STOCHASTIC MODELS AND ESTIMATION OF SUBTHRESHOLD NEURONAL ACTIVITY

by

Muhammad K. Habib[1] and Thomas M. McKenna[2]

Department of Biostatistics [1]

The University of North Carolina at Chapel Hill

Center for the Neurobiology of Learning and Memory [2]

University of California, Irvine

Institute of Statistics Mimeo Series No. 1498

January 1986

STOCHASTIC MODELS AND ESTIMATION OF SUBTHRESHOLD NEURONAL ACTIVITY

by

Muhammad K. Habib[1] and Thomas M. McKenna[2]

Department of Biostatistics[1]

The University of North Carolina at Chapel Hill

Center for the Neurobiology of Learning[2]

and Memory

University of California, Irvine

AMS 1980 Subject Classification: 60G55, 60K99, 62F99

KEY WORDS AND PHRASES: Diffusion process, learning, maximum likelihood, neural models, neurons, parameter estimation, synaptic plasticity.

Research supported by the Office of Naval Research Contract Number N00014-83-k-0387

ABSTRACT

The subthreshold somal transmembrane potential of a neuron is modeled as a diffusion process with constant parameters. These parameters reflect interesting neurophysiological properties such as the effective somal-membrane time constant, amplitudes of post-synaptic potentials, excess of excitation over inhibition, and variability of synaptic input. Estimators of these properties are explicitly stated and their properties are briefly discussed. These methods enable experimental neurophysiologists and psychologists to estimate these parameters using experimentally generated data under different laboratory and environmental conditions. These methods then offer means to study plasticity in the nervous system. As an example, applications to visual neuronal plasticity are considered.

1. INTRODUCTION.

Current knowledge of the cellular mechanisms underlying the discharge pattern of neurons is based primarily on two kinds of data: (1) the biophysics of excitable membranes (especially of invertebrate neurons (Connor and Stevens, 1971; Hille, 1984; Hodgkin and Huxley, 1952; and Jack et al., 1983) and (2) the physiology of synapses, obtained from electrophysiological recording of the cellular responses to the stimulation of a few synapses (Burke, Rudomin, 1977; Eccles, 1964; Mendell and Henneman, 1971). However, neurons in the central nervous system (CNS) of vertebrates exhibit discharge patterns which are random in nature. This is because these neurons receive a large number of synapses in the order of approximately 5,000 to 100,000 depending on the type of the neuron (Chan-Palay, et al., 1974; Cragg, 1967; Gelfon, 1963; Palkovits et al., 1972). The presynaptic afferents of many of these synapses may be active in the awake, behaving animal. Hence, the fluctuations in membrane potential in vivo reflects the activity of hundreds, or even thousands of synapses. Thus both the timing of the neuronal output, and the subthreshold events leading to action potential initiation are stochastic in nature.

One approach to analyzing the integration of synaptic activity has been to study the summation of synaptic potential elicited by stimulation of a few afferent fibers (Mendell and Hennman, 1971; Asanuma and Rosen, 1973). Recent studies utilizing such techniques have provided estimates of the number of synapses sufficient to elicit an action potential when

these synaptic potentials occur within a small time interval. While some specialized relay neurons will produce action potentials in response to trains of input in a single presynaptic afferent (Munoz-Martinez, 1975), most types of neurons require convergent input from a large number of synapses. For instance, in the case of dentate granule cells of the hippocampus approximately 400 coactive synapses are required to produce an action potential. This is estimated to be about 4% of the synapses on these neurons (McNaughton, et al., 1981). Estimates of the number of simultaneously active synapses required to discharge pyramidal neurons in sensory cortex have been estimated to as high as several hundred (Martin, 1984). On the other hand several investigators have estimated that approximately 30 coactive synapses would be sufficient for a neuron's membrane potential to reach threshold for some types of cortical neurons. Based on cross-correlation analysis of spike trains of lateral geniculate neurons converging on visual cortical cells, Tanaka (1983) estimated that about 30 geniculate cells contact one complex cell. Abeles (1982) calculated that 29 simultaneous excitatory post-synaptic potentials (EPSPs) are sufficient for a neuron to reach threshold. However, his calculations do not take into account the non-linear summation of PSPs (McNaughton, et al., 1981). Shaw, Harth and Scheibel (1982) have presented anatomical, physiological and theoretical evidence for cortical neurons functioning in assembles of approximately 30 neurons.

While it may be the case that simultaneous activation of a relatively small fraction of the synapses on some central neurons may be sufficient

to evoke action potentials, analyzing the synaptic actions of a few isolated inputs cannot address the broader question of how information from multiple inputs is processed in neurons networks which receive continuous "background" or "spontaneous" activity.

An alternative approach is to treat the subthreshold membrane fluctations as a stochastic process resulting from the activity of a large number of excitatory and inhibitory synapses arriving at random times with a specified mean rate. Such a model can be based on one of two simplifying assumptions: (1) the post-synaptic potentials (PSPs) have small amplitudes and occur at a high rate (rate of presynaptic activity X number of synapses), or (2) the PSP's have a large amplitude relative to the threshold level of depolarization and occur at times described by a point process.

The first assumption describes the situation where synaptic activity arrives as sites elecrotonically remote from the neurons initial segment (the site of lowest threshold). In awake behaving animals this model is appropriate for describing the spontaneous activity of cortical neurons receiving tonic activity on distal dendrites. This model is a diffusion model. The second assumption describes the more proximally located synapses which contribute larger PSP's. In sensory cortical neurons, presentation of effective stimuli produce increases in the rate of these large PSPs, and for the most effective stimuli these PSPs sum to produce sustained depolarizations or hyper-polarizations. Estimates of the number of thalamic neurons whose conjoint activity is sufficient to drive sensory cortical neurons during presentation of effective sensory stimuli range from 10 to 30. In this case the

second model, termed the discontinuous stochastic model, is a linear combination of stochastic point processes. This model is appropriate for describing sensory neurons receiving synaptic input evoked by effective sensory stimuli.

However, sensory events always occur within the context of the internal state of the nervous system, that is, neurons receive both tonic and phasic stochastic synaptic inputs. Moreover, examination of intracellular records of cortical neruons in awake animals reveals both a low amplitude "white noise" component, and discrete PSPs. Hence we are led to postulate a mixed model with membrane potential fluctuations being described as a sum of both tonic, white noise synaptic input, and large discontinuous PSPs inputs.

Previous analyses of these two modeling approaches have not treated such a mixed model. These studies have been concerned with the problem of deriving closed form solutions of the probability density function of the first passage times of such stochastic models in terms of the model's parameters. Other studies are concerned with describing the relation between the moments of the first passage time, or with establishing the conditions under which the discontinuous model converges to the diffusion model. Since the probability density function of the first passage time has not been explicitely obtained, for most interesting cases, interest in the stochastic approximations has waned among neural modelers. Furthermore, previous investigations failed to provide experimental neurobiologists with techniques for making inferences concerning the mechanisms underlying stochastic neuronal discharges based on the statistics of extracellularly recorded spike times.

On the other hand, since it is feasable to record intracellularly from many types of neurons and to digitize the continuous records of membrane potential fluctuations due to synaptic inputs, it is demonstrated here that such inference maybe based on models of intracellular records of the subthreshold membrane potential. These models contain parameters which reflect the influence of synaptic inputs. Therefore, maximum likelihood extimates of the synaptic parameters as functions of discrete samples of the subthreshold membrane potential are derived. The results will permit estimates to be made of the following neuronal parameters: (a) balance of excitatory and inhibitory synaptic inputs during spontaneous or stimulus driven activity, (b) effective membrane time constant, (c) variance of membrane potential fluctuations, (d) amplitude of tonic white noise input contributed by remote synapses, and (e) amplitude and rate of large PSP's elicited by effective stimuli.

In section 2, a temporal neuronal model is developed where the membrane potential is expressed interms of the amplitudes and rates of occurrence of post-synaptic potentials. It is also argued that the membrane potential may be modeled as a diffusion process. In section 3, estimates of the parameters contained in such models are explicitly given and determination of there values using experimentally generated data is discussed. More general models are developed in section 4, where important neurophysiological properties such as reversal potential and the spatial aspects of synaptic input are taken into consideration.

Finally, in section 5, applications of these methods to studies of visual plasticity and inparticular of the development of orientation specificity are considered.

2. TEMPORAL NEURONAL MODELS

In this section the membrane potential of a model neuron is expressed in terms of the amplitudes and rates of occurrence of PSPs. It is also assumed that in the absence of synaptic activity, the membrane potential decays exponentially. For this reason, this neuronal model is known as the leaky integrator. The membrane potential in this case is modeled as a stationary Markov process with discontinuous sample paths (see e.g. Karlin and Taylor (1975) for a definition of Markov processes and related material). The discontinuities of this process occur at the moments of arrival of the PSPs. This model may contain a large number of parameters (in the order of hundreds or even thousands) which create serious identfication problems and may in turn be inappropriate for parameter identification purposes. Under the appropriate conditions, i.e. if the amplitudes of the PSPs are assumed to be very small and their rates of occurrence are 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 with constant coefficients which is driven by a Wiener process. This model is particularly appropriate for describing the subthreshold behavior of the membrane potential of spontaneously active neurons or neurons which receive extensive synaptic input with small PSP amplitudes occurring at high rate and with no dominating PSPs with relatively large amplitudes.

The state of the neuron is assumed to be characterized by the difference in potential across its membrane at a spatially restricted area connected to the soma called the initial

segment for trigger zone. In this area the membrane contains a higher concentration of voltage-dependent sodium and potassium channels, per unit area, than the remaining somal membrane. Hence this region exhibits the lowest threshold voltage level for action potential initiation.

The membrane potential, $V(t)$, at any point in time t is a random variable defined on a probability space (Ω,F,P). The membrane potential is subject to instantaneous changes due to the occurrence of post-synaptic potentials (PSP) of two different types: excitatory post-synaptic potentials (EPSP) which occur according to mutually independent Poisson processes $P(\lambda_k^e;t)$ with rates λ_k^e $(k=1,2,\ldots,n_1)$, each accompanied by an instantaneous displacement of $V(t)$ by a constant amount $\alpha_k^e > (k=1,2,\ldots,n_1)$; and inhibitory post-synaptic potentials (IPSP) which occur according to independent Poisson processes $P(\alpha_k^i;t)$ with amplitudes $\alpha_k^i > 0$ $(k=12,\ldots,n_2)$. Between PSPs, $V(t)$ decays exponentially to a resting potential with time constant ρ^{-1}. The PSPs sum linearly at the trigger zone, and when $V(t)$ reaches a certain (constant) level S, called the neuron's threshold, an action potential (spike) takes place. Following the action potential, $V(t)$ is reset to the resting potential with a time constant ρ^{-1}. Based on this physical model and considering n_1 excitatory synapses and n_2 inhibitory ones, the membrane potential $V(t)$, is modeled as a solution of the stochastic differential equation

$$(2.1) \qquad dV(t) = -\rho V(t)dt + \sum_{k=1}^{n_1} \alpha_k^e \, dP(\lambda_k^e;t) - \sum_{k=1}^{n_2} \alpha_k^i \, dP(\lambda_k^i;t),$$

$V(0) = V_0$. The solution of (2.1) is a homogeneous Markov process with discontinuous sample paths. Diffusion models in which the discontinuities of V(t) are smoothed out, have been sought as approximations to the discontinuous model (2.1) (see Ricciardi and Sacerdote 1979). These approximations are justified on the grounds that for many types of neurons in the central nervous system, synapses are densely packed along the dentritic tree. For example, there exists on the order of 20,000 synapses on the surface of a typical motorneuron. As a result of this extensive input, if the jumps of V(t) are small and the rates of occurrence of the post-synaptic potentials are very large, then the approximation to a diffusion model is approximate and is accomplished by allowing the amplitudes α^e, α^i to become small and the frequencies λ^e,λ^i to become large in a certain manner. The accuracy of the diffusion approximation (and its use in studies of interspike interval calculations) is discussed by Tuckwell and Cope (1980). From a practical point of view, the diffusion model is of greater utility to experimentalists who are not interested in the individual characteristics and the functional impact of individual synapses on the surface of the neuron, but rather in the collective behavior of these synapses. It should be noted, though, that diffusion models are inappropriate for describing the membrane potential which exhibits frequent ESPSs with large amplitudes. These require more complicated models, namely, mixed models which are driven by Wiener as well as point processes. These are called Itô-Markov processes. A model of this type is developed in Section 4.

Kallianpur (1983) established the diffusion approximation using the functional central limit theorem of Liptser and Shiryayev ((1980, 1981). Under some regularity conditions it was shown that the model (2.1) can be approximated by the diffusion model

$$(2.2) \qquad dV(t) = (-\rho V(t) + \mu)\, dt + \sigma\, dW(t),\ 0 \leq t \leq T,$$

$V(0) = V_0$, where W is the 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, with mean zero and variance $t_1,\ t_2-t_1,\ldots,t_n-t_{n-1}$, respectively. As it has been discussed above, this model is appropriate for neurons with extensive synaptic input where the rate of arrival of PSPs is very large and the amplitudes of the PSPs are very small relative to the difference between the neuron's resting potential and its threshold. Furthermore, it is assumed that there are no dominant PSPs with large amplitudes. This model is in particular suited to studies of the spontaneous activity of neurons.

It should be noted that models similar to (2.1) have been proposed and extensively studied in the literature with very little if any impact on experimental neurophysiology. This is in part due to the fact that these models have been presented as descriptive models and used mainly for simulation studies. Estimation of the parameters of the model from real data is then considered in the next section.

3. 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 ρ and μ of the stationary diffusion neuronal model (2.2) are explicitly derived. Statistical inference for the more involved models (4.1) - (4.3) is a more delicate matter and will be considered in future work. In order to address the problem of parameter estimation at hand, the problems of likelihood function and 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 during the inter-spike interval. 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. 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 neural diffusion model:

$$(3.1) \qquad dV(t) = (-\rho V(t) + \mu)\, dt + \sigma\, dW(t), \quad 0 \leq t \leq T,$$

$V(0) = V_0$. The statistical problem at hand is to estimate the parameters ρ and μ based on the observation of n independent trajectories $\{V_k(t),\ \tau_{k-1} < t \leq \tau_k\}$, $k=1,2,\ldots,n$. From Sørensen (1983) the log-likelihood function is given by

$$(3.2) \qquad L_n(\rho,\mu) = \sum_{k=1}^{n} \{\int_{\tau_{k-1}}^{\tau_k} (-\rho V_k(t) + \mu)\, dV_k(t) - 1/2 \int_{\tau_{k-1}}^{\tau_k} (-\rho V_k(t) + \mu)^2\, dt\}.$$

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

(3.3)

$$\hat{\rho}_n = \frac{[\sum_{k=1}^{n} (\tau_k - \tau_{k-1})][\sum_{k=1}^{n} \int_{\tau_{k-1}}^{\tau_k} V_k(t)dV_k(t)] - [\sum_{k=1}^{n} \int_{\tau_{k-1}}^{\tau_k} V_k(t)dt][\sum_{k=1}^{n} \int_{\tau_{k-1}}^{\tau_k} dV_k(t)]}{[\sum_{k=1}^{n} \int_{\tau_{k-1}}^{\tau_k} V_k(t)dt]^2 - [\sum_{k=1}^{n} (\tau_k - \tau_{k-1})][\sum_{k=1}^{n} \int_{\tau_{k-1}}^{\tau_k} V_k^2(t)dt]},$$

and

(3.4)

$$\hat{\mu}_n = \frac{[\sum_{k=1}^{n} \int_{\tau_{k-1}}^{\tau_k} V_k^2(t)dt][\sum_{k=1}^{n} \int_{\tau_{k-1}}^{\tau_k} dV_k(t)] - [\sum_{k=1}^{n} \int_{\tau_{k-1}}^{\tau_k} V_k(t)dV_k(t)][\sum_{k=1}^{n} \int_{\tau_{k-1}}^{\tau_k} V_k(t)dt]}{[\sum_{k=1}^{n} (\tau_k - \tau_{k-1})][\sum_{k=1}^{n} \int_{\tau_{k-1}}^{\tau_k} V_k^2(t)dt] - [\sum_{k=1}^{n} \int_{\tau_{k-1}}^{\tau_k} V_k(t)dt]^2}.$$

Using the fact that the membrane potential $V(t)$ is observed continuously over random intervals, the diffusion coefficient σ^2 may be calculated from an observed trajectory $V_k(k=1,2,\ldots,n)$ by the formula

$$(3.5) \quad \sigma^2(k) = \frac{1}{d_k} \lim_{m_k \to \infty} \sum_{j=1}^{2^{m_k}} [V_k(\tau_{k-1}+jd_k2^{-m_k}) - V_k(\tau_{k-1}+(j-1)d_k2^{-m_k})]^2,$$

Where $d_k = \tau_k - \tau_{k-1}$. This result may be proved using the corresponding result of Lévy for Brownian motion by transforming V_k via time substitutions into Brownian motion (or Wiener process). A natural estimate of σ^2 which employes all the observed trajectories is given by

$$(3.6) \qquad \hat{\sigma}_n^2 = \frac{1}{n} \sum_{k=1}^{n} \sigma^2(k)$$

By sampling the trajectories $\{V_k(t),\ \tau_{k-1} \leq t \leq \tau_k\}$ $k=1,2,\ldots,n$, one obtains $\{V_{t_{k,1}}, V_{t_{k,2}}, \ldots, V_{t_{k,m_k}}\}$ where $\tau_{k-1} \leq t_{k,1} < \ldots < \tau_{k,m_k} \leq \tau_k$, for $k=1,2,\ldots,n$. In this case the integrals in (3.3) and (3.4) may be replaced by sums.

At this point, it is natural to ask whether the new estimators, $\hat{\rho}_{n,N}$ and $\hat{\mu}_{n,N}$ are asymptotocially equivalent to the MLEs $\hat{\rho}$ and $\hat{\mu}$ i.e. as the sampling becomes more dense. The answer to this question is affirmative. Le Breton (1976) showed that $\hat{\rho}_{n,N} - \hat{\rho}_n \to \infty$ and $\hat{\mu}_{n,N} - \hat{\mu}_n \to 0$ as $N \to \infty$ 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, during and after animals acquire associative learning in order to measure the impact of this form of learning on the effective membrane time constant, the drift parameter which reflects of 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 analysis of parameters of neuronal mechanisms has not been previously examined during learning.

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

THEOREM 2.1

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

Results concerning the asymptotic distributions of $\hat{\rho}_n$ and $\hat{\mu}_n$ have also been established in Habib (1985).

Notice that the integrals in (3.3) and (3.4) are Itô-type stochastic integrals where, for instance, $\int_{\tau_{k-1}}^{\tau_k} V_k(t)\, dV_k(t)$ 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,...,n; $0 = \tau_0 = t_{11} < t_{12} < \ldots < t_{1,m_1+1} \leq \tau_1 \leq t_{21} < \ldots < t_{n,m+1} \leq \tau_n$, and let $\sum_{k=1}^{n} m_k = N$. Replacing the integrals with the appropriate sum, (3.3) and (3.4) 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

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

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

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

$$D_{n,N}(V,\tau) = \Big[\sum_{k=1}^{n} (\tau_k - \tau_{k-1})\Big]\Big[\sum_{k=1}^{n}\sum_{j=1}^{m_k} V_k^2(t_{kj})(t_{k,j+1} - t_{kj})\Big]$$

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

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

Close inspection of intracellular records of the subthreshold trajectories of membrane potential clearly reveal that the drift parameter in model (2.2) may be a function of t rather than a constant. Furthermore, replacing the rate of decay of the membrane p in (2.2) by a function of time t may compensate for considering only temporal aspects of synaptic input and ignoring their spatial properties. For these reasons the following extended model may prove to be more adequate in describing the subthreshold membrane potential of a certian type of neurons.

$$(3.7) \qquad dX(t) = (\rho(t)\, X(t) + \mu(t))dt + \sigma dW(t),\ 0 \leq t \leq T.$$

The problem of parameters estimation of such model is treated in Habib and McKeague (1985). The next section contains further extensions of the models discussed above.

4. MORE GENERAL NEURONAL MODELS.

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 large PSPs produced violate the assumption of 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 amplitudes 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 $N(\lambda_k^e(t),t)$ with random intensities $\lambda_k^e(t)$, and EPSP amplitudes α_k^e, $k=1,2,\ldots,n_1$. In addition, IPSPs are arriving according to the independent processes $N(\lambda_k^i(t),t)$, with the corresponding parameters $\lambda_k^i(t)$ and α_k^i, $k=1,2,\ldots,n_2$. We propose the following extended mixed model to describe the membrane potential of a stimulus driven neuron:

$$(4.1)\qquad dV(t) = (-\rho V(t) + \mu)\,dt + \sigma\,dW(t) + \sum_{k=1}^{n_1} \alpha_k^e\, dN(\lambda_k^e(t),t) - \sum_{k=1}^{n_2} \alpha_k^i\, dN(\lambda_k^i(t),t).$$

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 only 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. 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 $\alpha^e(\alpha^i)$ 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 (4.1) 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 (4.1) is then extended to taked the form

$$
\begin{aligned}
(4.2) \qquad dV(t) = (-\rho V(t) + \mu)\, dt + \sigma\, dW(t) \\
+ \sum_{n=1}^{n_1} \alpha_n^e [V_n^e - V(t)]\, dN(\lambda_n^e(t), t) \\
- \sum_{k=1}^{n_2} \alpha_k^i [V_k^i - V(t)]\, dN(\lambda_k^i(t), t),
\end{aligned}
$$

where it is assumed that the neuron has excitatory synapses which, when activated, result in displacing $V(t)$ toward the the reversal potential V_m^e $(m=1,2,\ldots,n_1)$, and inhibitory synapses, which when activated, result in displacing $V(t)$ away from the reversal potential $V_k^i (k=1,2,\ldots,n_2)$.

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 dentritic 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 dentritic tree. 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.

Spatial Synaptic Distribution. 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 a 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

$$(4.3)\quad dV(t,x) = (-\rho V(t,x) + (\partial^2/\partial x^2)V(t,x) + \mu)\,dt + \sigma\,dW(t,x)$$

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

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

where δ is the delta distribution (or generalized function, and $x_j^e(x_k^i)$ is the location of the excitatory (inhibitory) synaptic inputs which occur according to independent point-processes with rates $\lambda_j^e(\lambda_k^i)$ and amplitudes of $\alpha_j^e(\alpha_k^i)$, $j=1,2,\ldots,n_1$; $k=1,2,\ldots,n_2$. 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 (4.3). 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 Örnstein-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).

5. APPLICATIONS TO VISUAL NERONAL PLASTICITY

In the preceding analysis, the nature of the source of synaptic inputs was not considered. Neurons in sensory systems are connnected so as to form orderly arrays. Because of these highly specific connections, which map onto peripheral sensory sheets, the neurons exhibit "receptive fields". The receptive field of a neuron is the locus of points in the source periphery (visual field, skin, etc) which when sitmulated produce a detectable and reliable change in the discharge rate of that neuron. One of the properties of the receptive fields of visual cortical neurons is that many of them respond preferentially to a bar with a particular orientation swept accross their visual receptive field. In this section it is shown how the mixed model (4.1) can be applied to analyze the development and plasticity of "orientation specificity".

Higher neural centers and networks involved in visual information processing, especially visual cortex, exhibit remarkable plasticity in the formation of synaptic connections, most notably during a "critical period" early in life (occurring in kittens reared in a normal environment between the ages of 4-12 weeks, see Fregnac, Impert, 1984 for a review). Hubel and Weisel (1963), Pettigrew (1974) and Blakemore and Van Sluyters (1975) found that many cortical cells in newborn animals also responded best to a stimulus having specific axes of orientation. During the critical period, however, their properties are developed further and, for example, orientations selectivity is enhanced. It is plausible, then, to assume that during the ciritcal period, the potency of

excitatory synapses connnecting the post-synaptic neuron of interest to the pre-sysnaptic neurons which are most responsive to the optimal orientation is enhanced. On the other hand, according to Sillito (1979, 1980) orientation selectivity is abolished if intracortical inhibition is blocked, showing that intracortical circuits are important and that excitatory afferent organization is not sufficient to account for orientation selectivity. Based on these studies, we propose here that in addition to the enhancement of the potency of the excitatory synapses connecting the post-synaptic neuron to pre-synaptic neurons which respond maximally to the preferred direction, the efficacy of the inhibitory synapses connecting the post synaptic neuron to pre-synaptic neurons which respond maximally to orientations other than the preferred one is also enhanced. Our model is based on the following assumptions:

Let s be a parameter representing time within the critical period, or the period of the acquisition of learning. For simplicity, we will assume that there are only (2L + 1) effective orientations to which the post-synaptic neuron responds at the beginning of a ciritical period. The neuron responds preferably though sluggishly to a certian orientation (which is thought of as the innately preferred orientation) and arbitrarily call this preferred orientation the zero orientation. Assume also that the neuron responds to a lesser extent to 2L other orientations on either side of the preferred one. For simplicity, assume also that the cell excitatory inputs activated maximally by a specific orientation are idealized by one excitatory modifiable synapse. Assume that these idealized inputs arrive according to independent Poisson processes

$P(\lambda_k^s,t)$ and modifiable synaptic weights or amplitudes E_k^s, $k=0, \pm1, \pm2,\ldots,\pm L$. The neuron also receives inhibitory inputs through idealized modifiable synapses activated maximally by orientations <u>other than</u> the zero orientation. These inhibitory inputs arrive according to independent Poisson processes $P(\nu_k^s,t)$ and modifiable synaptic amplitudes I_k^s, $k=\pm1, \pm2, \ldots,\pm L$.

Based on these assumptions, the membrane potential $V_s(t)$ may be modeled as the unique solution of the Itô-type stochastic differential equation

(5.1)

$$dV_s(t) = -\rho_s V_s(t)dt + \sum_{k=-L}^{L} E_k^s(dP(\lambda^s,t) - \sum_{0\neq k=-L}^{L} I_k^s\, dP(\nu_k^s,t) + \mu_s dt + \sigma_s\, dW(t)$$

where μ_s and σ_s are parameters depending only on s, and W is a standard Wiener process. However, since it is technically difficult to record intracellularly from a neuron on a continuous basis during the acquisition of learning, the continuous time parameter s in model (5.1) is replaced with a discrete time parameter n (measured in hours or days or even weeks). Model (5.1) in this case takes the form

(5.2)

$$dV_n(t) = -\rho_n V_n(t)dt + \sum_{k=-L}^{L} E_k^n\, dP(\lambda_k^n,t) - \sum_{0\neq k=-L}^{L} I_k^n\, dP(\nu_k^n,t) - \mu_n dt + \sigma_n\, dW(t)$$

Hence, using intracellular recordings from several neurons of experimental subjects of several ages n=1,2,...,N (say), we can estimate the parameters

ρ_n, E_k^n, λ_k^n, I_k^n, ν_k^n, μ_n and σ_n, $k=0, \pm,\ldots,\pm L$. From the estimates of the synaptic weights at different time points during the critical period, one can then reconstruct the sequence of changes in synaptic efficency during this period.

SUMMARY

Stochastic models are developed to describe the subthreshold activity of the membrane potential of a model neuron. Only temporal aspects of synaptic input are taken into consideration. The models developed here contain parameters which reflect important physiological properties such as effective somal-membrane time constant, potency or amplitudes of post-synaptic potentials (PSPs), and variability of synaptic input. Estimators of these parameters are explicitaly stated and their properties are briefly discussed. These methods enable neurophysiologists to estimate physiologically interesting parameters using experimentally generated data. This should allow drawing inference concerning the way the parameters may change in response to different experimental conditions or to experience in general. Applications of these methods to studies of visual neuronal plasticity are included as a concrete example.

REFERENCES

M. Abeles, Local Cortical Circuits, Springer-Verlag, New York, 1982.

H. Asanuma and I. Rosen, Spread of mono- and polysynaptic connections within cat's motor cortex, Exp. Brain Res. 16:507-520 (1973).

I. V. Basawa and B. L. S. Prakasa Rao, Statistical Inference for Stochastic Processes, Academic Press, New York, 1980.

C. Blakemore and R. C. Van Sluyters, Innate and environmental factors in the development of the kitten's visual cortex, J. Physiology, London, 248:663-716 (1975).

R. E. Burke, and P Rudomin, Spinal neurons and synapses. In: Handbook of Physiology. Section 1, Vol. 1, Cellular Biology of Neurons, E. C. Kandel, ed., American Physiological Society, Bethesda, Maryland, 1977, pp. 877-944.

V. Chan-Palay, S. L. Palay and S. M. Billings-Gagliardi, Meynert cells in the primate visual cortex, J. Neurocytol. 3:631-658 (1974).

J. A. Connor and C. F. Stevens, Prediction of repetitive firing behavior from voltage clamp data on an isolated neurone soma, J. Physiol., London, 213:31-53 (1971).

B. G. Cragg, The density of synapses and neurons in the motor and visual cortical areas of the cerebral cortex, J. Anatomy 101:639-654 (1967).

J. C. Eccles, The Physiology of Synapses, Academic Press, New York, 1964.

L. Favella et al., First passage time problems and related computational methods, Cybernetics and Systems. 13:95-178 (1982).

R. D. Fernald, A neuron model with spatially distributed synaptic input, Biophys. 11:323-340 (1971).

Y. Fregnac and M. Imbert, Development of neuronal selectivity in primary visual cortex of cat, Physiological Reviews 64:325-434 (1984).

S. Gelfan, Neurone and synapse populations in spinal cord: indication of role in total integration, Nature 198:162-163 (1963).

M. K. Habib, Parameter estimation for randomly stopped diffusion processes and neuronal modeling. Institute of Statistics. Department of Biostatistics. The University of North Carolina at Chapel Hill. Mimeo Series Number 1492.

M. K. Habib and I. W. McKeague, Parameter estimation in randomly stopped non-stationary diffusion neuronal models. In preparation.

M. K. Habib and P. K. Sen, Non-stationary stochastic point-process models in neurophysiology with applications to learning. Biostatistics - Statistics in Biomedical, Public Health and Environmental Sciences, The Brenard G. Greenberg Volume, P. K. Sen, ed., North Holland, Amsterdam, 1985, pp. 481-509.

B. Hille, Ionic Channels of Excitable Membranes, Sinauer Associates Sunderland, Massachusetts, 1984.

A. L. Hodgkin and A. F. Huxley, A quantitative description of membrane current and its application to conduction and excitation in nerve, J. Physiol., London 117:500-544 (1952).

D. H. Hubel and T. N. Wiesel, Receptive fields of cells in striate cortex of very young, visually inexperienced kittens, J. Neurophysiology 26:994-1002 (1963).

N. Ikeda and S. Watanabe, Stochastic Differential Equations and Diffusion Processes, North Holland/Kodansha, New York, 1981.

J. J. B. Jack, D. Noble and R. W. Tsien, Electric Current Flow in Excitable Cells, Oxford University Press, Oxford, 1983.

J. J. B. Jack, S. J. Redman and K. Wong, The components of synaptic potentials evoked in cat spinal motoneurones by impluses in single group 1a afferents, J. Physiol., London 321:65-96 (1981).

G. Kallianpur, On the diffusion approximation to a discontinuous model for a single neuron, Contributions to Statistics: Essays in Honor of Norman L. Johnson, P. K. Sen ed., North Holland, Amsterdam, 1983.

G. Kallianpur and R. Wolpert, Infinite dimensional stochastic differential equation models for spatially distributed neurons, Appl. Math. Optimizat. 12:125-172, (1984a).

G. Kallianpur and R. Wolpert, Weak convergence of solutions of stochastic differential equations with applications to non-linear neuronal models. Center for Stochastic Processes, Department of Statistics, The University of North Carolina at Chapel Hill, Tech. Report #60, (1984b).

S. Karlin and H. Taylor, A First Course in Stochastic Processes, Academic Press, New York, 1975.

P. Lánský, Inference for the diffusion models of neuronal activity, Math. Bioscience 67:247-260 (1983).

A. Le Breton, On continuous and discrete sampling for parameter estimation in diffusion type processes, Math. Program. Study 5:124-144 (1976).

R. S. Liptser and A. N. Shiryayev, A functional central limit theorem for semi-martingales, Theor. Probab. Appl. XXV 4:683-703 (1980).

R. S. Liptser and A. N. Shiryayev. On necessary and sufficient conditions on a central limit theorem for semi-martingales, Theor. Prob. Appl. XXVI 1:132-137 (1981).

K. A. C. Martin, Neuronal circuits in cat striate cortex. In: Cerebral Cortex., E. G. Jones and A. Peters, ed., Plenum Press, New York, p. 241-284, 1984.

B. L. McNaughton, C. A. Barnes and P. Anderson, Synaptic efficacy and EPSP summation in granule cells of rat fascia dentata studied in vitro, J. Neurophysiol. 46:952-966 (1981).

L. M. Mendell and E. Henneman, Terminals of single Ia fibers: Location density, and distribution within a pool of 300 homonymous motoneurons, J. Neurophysiol. 34:171-187 (1971).

E. J. Munoz-Martinez, Effects of activity in single sensory fibres on the discharge patterns of dorsal spinocerebellar tract cells, J. Physiol., London 245:1-12 (1975).

M. Palkovits, P. Magyar and J. Szentagothai, Quantitiative histological analysis of the cerebellar cortex in the cat. IV. Mossy fiber-Purkinje cell numberical transfer, Brain Res. 45:15-29 (1972).

J. D. Pettigrew, The effect of visual experience on the development of stimulus specificity by kitten cortical neurons: effect on developing cortical neurons, J. Physiol., London 237:49-74 (1974).

W. Rall, Branching dentritic trees and monotomous membrane resistivity, Exptl. Neurol. 1:491-527 (1959).

W. Rall, Electrophysiology of a dentritic neuron model, Biophys. J. 2 2:145-157 (1962).

W. Rall, Theoretical significance of dentritic trees for neuronal input-output relations. In: Neural Theory and Modeling, R. Reiss, ed., Stanford University Press, Stanford, (1964) 73-97.

W. Rall, Core conductor theory and cable properties of neurons, Handbook of Physiology - The Nervous System I. Volume I, American Physiological Society, Bethesda, Maryland, 1978.

G. L. Shaw, E. Harth and A. B. Scheibel, Cooperativity in brain function: assemblies of approximately 30 neurons, Experimental Neurol. 77:324-358 (1982).

G. M. Shepard, The Synaptic Organization of the Brain, Oxford University Press, Oxford, 1979.

A. M. Sillito, Inhibitory mechanisms influencing complex cell orientation selectivity and their modification at high resting discharge levels, J. Physiol., London, 289:33-53 (1979).

A. M. Sillito, Orientation selectivity and the spatial organization of the afferent input to the striate cortex, Exp. Brain Res. 41:A9 (1980).

L. M. Sørensen, On maximum likelihood estimation in randomly stopped diffusion-type processes, Intern. Statist. Rev. 51:93-110 (1983).

K. Tanaka, Cross-correlation analysis of geniculostriate neuronal relationships in cats, J. Neurophysiol. 49:1303-1318 (1983).

N. Tsukahara, Brain Plasticity: The themes and case studies of neuro-biophysics, Adv. Biophys. 15:131-172 (1982).

H. C. Tuckwell and D. K. Cope, The accuracy of neuronal intespike calculated from a diffusion approximation, J. Theor. Biol. 83:377-387 (1980).

J. B. Walsh, A stochastic model of neural response, Adv. Appl. Prob. 12:231-281 (1981).

REPORT DOCUMENTATION PAGE

1a. REPORT SECURITY CLASSIFICATION UNCLASSIFIED	1b RESTRICTIVE MARKINGS
2a. SECURITY CLASSIFICATION AUTHORITY	3 DISTRIBUTION/AVAILABILITY OF REPORT UNLIMITED
2b. DECLASSIFICATION/DOWNGRADING SCHEDULE	
4. PERFORMING ORGANIZATION REPORT NUMBER(S)	5. MONITORING ORGANIZATION REPORT NUMBER(S)
6a. NAME OF PERFORMING ORGANIZATION The University of North Carolina Department of Biostatistics 6b OFFICE SYMBOL (If applicable)	7a. NAME OF MONITORING ORGANIZATION Statistics and Probability Program
6c ADDRESS (City, State, and ZIP Code) Chapel Hill, North Carolina 27514	7b ADDRESS (City, State, and ZIP Code) Office of Naval Research Arlington, VA 22217
8a. NAME OF FUNDING/SPONSORING ORGANIZATION Office of Naval Research 8b. OFFICE SYMBOL (If applicable)	9 PROCUREMENT INSTRUMENT IDENTIFICATION NUMBER N00014-83-0387
8c. ADDRESS (City, State, and ZIP Code) Arlington, VA 22217	10 SOURCE OF FUNDING NUMBERS PROGRAM ELEMENT NO. / PROJECT NO. / TASK NO. / WORK UNIT ACCESSION NO.

11 TITLE (Include Security Classification)
Stochastic Models and Estimation of Subthreshold Neuronal Activity (Unclassified)

12. PERSONAL AUTHOR(S)
Muhammad K. Habib and Thomas M. McKenna

13a. TYPE OF REPORT	13b. TIME COVERED	14 DATE OF REPORT (Year, Month, Day)	15 PAGE COUNT
Technical	FROM _____ TO _____	1986 January 8	30

16. SUPPLEMENTARY NOTATION

17. COSATI CODES			18 SUBJECT TERMS (Continue on reverse if necessary and identify by block number)
FIELD	GROUP	SUB-GROUP	

19 ABSTRACT (Continue on reverse if necessary and identify by block number)

The subthreshold somal transmembrane potential of a neuron is modeled as a diffusion process with constant parameters. These parameters reflect interesting neurophysiological properties such as the effective somal-membrane time constant, amplitudes of post-synaptic potentials, excess of excitation over inhibition, and variability of synaptic input. Estimators of these properties are explicitly stated and their properties are briefly discussed. These methods enable experimental neurophysiologists and psychologists to estimate these parameters using experimentally generated data under different laboratory and environmental conditions. These methods then offer means to study plasticity in the nervous system. As an example, applications to visual neuronal plasticity are considered.

20. DISTRIBUTION/AVAILABILITY OF ABSTRACT ☒ UNCLASSIFIED/UNLIMITED ☐ SAME AS RPT. ☐ DTIC USERS	21. ABSTRACT SECURITY CLASSIFICATION UNCLASSIFIED
22a NAME OF RESPONSIBLE INDIVIDUAL Muhammad K. Habib	22b TELEPHONE (Include Area Code) (919) 966-4887 / 22c. OFFICE SYMBOL