of temporal summation of synaptic inputs. More specifically, it has conventionally been assumed that the synaptic inputs to a neuron can be treated as inputs delivered to a single summing point on the neuron's surface (triggering zone). That such an assumption is unjustified is clearly indicated by the well-established anatomical fact that a great number of the neurons in the CNS have extensively branched dendritic receptive surfaces, and that synaptic inputs may occur both on the somatic region and the dendrites. Another common assumption is that synapses located on distal dendritic branches have little effect on the spike initiation zone of a neuron. According to this view, distally-located synapses would merely set the overall excitability of the neuron and would be ineffective in generating neural discharge activity. Synapses located near the soma of a neuron, on the other hand, are widely believed to influence directly and strongly neuronal firing behavior. A major extension of this view was suggested by Rall (1959, 1962), based on calculations of passive electronic current spread through the dendritic
Rall's work showed that distal synapses can play a functionally much more interesting role than previously assumed. More specifically, if the synaptic input to the dendrite has the appropriate spatio-temporal characteristics, distal synapses can influence neuronal firing to a much greater extent than is predicted on the basis of their dendritic location.

In view of Rall's demonstration and in recognition of the suggestions (based on experimental evidence) that such a mechanism plays an important role in feature-extraction by single sensory neurons (Fernald, 1971), it seems necessary to carry out modeling studies to evaluate the potential for different spatial distributions of synaptic inputs to influence sensory neuron behavior.

Model (2.5) may be extended to incorporate the important feature of spatial distribution. This extension is based on Rall's model neuron (Rall, 1978). In Rall's model neuron the cable properties of a system of branched dendrites are reduced to a one-dimensional equivalent dendrite, with synapses made at specific distances along the equivalent dendrite. Considering the nerve cell as a line segment of finite length L, we propose that the subthreshold behavior of the membrane's potential, \( V(t, x) \) be modeled as

\[
(2.6) \quad \frac{dV(t, x)}{dt} = (-\rho V(t, x) + (\partial^2 / \partial x^2) V(t, x) + \mu) \, dt + \sigma \, dW(t, x)
\]

\[
+ \sum_{j=1}^{n_1} a_j^e \delta(x-x_j^e) \left[ V_j^e(x) - V(t, x) \right] \, dN(\lambda_j^e(t), x, t)
\]

\[
- \sum_{k=1}^{n_2} a_k^i \delta(x-x_k^i) \left[ V_k^i(x) - V(t, x) \right] \, dN(\lambda_k^i(t), x, t)
\]

where \( \delta \) is the delta distribution (or generalized function), and \( x_j^e(x) \)
is the location of the excitatory (inhibitory) synaptic inputs which
occur according to independent point-processes with rates $\lambda_j^{(i)}$ and
amplitudes of $\alpha_j^{(i)}$, $j=1,2,\ldots,n_1$; $k=1,2,\ldots,n_2$. The solution of (2.6)
is a stochastic process $\{V(t,x), 0 < x < L, t \geq 0\}$.

Walsh (1981) considered a partial stochastic differential equation
model that describes the subthreshold behavior of the membrane potential
and studied the properties of the sample paths of the solution of the
partial stochastic differential equation. This model is a special case
of the neuronal model (2.6). Kallianpur and Wolpert (1984a) modeled the
membrane potential as a random field driven by a generalized Poisson process.
The authors studied the approximation of this model by an Ornstein-Uhlenbeck
type process in the sense of weak convergence of the probability measures
induced by solutions of stochastic differential equations in Skorokhod
space. The problem of reversal potential was taken into consideration in
modeling the membrane potential of a neuron by Kallianpur and Wolpert
(1984b).
2.2 Parameter Estimation for Stationary Diffusion Processes

This section is concerned with the problem of parameter estimation for continuous-time stochastic models describing the subthreshold behavior of the membrane potential of model neurons. In particular, maximum likelihood estimators (MLE) of the parameters $\rho$ and $\mu$ of the stationary diffusion neuronal model (2.2) are explicitly derived. Statistical inference for the more involved models (2.3) - (2.6) is a more delicate matter and will be considered in future work. In order to address the problem of parameter estimation at hand, the problem of absolute continuity of probability measures induced by solutions of stochastic differential equations is briefly considered (Basawa and Prakasa Rao, 1981). The reason for considering this more sophisticated approach of maximum likelihood estimation of parameters of stationary diffusion processes over the classic approach of maximizing the transition density function of the process (where it exists) is that the density function has a complicated form for most of the models of interest, which makes the classical approach impractical.

The diffusion processes considered here are assumed to be continuously observed over random intervals. The reason for considering processes that are observed on a random interval $[0, \tau]$, say, is because one is only interested in the subthreshold behavior of the membrane potential, $V(t)$, of neurons. That is, $V(t)$ is continuously observed from a certain point of time (e.g. the point of time $V(t)$ is equal to the resting potential) up to the moment it reaches the neuronal threshold. First, discuss are conditions for absolute continuity as well as the existence of the corresponding Radon-Nikodym derivative of probability measures.
induced by diffusion-type processes (which are more general than the ordinary diffusion processes) observed over random intervals. This problem has been considered by Sørensen (1983). Maximum likelihood estimators of parameters in the special case of stationary diffusion processes are derived. It should be noted here, though, that non-stationary diffusion processes are more realistic models for neuronal membrane potential. The discussion of maximum likelihood estimation of (infinite dimensional) parameters in non-stationary diffusion processes will be deferred to Section 2.3.

Now consider the diffusion process

\[
(2.7) \quad dX(t) = a(t, X(t)) \, dt + b(t, X(t)) \, dW(t), \quad 0 \leq t \leq T.
\]

Necessary and sufficient conditions for the existence of a unique solution (in some sense or another) are well known in the literature. See, for instance, Section 2.6 of Malliaris and Brock (1984) and also Gihman and Skorohod (1972). These conditions concern the smoothness of the functions \(a(t, x)\) and \(b(t, x)\). The first is a Lipschitz type continuity condition on \(a\) and \(b\) as functions in \(x\) and the second condition regulates the rate of growth of \(a\) and \(b\) with respect to the argument \(t\). Furthermore, conditions for absolute continuity of measures induced by a solution of equation \((2.7)\) with respect to a measure induced by a Wiener process (Wiener measure for short) are discussed in Chapter 7 of Liptser and Shiryaev (1977). Recently, Sørensen gave sufficient conditions for absolute continuity of probability measures induced by solutions of two stochastic
differential equations in the case where these solutions are diffusion type processes which are observed over random intervals. Diffusion-type processes are more general than diffusion processes in that they are solutions of SDEs of the general form (2.7), but with the functional a and b depending on the past as well as present values of the process X(t).

Now let X and Y be stochastic processes of the diffusion type satisfying the SDEs

\begin{align*}
\text{(2.8)} & \quad dX(t) = A_t(X)dt + b_t(X) \ dW(t) \\
\text{(2.9)} & \quad dY(t) = a_t(Y) \ dt + b_t(Y) \ dW(t)
\end{align*}

observed over a random interval \([0, \tau]\) where \(\tau\) is a random variable. Under certain regulatory conditions (see Sørensen, 1983) the probability measures \(\mu_{\tau,X}\) and \(\mu_{\tau,Y}\) induced by X and Y respectively (on the appropriate measurable space) are mutually absolutely continuous with likelihood function (or Radon-Nikodym derivative)

\begin{align*}
\text{(2.10)} & \quad (d\mu_{\tau,Y}/d\mu_{\tau,X})(X) = \exp\left(-\int_0^{\tau \wedge T} b_t^-(X)^2 \ (A_t(X) - a_t(X)) \ dX_t \right) \\
& \quad \quad \quad + 1/2 \ \int_0^{\tau \wedge T} b_t^+(X)^2 \ (A_t(X) - a_t(X))^2 \ dt,
\end{align*}

where

\[
\begin{align*}
\frac{\partial}{\partial t} & = \begin{cases} 
\frac{1}{b_t(X)} & \text{if } b_t(X) \neq 0 \\
0 & \text{if } b_t(X) = 0.
\end{cases}
\end{align*}
\]
Notice that the likelihood function (2.10) plays a role in inference in stochastic processes similar to the one played by the likelihood ratio in classical statistical inference.

Now, consider the simpler neural diffusion model (2.2), namely

\[ (2.11) \quad dV(t) = (-\rho V(t) + \mu) \, dt + \sigma \, dW(t), \quad 0 \leq t \leq T, \]

\[ V(0) = V_0. \]  
The statistical problem at hand is to estimate the parameters \( \rho \) and \( \mu \) based on the observation of \( n \) independent trajectories \( \{V_k(t), \tau_{k-1} < t < \tau_k\}, k=1,2,\ldots,n. \) Assume that \( P(\tau_k < \infty) = 1, k=1,2,\ldots,n. \)

Then every \( \tau_i \) in (2.10) may be replaced by \( \tau. \) From (2.10) the log-likelihood function is given by

\[ (2.12) \quad L_n(\rho, \mu) = \sum_{k=1}^{n} \left[ \int_{\tau_{k-1}}^{\tau_k} (-\rho V_k(t) + \mu) \, dV_k(t) \right] - \frac{1}{2} \sum_{k=1}^{n} \int_{\tau_{k-1}}^{\tau_k} (-\rho V_k(t) + \mu)^2 \, dt. \]

The maximum likelihood estimator (MLE) of \( \hat{\rho}_n \) and \( \hat{\mu}_n \) of \( \rho \) and \( \mu \) respectively are simply those values of \( \rho \) and \( \mu \) which maximize (2.12). The MLEs are given by

\[ (2.13) \quad \rho_n = \frac{\sum_{k=1}^{n} \int_{\tau_{k-1}}^{\tau_k} V_k(t) \, dV_k(t) - \sum_{k=1}^{n} \int_{\tau_{k-1}}^{\tau_k} V_k(t) \, dt}{\sum_{k=1}^{n} \int_{\tau_{k-1}}^{\tau_k} V_k(t)^2 \, dt - \sum_{k=1}^{n} (\tau_k - \tau_{k-1}) \sum_{k=1}^{n} \int_{\tau_{k-1}}^{\tau_k} V_k(t)^2 \, dt}. \]
Using the fact that the membrane potential $V(t)$ is observed continuously over random intervals, the diffusion coefficient $\sigma^2$ may be estimated from an observed trajectory $V_k^k$ ($k=1,2,\ldots,n$) by the formula

$$\hat{\sigma}^2(k) = \lim_{m \to \infty} \frac{1}{\tau_k^k - \tau_{k-1}^k} \sum_{m=0}^{m_k} \left[ V_k^k(\tau_{k-1}^k + jd_k^k)^{-m_k} - V_k^k(\tau_{k-1}^k + (j-1)d_k^k)^{-m_k} \right].$$

This result may be proved using the corresponding result of Lévy for Brownian motion by transforming $V_k^k$ via time substitutions into Brownian motion (or Wiener process). A natural estimate of $\sigma^2$ which employs all the observed trajectories is given by

$$\hat{\sigma}^2 = \frac{1}{n}\sum_{k=1}^{n} \hat{\sigma}^2(k).$$

By sampling the trajectories $\{V_k(t), \tau_{k-1}^k \leq t \leq \tau_k^k\}$ $k=1,2,\ldots,n$, one obtains $\{V_{t_{k,1}}, V_{t_{k,2}}, \ldots, V_{t_{k,m_k}}\}$ where $\tau_{k-1}^k \leq t_{k,1} < \cdots < t_{k,m_k} \leq \tau_k^k$, for $k=1,2,\ldots,n$. In this case the integrals in (2.13) and (2.14) may be replaced by sums.
Notice that the integrals in (2.13) and (2.14) are Ito-type stochastic integrals where, for instance, $\int_{\tau_{k-1}}^{\tau_k} V(t) dV_k(t)$ can be replaced by $\frac{1}{2} \{V^2(\tau_k) - V^2(\tau_{k-1}) - (\tau_k - \tau_{k-1})\}$. Now in order to replace the above integrals with sums, consider the following partition of the $n$ observed random intervals $(\tau_{k-1}, \tau_k), k=1,2,\ldots,n$; $0 = \tau_0 = t_{11} < t_{12} < \ldots < t_{1,m+1} < \tau_1 < t_{21} < \ldots < t_{n,m+1} < \tau_n$, and let $\sum_{k=1}^{m} \tau_k = N$. Replacing the integrals with the appropriate sum, (2.13) and (2.14) take the form

$$\hat{\rho}_{n,N} = \frac{A_{n,N}(V,\tau) - B_{n,N}(V,\tau)}{C_{n,N}(V,\tau) - D_{n,N}(V,\tau)},$$

$$\hat{\mu}_{n,N} = \frac{E_{n,N}(V,\tau) - F_{n,N}(V,\tau)}{C_{n,N}(V,\tau) - D_{n,N}(V,\tau)},$$

where

$$A_{n,N} = (V,\tau) = \sum_{k=1}^{n} (\tau_k - \tau_{k-1}) \sum_{j=1}^{m} V_k(t_{kj}) [V_k(t_{k,j+1}) - V_k(t_{kj})]$$

$$B_{n,N}(V,\tau) = \sum_{k=1}^{n} \sum_{j=1}^{m} V_k(t_{kj}) (t_{k,j+1} - t_{kj}) [V_k(t_{k,j+1}) - V_k(t_{kj})]$$

$$C_{n,N}(V,\tau) = \sum_{k=1}^{n} \sum_{j=1}^{m} V_k(t_{kj}) (t_{k,j+1} - t_{kj})^2$$

$$D_{n,N}(V,\tau) = \sum_{k=1}^{n} (\tau_k - \tau_{k-1}) \sum_{j=1}^{m} V_k(t_{kj}) (t_{k,j+1} - t_{kj})$$

$$E_{n,N}(V,\tau) = \sum_{k=1}^{n} \sum_{j=1}^{m} V_k^2(t_{kj}) (t_{k,j+1} - t_{kj}) [V_k(t_{k,j+1}) - V_k(t_{kj})]$$

$$F_{n,N}(V,\tau) = \sum_{k=1}^{n} \sum_{j=1}^{m} V_k(t_{kj}) [V_k(t_{k,j+1}) - V_k(t_{kj})] [V_k(t_{k,j+1} - t_{kj})]$$
At this point, it is natural to ask whether the new estimators, $\hat{\rho}_{n,N}$ and $\hat{\mu}_{n,N}$ are asymptotically equivalent to the MLEs $\hat{\rho}_n$ and $\hat{\mu}_n$ i.e. as the sampling becomes more dense. The answer to this question is affirmative. Le Breton (1976) showed that $\hat{\rho}_{n,N} \rightarrow \hat{\rho}_n \rightarrow \infty$ and $\hat{\mu}_{n,N} \rightarrow \hat{\mu}_n \rightarrow 0$ as $N \rightarrow \infty$ in probability, in the special case where the diffusion process is observed continuously over a fixed interval. A similar result for randomly stopped diffusion processes is lacking.

The above methods can be used to estimate the model's parameters for neurons before and after they are subjected to experiments of neuronal conditioning, in order to measure the impact of this form of neuronal learning on the membrane time constant, the drift parameter which reflects the excess of excitation over inhibition in the synaptic input, and on the variability in synaptic input. It should be noted that this kind of quantitative study of neuronal learning has not been performed before.

The consistency of the estimators $\hat{\rho}_n$ and $\hat{\mu}_n$ as $n \rightarrow \infty$ was established in Habib (1985).

**THEOREM 2.1**

The maximum likelihood estimators $\hat{\rho}_n$ and $\hat{\mu}_n$ of $\rho$ and $\mu$ which are given by (2.13) and (2.14) are strongly consistent, i.e. $\hat{\rho}_n \rightarrow \rho$ and $\hat{\mu}_n \rightarrow \mu$ a.s. [P] as $n \rightarrow \infty$.

Results concerning the asymptotic distribution of $\hat{\rho}_n$ and $\hat{\mu}_n$ have not been established as yet.
2.3 **Randomly Stopped Non-Stationary Diffusion Processes**

In this section, considered is the problem of maximum likelihood estimation of infinite dimensional parameters in non-stationary randomly stopped diffusion processes. This is a more realistic model of the membrane potential of a neuron than (2.2), since close inspection of records of subthreshold trajectories of membrane potential clearly reveal that the drift parameter $\mu$ in (2.2) is a function of time rather than a constant. Furthermore, replacing the membrane time instant $\rho^{-1}$ in (2.2) by a function of $t$ compensates for considering only temporal aspects of synaptic input and ignoring their spatial properties. For these reasons the following more general model of neuronal membrane potential is considered.

\begin{equation}
(2.19) \quad dX(t) = \left( \theta(t) X(t) + \mu(t) \right) dt + \sigma dW(t), \quad 0 \leq t \leq T,
\end{equation}

where $X(0) = X_0$ is a random variable which is assumed to be independent of the standard Wiener processes $W$. Also assume that $\theta(\cdot)$ and $\mu(\cdot)$ are members of the space $L^2([0,T], dt)$ of all square integrable functions defined on $[0,T]$. This is a Hilbert space with the inner product

\[ (f, g) = \int_0^T f(t) g(t) \, dt. \]

Since we are observing stochastic processes over random intervals, consider the stopping time

\[ \tau = \inf\{t > 0, X(t) > S\} \]
where $S$ represents the neuron's threshold. The statistical problem at hand then is to estimate the $L^2([0,T], dt)$-unknown functions $\theta(t), \mu(t), t \in [0,T]$, from the observation of $n$ independent trajectories

$$\{X_k(t), \tau_{k-1} \leq t \leq \tau_k\}, \quad k=1,2,\ldots,n.$$  

From 2.10, the log-likelihood function is given by

$$L_n(\theta, \mu) = \sum_{k=1}^{n} \left\{ \int_{\tau_{k-1}}^{\tau_k} [\theta(t)X_k(t) + \mu(t)] dX_k(t) \right\} - \frac{1}{2} \int_{\tau_{k-1}}^{\tau_k} [\theta(t)X_k(t) + \mu(t)]^2 dt.$$

It should be noted here that the technique for estimating finite dimensional parameters usually fails in the finite dimensional case, and we are forced to consider the method of sieves (see Grenander, 1981). In this method, for each sample size $n$ ($n$ is the number of observed trajectories) a sieve which is, roughly speaking, a suitable subset of the parameter space is chosen. The likelihood function is maximized on the sieves yielding a sequence of estimators. For a discussion of some general results on the existence of sieves leading to estimators with interesting asymptotic properties see Geman and Hwang (1982). Notice here that in general the method of sieves leads to consistent 'non-parametric estimators. This is accomplished by choosing a metric for the parameter space and proving consistency with respect to this metric. It should be also remarked that Geman and Hwang discuss the relationship of the method of sieves to other well
known methods of density estimation such as the method of penalized
maximum likelihood (see e.g. Tapia and Thompson, 1978) and the
maximum likelihood admissible estimator introduced by Wegman (1975).

A detailed treatment of parameter estimation using the method of
sieves applied to our model (2.14) is given in Habib and McKeague (1984).
The following is a brief discussion of the results. Following Nguyen
and Pham (1982), one uses as sieves increasing sequences $U_n$ and $V_n$ of
finite dimensional subspaces of $L^2([0,T], dt)$ with dimensions $d_n$ and
$d'_n$ such that $U_n < U_{n+1}$, $V_n < V_{n+1}$, and $U_n$ and $V_n$ are dense in
$L^2([0,T], dt)$ such that $\{\phi_1, \ldots, \phi_{d_n}\}$ and $\{\psi_1, \ldots, \psi_{d'_n}\}$ form the basis of
$U_n$ and $V_n$ respectively, for all $n \geq 1$. For $\theta \in U_n$ and $\mu \in V_n$ with

$$\theta(\cdot) = \sum_{i=1}^{d_n} \theta_i \phi_i(\cdot),$$

$$\mu(\cdot) = \sum_{j=1}^{d'_n} \mu_j \psi_j(\cdot).$$

We have from (2.8) the Radon-Nikodym derivative

$$L_n(\theta, \mu) = \sum_{k=1}^{\tau_k} \left( \sum_{i=1}^{d_n} \theta_i \phi_i(t) X_k(t) + \sum_{j=1}^{d'_n} \mu_j \psi_j(t) \right) dX_k(t)$$

$$- \frac{1}{2} \int_{\tau_{k-1}}^{\tau_k} \left( \sum_{i=1}^{d_n} \theta_i \phi_i(t) X_k(t) + \sum_{j=1}^{d'_n} \mu_j \psi_j(t) \right)^2 dt.$$

The objective now is to maximize the likelihood function (2.21) on the
sieves to yield a sequence of estimators, and to find sufficient conditions
in order to prove asymptotic consistency and normality of the estimators.
These conditions place restrictions on the rate of growth of the dimensions $d_n$ and $d'_n$ of sieves as $n \to \infty$.

Now define

$$X(t) \quad \text{if } 0 \leq t \leq \tau$$  
$$Y(t) = \begin{cases} 
X(t) & \text{if } 0 \leq t \leq \tau \\
0 & \text{if } \tau < t \leq T 
\end{cases}$$

and consider the function spaces

$$L^2([0,T], dt) \subseteq L^2([0,T], d\nu) \subseteq L^2([0,T], dy),$$

where

$$d\nu(t) = EX^2(t) \, dt, \quad d\gamma(t) = EY^2(t) \, dt.$$ 

Consider the conditions:

A.1 \quad \inf_{t \in [0,T]} EY^2(t) > 0,

A.2 \quad d_n \to \infty, \quad d_n^2/n \to 0, \quad d'_n \to \infty, \quad \text{and} \quad d'_n/n \to 0 \quad \text{as} \quad n \to \infty,

A.3 \quad \frac{1}{T} \int_0^T \frac{[EY(t)]^2}{EY^2(t)} \, dt < E'(\tau).

The following propositions address the asymptotic properties of these estimators.
PROPOSITION 2.1. Under the assumptions (A.1) - (A.3), we have

\[ \int_0^T |\hat{\theta}(n)(t) - \theta(n)(t)|^2 \mathbb{E}Y^2(t) \, dt \to 0, \]

and

\[ \int_0^T |\mu(n)(t) - \mu(n)(t)|^2 P(\tau \geq t) \, dt \to 0, \]

as \( n \to 0 \) in probability.

PROPOSITION 2.2. Let \( h \) be a function in \( L^2([0,T], dt) \) such that

\[ \int_0^T [h^2(t)/\mathbb{E}X^2(t)] \, dt < +\infty \]

and let \( g \in L^2([0,T], dt) \). Then under assumptions (A.1) and (A.3) and

A.4 \( d^3_n/n \to 0 \) and \( d^3_n/n \to 0 \) as \( n \to \infty \),

\[ \sqrt{n} \int_0^T h(t)\{\hat{\theta}(n)(t) - \theta(n)(t)\} P(\tau \geq t) \, dt \]

is asymptotically normal with zero mean and variance

\[ \int_0^T [h^2(t)/\mathbb{E}X^2(t)] \, dt, \]

and
\[ \sqrt{n} \int_0^T \{ \hat{\mu}(n)(t) - \mu(n)(t) \} \, P(\tau > t) \, dt \]

is asymptotically normal with zero mean and variance

\[ \int_0^T g^2(t) \, dt. \]
3. STOCHASTIC POINT-PROCESS MODELS AND APPLICATIONS
   TO NEURONAL PLASTICITY

3.1 Overview

The objective of this section is to develop quantitative methods to study neuronal plasticity of assemblies of neurons in the central nervous system (CNS). Studied are changes in the correlated temporal firing patterns of neurons, in the CNS of experimental subjects, whose synaptic connections are in the process of being altered by either normal or experimentally manipulated experience. This is made feasible by modern techniques of multiple electrode recording along with computer-aided separation techniques of action potentials generated by different neurons, hence permitting simultaneous recordings of times of occurrences of action potentials of two or more neurons. Experimental aspects as well as computer analysis issues of multicellular recording of spike trains has recently been addressed by Gerstein et al. (1983).

In order to analyze quantitatively the relationship of temporal firing patterns of assemblies of neurons, non-stationary stochastic point-process models for the study of spike discharge activity of neurons are developed. In this study trains of action potentials are modeled as realizations of stochastic point-processes with random intensity. In order to study the joint behavior of networks of neurons, measures of association such as cross-correlation surfaces of simultaneously recorded spike trains of two or more neurons are derived. For details of this work see Habib and Sen (1985).
A systematic analysis of the shape of cross-correlation surfaces of spike trains recorded simultaneously from two or more neurons should indicate details of neuronal interactions and may be employed in studies of neuronal plasticity in order to shed light on some fundamental aspects of the dynamics of changes of functional connectivity in neural networks. These connections may be monosynaptic connections, or polysynaptic connections through interneurons, or may reflect the influence of shared synaptic input. Also, the types of cells with correlated firing patterns may be identified. For instance, in studies of visual cortical neurons, the cells may be identified as simple, complex, hypercomplex, etc. Furthermore, the shape of the cross-correlation surface makes it possible to identify the type of interaction as excitatory or inhibitory. In addition, the analysis of cross-correlation surfaces may reveal important aspects of physiological properties such as facilitation, adaptation, etc. It should be noted that the classic studies of cross-correlation functions of stationary spike trains are not capable of investigating such neuronal properties as the assumption of stationarity precludes their presence. The method of cross-correlation surfaces which is developed by Habib and Sen (1985) makes it possible for the first time to study synaptic properties using the method of extracellular recording in many areas of the CNS, including sensory cortical areas such as the visual and auditory cortices. It should be further noted that studies of such delicate physiological properties are presently only possible using methods of intracellular recordings in simple preparations such as studies of the nervous system of *Aplysia* and studies conducted in vitro.
To that end, maximum likelihood estimators of cross-correlation surfaces are derived and their asymptotic properties, such as consistency and asymptotic normality, are studied. Under the condition that the random intensity of the counting process, associated with the spike train, solely depends on initial events and hence is independent of the process itself, the counting process is a doubly stochastic Poisson process (Snyder, 1975). This condition means physiologically that the neuronal mechanism generating the action potentials is independent of the firing history of the neuron. In other words, it may be that the behavior of the synapses as well as the way the somal membrane integrates the synaptic input is independent of the immediate history of firing of the neuron. It may depend, though, on initial properties, including information concerning the stimulus which may be driving the cell, the properties of the receptive field of the neuron, and so on. Given this model, we have derived (maximum likelihood) estimators of the cumulative intensity process as well as the cross-correlation surface of simultaneously recorded spike trains of two or more neurons.

In Section 3.2, a brief review of non-stationary point-process models of spike trains, the estimation of the cumulative random intensity of a doubly stochastic Poisson process, and the estimation of cross-correlation surfaces of two such processes is given. In Section 3.3 a summary of some extensions of the models which have been developed here to more general models of stationary processes with random intensities, which may depend on the past history of the process itself, is given. Also, a discussion is given of the need to derive tight confidence regions for estimates of the cross-correlation surfaces to facilitate the identification
of regions of statistically significant correlations. In Section 3.4, applications of developed methods to multicellular recordings of pairs of neurons in the visual cortex of the cat are discussed.
3.2 Cross-Correlation Surfaces of Simultaneously Recorded Spike Trains.

Let \( T_1, T_2, T_3, \ldots \) be the occurrence times of action potentials (spikes) recorded from a certain neuron. Statistically, this may be modeled as a realization of a stochastic point-process. Let \( N(t) \) be the number of spikes recorded in the time interval \((0, t]\). That is, \( N(t) \) is the counting process

\[
N(t) = \begin{cases} 
  k, & \text{if } t \in [T_k, T_{k+1}) \\
  \infty, & \text{if } t > T_\infty
\end{cases}
\]

where \( T_\infty = \lim_{n \to \infty} T_n \).

The intensity or the rate of \( N(t) \) is defined by

\[
\lambda(t) = \lim_{h \to 0} \frac{1}{h} \mathbb{E}\{[N(t+h) - N(t)]/H_t\},
\]

where \( H_t \) is the history of the process \( N(t) \). For example, if \( S \) is a random variable representing information concerning the stimulus, \( N(t) \) and the firing time \( \{T_1, T_2, \ldots\} \) are as defined above, then a history of \( N(t) \) is

\[
H_t = \sigma\{N(s), 0 \leq s \leq t, T_1, \ldots, T_n(t); S\}, \quad t \in [0, T].
\]

Definition. A counting process \( N(t), 0 \leq t \leq T \), with a random intensity \( \lambda(t) \) that is \( H_0 \)-measurable and integrable, is called a doubly stochastic Poisson process if
Let us partition the observation period \((0,T]\) by the points \(t_1, t_2, \ldots, t_p\) such that \(t_0 = 0, t_i - t_{i-1} = b (i=1,2,\ldots,p), t_p = T\). Let \(N(0) = 0\),

\[
(3.2) \quad N_k = N(t_k) - N(t_{k-1}).
\]

Then \(\{N_k, 0 \leq k \leq 0\} \) is the histogram (counting process). Now assume that the experiment is repeated \(m\) times. Statistically, this means that there is \(m \geq 1\) independence and identically distributed (i.i.d.) copies \(\{N_{k}^{(i)}, 0 \leq k \leq p\}, i=1,2,\ldots,m\) of the histogram processes. Let

\[
(3.3) \quad \Lambda_k = \int_{\tau_{k-1}}^{\tau_k} \lambda(u) \, du, \quad \text{for } k=1,2,\ldots,p.
\]

The maximum likelihood estimator \(\hat{\Lambda}_k\) of \(\Lambda_k\) is given by

\[
(3.4) \quad \hat{\Lambda}_k = \frac{1}{m} \sum_{i=1}^{m} N_{k}^{(i)}, \quad N \leq k \leq p.
\]

See Habib and Sen (1985), Section 3.1 for the details of these calculations.

Note that (3.4), implicit in the above derivation, amounts to assuming that the intensity process \(\lambda(t)\) of the counting process \(N(t)\) depends only on events at time \(t_0 (=0)\), along with the stimulus, but not on events after the beginning of the trial, i.e., \(\lambda(t)\) is \(H_0\)-measurable and is independent of \(N([0,t])\). In many neurophysiological studies, such a model seems appropriate, and in particular for neurons with low firing rates.
Let us proceed on to the study of the association pattern of spike trains recorded simultaneously for two or more neurons. For two cells, say, A and B, let \((N_{k,A}, N_{k,B}, 0 \leq k \leq 0), i=1, \ldots, m\) be i.i.d. copies of the simultaneously recorded spike trains. Then, one may consider a cross-covariance function

\[
\sigma_{AB}(\ell,k) = E\{N_{\ell,A} N_{\ell+k,B}\} - E\{N_{\ell,A}\} E\{N_{\ell+k,B}\}
\]

for all permissible \((\ell,k)\) such that \(0 \leq \ell \leq p, 0 \leq \ell+k \leq p\) (\(k\) may be positive or negative). One may define similarly \(\sigma_{AA}(\ell)\) and \(\sigma_{BB}(\ell+k)\), and consider the cross-correlation function

\[
\rho_{AB}(\ell,k) = \frac{\sigma_{AB}(\ell,k)}{\sigma_{AA}(\ell) \sigma_{BB}(\ell+k)}^{1/2}.
\]

In a homogeneous model, \(\rho_{AB}(\ell,k) = \rho_{AB}(k)\) for all \(\ell\), but, in a non-homogeneous model, (3.5) is defined in terms of the two-dimensional time-parameters \((\ell,k)\).

Note that for every permissible combination of \((\ell,k)\), a symmetric, unbiased and optimal estimator of \(\sigma_{AB}(\ell,k)\) is

\[
\hat{\sigma}_{AB}(\ell,k) = \frac{1}{m-1} \sum_{i=1}^{m} (N_{\ell,A}^{(i)} - \bar{N}_{\ell,A}) (N_{\ell+k,B}^{(i)} - \bar{N}_{\ell+k,B}).
\]

Similarly,
are both U-statistics and therefore unbiasedly estimate their population counterparts. Then the following estimator is considered.

\[
\hat{\sigma}_{AA}(\ell) = (m-1)^{-1} \sum_{i=1}^{m} (N(i)_{\ell,A} - \bar{N}^{\ell}_A)^2
\]

\[
\hat{\sigma}_{BB}(\ell+k) = (m-1)^{-1} \sum_{i=1}^{m} (N(i)_{\ell+k,B} - \bar{N}^{\ell+k}_B)^2
\]

For various plausible combinations of \((\ell,k)\), these estimators can be incorporated to generate cross-correlation surfaces.

For the study of the statistical properties of the estimators in (3.6), we may exploit the basic results of Hoeffding (1948) on U-statistics. As has been noted earlier, for every plausible \((\ell,k)\), \(\hat{\rho}_{AB}(\ell,k)\) is a function of three U-statistics \(\hat{\sigma}_{AB}(\ell,k)\), \(\hat{\sigma}_{AA}(\ell)\) and \(\hat{\sigma}_{BB}(\ell+k)\). The exact distribution theory of these \(\hat{\rho}_{AB}(\ell,k)\) may be quite involved (in a general non-homogeneous model). Nevertheless, for large \(m\), this can be considerably simplified by incorporating the general results of Hoeffding (1948), and, in neurological investigations, usually \(m\) can be taken quite large, so that these asymptotic results remain very much applicable.

By virtue of Theorem 7.5 of Hoeffding (1948), we may conclude that for every plausible \((\ell,k)\), as \(m \to \infty\),

\[
(m^{-1/2}(\hat{\rho}_{AB}(\ell,k) - \rho_{AB}(\ell,k)) - N(0, \sigma^{2}_{\ell,k})
\]
where \( \sigma^2_{\ell,k} \) depends on the underlying probability law and \((\ell,k)\). In fact, (3.8) naturally extends to the joint asymptotic normality of \((l+p)^2\) elements: 
\[
m^{1/2}(\hat{\rho}_{AB}(\ell,k) - \rho_{AB}(\ell,k)), 0 \leq \ell \leq p, 0 \leq \ell+k \leq p.
\]
The fact that the dispersion matrix of such a multi-normal distribution is generally unknown does not raise any serious alarm. For U-statistics, one may use suitable jackknifed estimators \(\text{viz., Sen (1960, 1977)}\) which are (strongly) consistent under quite general regularity conditions. Thus, having obtained such an estimator \(V_m\) of the dispersion matrix, one may readily proceed on to construct suitable (simultaneous) confidence intervals for the \(\rho_{AB}(\ell,k)\) or to test suitable hypotheses on these correlations, without necessarily assuming that one has a homogeneous model. For the homogeneous model, one may further simplify the theory by combining the estimates \(\{\hat{\rho}_{AB}(\ell,k), \ell=1,\ldots\}\) for a given \(k\), and then studying the pattern for variation on \(k (=0, \pm 1, \pm 2,\ldots)\).

Now the above derived cross-correlation estimators may be used to generate cross-correlation surfaces of real data. If the recorded spike trains are (jointly weakly) stationary, the three-dimensional shape of the cross-correlation will show a fixed peak \(\hat{\rho}_{AB}(\ell, \ell+k)\) as \(\ell\) charges (for a fixed \(k\), say). See Figure 1 for a (simulated) example of a surface which indicates the existence of a stationary delayed excitation. Of course, the classic methods of stationary cross-correlation analysis are applicable here. On the other hand, if the two spike trains are (jointly) non-stationary, then a careful study of such correlation surfaces may cast light on the dynamic aspects of the synaptic interactions of the observed neurons. For example, in the case of a direct excitatory synaptic connection between the two neurons \((A,B)\), it may be noticed that
the correlation $\rho_{AB}(\tau, k)$ is increasing in $\tau$ (for a given $k$), indicating that the synaptic efficiency is increasing during the presentation of the stimulus. This reflects, for instance, synaptic potentiation or facilitation as a result of the firing of the pre-synaptic cell. In Figure 2, the cross-correlation surface reflects the presence of a non-stationary delayed excitation which is increasing during the period of stimulus presentation. In Figure 3, the strength of the cross-correlation is diminishing during the stimulus presentation. This may indicate the presence of anti-facilitation or may reflect on the depletion of neural transmitters at the synaptic junctions functionally connecting the observed neurons.
3.3 \textbf{Estimation of Cross-Correlation Surfaces and Intensity Processes}

In this section, four main issues are discussed. The first is the development of more general stochastic point-process models of neuronal spike trains. The doubly stochastic Poisson model which was considered in Section 3.2 may be appropriate for describing the firing behavior of many types of neurons, such as neurons with low firing rates. For this type of neurons, the cell usually recovers from the most recent spike before it generates the next one. This suggests that the firing behavior at any moment during the recording period is independent of the immediate history of the firing pattern of the neuron. This type may be found in many areas in the CNS such as the auditory cortex. On the other hand, the doubly stochastic Poisson process is a poor model for neurons with high firing rates during spontaneous and/or stimulus driven periods. For these types of neurons, the firing rate is certainly modulated by the immediate firing history of the neuron. Therefore, it is crucial to develop stochastic point-process models for which the random intensity of the counting process is a function of the immediate firing history of the neuron. One such model is discussed below.

The second issue, which is clear from the discussion in Section 3.2, is to develop advanced methods of estimation of the cross-correlation surface, $\rho_{AB}(s,t)$, $s,t \in [0,T]$, of two neurons A and B which are observed over a time interval, say, $[0,T]$. The goal of these advanced estimation methods is to develop powerful statistical tests of the cross-correlation surfaces. More specifically, for successful and efficient use of the technique of cross-correlation surfaces in studies of the temporal correlated
behavior of simultaneously recorded spike trains of two or more neurons, it is necessary to study a large number of cross-correlation surfaces and derive systematic findings concerning the pattern of correlation between cells in a certain neuronal network. A crude way of accomplishing this objective is the visual inspection by the experimenter of a great number of cross-correlation surfaces, a method which requires an easily recognizable way of determining visually and quickly the statistically significant portions of the cross-correlation surfaces. These statistically significant portions may then be plotted in a specific color which differs from the color of the statistically insignificant parts for ease of identification.

It is necessary, then, to construct confidence regions in the three dimensional space of the cross-correlation surface. To that end, the asymptotic statistical properties of the statistic

$$\max_{(\ell,k)} \sqrt{m} (\hat{\rho}_{AB}(m,\ell,k) - \rho_{AB}(\ell,k))$$

such as its asymptotic distribution need to be derived and hence used in establishing the confidence regions.

A stochastic counting process with linear intensity. A class of stochastic point-processes with linear intensity which includes the class of doubly stochastic point-processes is briefly considered. This provides a more general class of processes, which may more adequately represent spike trains of neurons of high firing rates. As in Section 1.2, let $T_1, T_2, \ldots, T_n$ be the moments of occurrence of action potentials recorded extracellularly
from an observed neuron. Let \( N(t) \) be the number of spikes recorded in the interval \((0,t]\). \( N(t) \), \( t \in [0,T] \) is a counting process which is defined on a probability space \((\Omega,F,P)\). Let \( \{H_t\}, t \in [0,T] \) be a history, i.e. a family of non-decreasing \( \sigma \)-fields which are contained in \( F \).

Recall that the internal history of a counting process \( N(t) \) is defined by \( F^N_t = \sigma\{N(s), 0 \leq s \leq t\} \). A family \( \{F_t\} \) of \( \sigma \)-fields is said to be a history of \( N(t) \) for every \( t \), \( F_t \) contains \( F^N_t \).

Now assume that \( N(t) \) satisfies the following conditions:

\[
(3.9) \quad P\{N(t + \Delta t) - N(t) - 1|H_t\} = \lambda(t|H_t) \Delta t + o(\Delta t)
\]

and

\[
(3.10) \quad P\{N(t + \Delta t) - N(t) \geq 2|H_t\} = o(\Delta t).
\]

This implies that

\[
(3.11) \quad E\{N(t + \Delta t) - N(t)|H_t\} = \lambda(t|H_t) \Delta t + o(\Delta t).
\]

Furthermore, assume that \( H_t \) consists of the histories of \( N(t) \) and another process \( X(t) \), which is independent of \( N(t) \), and that the random intensity \( \lambda \) is modeled as a linear process by

\[
(3.12) \quad \lambda(t|H_t) = \mu + \int_0^t g(t - s) \, dN(s) + \int_0^t h(t - s) \, dX(s)
\]
where \( \{X_t\} \) may be either an observable point-process or a cumulative process

\[
X_t = \int_{0}^{t} x(s) \, ds
\]

for some stochastic process \( \{X(t)\} \). The integrals in 3.12 are stochastic integrals (see Elliott, 1982). Notice that when \( g(t) \equiv 0 \) holds, this means that the intensity \( \lambda(t) \) is independent of \( N(t) \) and depends only on the observable process \( X(t) \), that is, \( N(t) \) in this case is a doubly stochastic Poisson process. It is clear, then, that a counting process \( N(t) \) with \( \lambda(t|H_t) \) of the form (3.12) is more general than the familiar double stochastic Poisson process. We consider here this more general process and call it a counting process with linear intensity. Its appropriateness for representing the spike trains of neurons with high firing rates is obvious since in this model the intensity of firing at any moment of time \( t \), \( \lambda(t) \), is allowed to depend on the history of the counting process itself. That is, the recent firing history of the neuron affects the firing behavior of the neuron at present. This problem has been partially tackled by Ogata and Akaike (1982), where the authors present the functions \( g(t) \) and \( r(t) \) as finite order Laguerre type polynomials and hence reduce the task to considering the problem of maximum likelihood estimation of finite dimensional parameters.

**On estimating the cross-correlation surface.** Using the above general model of counting processes, the problem of estimation of cross-correlation surfaces of two counting processes with linear random intensities of the
form (3.12) is considered.

Assume that extracellular recordings of the simultaneously generated action potentials of two neurons, A and B, are observed and the associated counting processes are denoted by $N_A(t)$ and $N_B(t)$. Consider the three independent counting processes $N_1(t)$, $N_2(t)$, and $N_3(t)$ with linear random intensities $\lambda_i(t)$, where

\begin{equation}
\lambda_i(t) = \mu_i(t) + \int_0^t g_i(t - s) \, dN_i(s) + \int_0^t r_i(t - s) \, dX_i(t),
\end{equation}

$i=1,2,3$. Assume that $N_A$ and $N_B$ are such that

\begin{equation}
N_A(t) = N_1(t) + N_2(t)
\end{equation}

\begin{equation}
N_B(t) = N_1(t) + N_3(t).
\end{equation}

This representation of neuronal behavior is particularly appealing if one thinks of $N_1(t)$ as a result of the presence of a stimulus which may be driving the two cells. In the absence of the stimulus, one may assume that $N_A(t) = N_2(t)$ and $N_B(t) = N_3(t)$. That is, the stimulus increases the firing of the observed neurons and hence has an excitatory effect on them. In the absence of the stimulus, that is, when the neurons A and B are firing spontaneously, they are firing independently of each other.

Now assume that we have a bivariate counting process \{\(N_A(s), N_B(t)\), \(s,t \in [0,T]\)\} where $N_A$ and $N_B$ are univariate counting processes defined
by (3.14) and (3.15). Of great interest is the problem of estimating the cross-correlation surface of \( (N_A(t), N_B(t)) \) defined by

\[
\rho_{AB}(s,t) = \frac{\sigma_{AB}(s,t)}{\sigma_{AA}(s) \sigma_{BB}(t)}^{1/2}
\]

for \( 0 \leq s \leq t \leq T \), where

\[
\sigma_{AB}(s,t) = E[N_A(s)N_B(t)] - E[N_A(s)]E[N_B(t)]
\]

\[
\sigma_{AA}(t) = E[N_A(t)]^2 - (E[N_A(t)])^2
\]

\[
\sigma_{BB}(t) = E[N_B(t)]^2 - (E[N_B(t)])^2.
\]

The estimates should be derived in terms of the intensities \( \lambda_1, \lambda_2, \) and \( \lambda_3 \), which are defined by (3.13). Of course, further conditions may have to be imposed on the intensities \( \lambda_1, \lambda_2, \) and \( \lambda_3 \) in order to ensure their estimability and in turn the estimability of the cross-correlation surfaces. In addition to the above problems, the asymptotic properties of the estimator \( \hat{\rho}_{AB}(s,t) \) of the cross-correlation surface \( \rho_{AB}(s,t) \) such as consistency and asymptotic normality should be studied. More specifically, assume that \( m \) independent and identically distributed copies \( \{N_A^{(k)}(t), N_B^{(k)}(s); s, t \in [0, T], k=1,2,\ldots,m\} \) of counting processes representing simultaneously recorded spike trains of two neurons A and B are given. One needs to prove that the statistic

\[
(3.16) \quad \sqrt{m} (\hat{\rho}_{AB}^{(m)}(s,t) - \rho_{AB}(s,t))
\]
converges weakly to a Gaussian sheet \( N(0, \sigma^2_{s,t}) \). That is, one has a
two-dimensional continuous time stochastic process \( \{ \rho_{AB}(s, t), 0 \leq s, t \leq T \} \),
and in addition to the convergence of its finite dimensional distributions,
we will also need to study the "tightness" of such processes. Of
course, use should be made of the theory of martingales and semimartingales
with multidimensional parameters (see e.g. Wong and Zakai, 1974; Métivier, 1982).
3.4 Applications to Multicellular Recordings in Studies of Neuronal Plasticity

The techniques of cross-correlation and surface analysis to the study of synaptic plasticity in the cerebral cortical neuronal networks have applied to experimentally generated data. Cross-correlation surfaces were generated from simultaneously recorded spike trains of two cortical neurons in kittens whose cortical synaptic connections are in the process of being altered by either normal or abnormal visual experience. In the analysis, spike trains were modeled as stochastic point-processes with random intensity. Cross-correlation surfaces of simultaneously recorded spike trains were then generated in order to study and infer the existence and nature of change of connectivity (synaptic plasticity) in the visual cortex.

Figures 4 and 5 are the auto-correlation surfaces of two neurons which were observed simultaneously. Figure 4 indicates that cell no. 1 fired in a non-stationary fashion since the positive part of the auto-correlation surface is increasing during the time period of stimulus presentation. To be definite, though, about drawing such conclusions, we need to construct confidence regions to indicate clearly the statistically significant parts of the auto-correlation (as well as cross-correlation) surface. Advanced stochastic analysis techniques are needed, then, to deal with this important problem. These new methods have been discussed in Section 3.3. Figure 5 does not reveal any significantly positive parts in the auto-correlation surface of cell 2. This indicates that the cell is firing in a non-correlated way. In inspecting Figure 6, it is quite difficult to determine the nature of cross-correlation of simultaneous temporal firing patterns of cells 1 and 2. This clearly indicates that
the problem of constructing **tight** confidence regions of the estimates of the cross-correlation surface is an important aspect of cross-correlation analysis of non-stationary spike trains.

It should be emphasized, though, that the method of cross-correlation surfaces must be embedded in appropriate experimental designs in order to allow inferences of biological significance to be drawn. Application of these techniques to isolated fragments of data is likely to be a futile exercise.
References


STATIONARY (CONSTANT) DELAYED EXCITATION

FIGURE 1
NON-STATIONARY INCREASING EXCITATION SIMULATION
NON-STATIONARY DECREASING EXCITATION

A SIMULATION

FIGURE 3
FIGURE 4
Stochastic Models of Neural Networks Involved in Learning and Memory

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Stochastic models of some aspects of the electrical activity in the nervous system at both the cellular and multicellular levels are developed. In particular, models of the subthreshold behavior of the membrane potential of neurons are considered along with the problem of estimation of physiologically meaningful parameters of the developed models. Applications to data generated in experimental studies of plasticity in the nervous system are discussed. In addition, non-stationary point-process models of trains of
20. Action potentials are developed as well as measures of association such as cross-correlation surfaces of simultaneously recorded spike trains from two or more neurons. Applications of these methods to studies of connectivity and synaptic plasticity in small neural networks are explored.