

**One - dimensional stochastic diffusion models
of neuronal activity and related first passage time problems.**

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ABSTRACT

This work is a survey of one-dimensional diffusion models for the membrane potential in a single neuron. While some biological modeling issues are discussed, the emphasis is on the probabilistic properties of the models and their corresponding first passage times. After the general methodology for diffusion processes and first passage time problems are reviewed, several specific processes are examined in more detail. The Wiener process and the Ornstein-Uhlenbeck process illustrate the variety of approaches available and some of the numerical procedures required. Several attempts to make the models more biologically realistic by using a nonconstant infinitesimal variance are outlined. Finally, some other model modifications are summarized.

1. INTRODUCTION

Stochastic models of neuronal activity are among the most advanced applications of the theory of stochastic processes in biology. Many of these neuronal models are based on the theory of diffusion processes. The reasons for this are several. The first one follows from the fact that the theory of stochastic diffusion processes is well developed and thus allows the neural modeler to apply many general results to this specific application area. The second reason is that, for neurons with many synaptic inputs, there is a relatively good correspondence between the models and the biology. Even when the assumptions underlying the model are not totally valid, the output behaviour of the neuron can often be well approximated by that of an appropriately chosen diffusion process. Finally, from a biophysical point of view, neuronal models of single cells reflect the electrical properties of the membrane via electric circuit models that contain energy storage elements. Such circuit models can be written in terms of a differential equation for the membrane voltage. When the inputs to the cell are random, then the differential equation has a "noisy" input and its solution can often be approximated by a diffusion process. In other cases, such as in neurons with one or a few synaptic inputs near the trigger zone, a Poisson driven differential equation may be a biologically more appropriate model (see Tuckwell, 1988, 1989 for a review). An action potential (spike) is produced when the membrane voltage exceeds a voltage threshold and corresponds to the first passage time for the associated diffusion process (for a more detailed biological description see, e.g., Schmidt, 1978; Kandel and Schwartz, 1985).

The aim of this contribution is to review the results from the theory of one - dimensional stochastic diffusion models of the membrane potential of a single neuron. Several

reviews on stochastic neuronal models are available (Fienberg, 1974; Holden, 1976; Sampath and Srinivasan, 1977; Yang and Chen, 1978; Lee, 1979; Tuckwell, 1988, 1989) and like these previous reviews we will be primarily concerned with mechanisms for the production of stationary spike trains. Said another way, we are modeling the spontaneous or resting activity of a neuron or the steady state response to a constant stimulus. Such an analysis is usually required before attempting to model the neuron's response to time varying stimuli. The emphasis of this review will be on the probabilistic properties of the models rather than on the biological motivation, statistical parameter estimation, or derivation of the models. The construction of the diffusion approximations examined here can be found in the above reviews or in a number of other papers concerning this topic (Gerstein and Mandelbrot, 1964; Gluss, 1967; Johannesma, 1968; Roy and Smith, 1969; Capocelli and Ricciardi, 1971; Ricciardi, 1976; Ricciardi and Sacerdote, 1979; Tuckwell and Cope, 1980; Hanson and Tuckwell, 1983; Kallianpur, 1983; Ricciardi et al., 1983, Lánský, 1984; Kallianpur and Wolpert, 1987; Lánský and Lánská, 1987; Giorno et al., 1988a). There are also many theoretically oriented monographs and reviews on stochastic diffusion processes containing results pertinent to neural modeling but not mentioning this specific application (e.g. Blake and Lindsey, 1973; Lindenberg et al., 1975; Karlin and Taylor, 1981; Gardiner, 1983; Abrahams, 1986). Finally, many results can be found in the monographs by Goel and Richter-Dyn (1974), and by Ricciardi (1977), where neuronal models serve as an example of primary importance. A natural extension of one dimensional neural models are multi- and infinite dimensional models, but are beyond the scope of the present review. For an overview of this topic see, e. g., Kallianpur and Wolpert (1987); Tuckwell (1988), (1989). At a more microscopic level, the biophysical properties of nerve membrane are based on the opening and closing of ionic channels. First passage time models are important here as well. The movement of an ion through a pore can be viewed as the random movement of a particle in a multistable potential well. For a recent review, see Cooper et al. (1988).

The scalar diffusion process $X = \{X(t); t \geq 0\}$ can be described by the stochastic differential equation

$$dX(t) = \mu(X(t),t) dt + \sigma(X(t),t) dW(t), \quad X(0) = x_0, \quad (1.1)$$

where $W = \{W(t); t \geq 0\}$ is a standard Wiener process and μ and σ are real-valued functions of their arguments satisfying certain regularity conditions (Karlin and Taylor, 1981). Here, the process X represents changes in the membrane potential between two consecutive neuronal

firings (spikes). The reference level for the membrane potential is usually taken to be the resting potential. The initial voltage (the reset value following a spike) is often assumed to be equal to the resting potential, $x_0 = 0$, i. e., there is no initial afterhyperpolarization.

The threshold potential denoted by $S = S(t)$ is commonly taken to be a deterministic time function. In studies on neuronal models, we are mainly interested in the properties of the random variable (r.v.) T_S , which is defined by the relationship

$$T_S = \inf \{t \geq 0; X(t) \geq S(t)\}, \quad (1.2)$$

where $S(0) > x_0$ is a constant. T_S is the theoretical counterpart of the interspike interval. The importance of interspike intervals follows as a consequence of the generally accepted hypothesis that the information transferred within the nervous system is usually encoded by the timing of spikes. Therefore the reciprocal relationship between the frequency on one hand and the interspike interval on the other leads to the study of the distribution of T_S . When the distribution is too difficult to obtain, the analysis is usually restricted to its moments, primarily the mean and the variance. The coefficient of variation is also widely used by both theoretical and experimental neurobiologists. It is one measure for the relative spread of the distribution and its deviation from exponentiality. Studying the properties of the r.v. T_S we solve the so called First Passage Time (FPT) problem. The simple relationship between T_S and the r.v. representing the maximum of X over a fixed time interval also permits us to use some results from the theory of extremes, for a recent review see Leadbetter and Rootzén (1988). For the remainder of the text we will denote the probability density function (p.d.f) of T_S by $g_S(t|x_0)$ and its n-th moment by $M_n(S|x_0)$.

An alternative description of X is either by the Fokker-Planck equation for the transition density, $f=f(x,t|x_0,t_0)$

$$\frac{\partial f}{\partial t} = - \frac{\partial}{\partial x} [\mu(x,t) f] + \frac{1}{2} \frac{\partial^2}{\partial x^2} [\sigma^2(x,t) f] \quad (1.3)$$

or the backward Kolmogorov equation

$$\frac{\partial f}{\partial t_0} = \mu(x_0,t_0) \frac{\partial f}{\partial x_0} + \frac{1}{2} \sigma^2(x_0,t_0) \frac{\partial^2 f}{\partial x_0^2} \quad (1.4)$$

with an initial condition $f(x,t_0|x_0,t_0) = \delta(x-x_0)$ and appropriate boundary conditions. For a

classification of boundary conditions see, e. g., Karlin and Taylor (1981).

The role of these two descriptions, (1.1) vs. (1.3) and (1.4), of the membrane potential X is now briefly outlined. As (1.1) describes the time evolution of the trajectories of the membrane potential, a discretized version of it can be obtained by a mesh of points t_i such that $t_0 < t_1 < \dots < t_n = t$. (1.1) can then be rewritten as

$$x(t_{i+1}) = x(t_i) + \mu(x(t_i), t_i) (t_{i+1} - t_i) + \sigma(x(t_i), t_i) (W(t_{i+1}) - W(t_i)) \quad (1.5)$$

An approximation procedure for solving (1.1) is to compute $x(t_{i+1})$ from the knowledge of $x(t_i)$ realizing that the increments of the standard Wiener process appearing in (1.5) are mutually independent, normally distributed r.v.'s with zero mean and variances $t_{i+1} - t_i$, independent of $x(t_i)$. More sophisticated methods for the simulation of (1.1) can be found in, e.g., Rümelin (1982), Pardoux and Talay (1985). In fact, for more complex diffusion models of neuronal activity simulation remains the most important tool. The second important role of (1.1) is in the application of the theory of parameter estimation for diffusion processes when the trajectories are measured directly. Finally, the form of (1.1) is easier to interpret physically than (1.3) and (1.4) and is a stochastic version of the generalized deterministic Lapique neuronal model in which the input signal is integrated up to the threshold crossing. Therefore for models specified by (1.1) the term "integrate and fire" is sometimes used.

The models met in applications of diffusion processes in neural modeling are predominantly time homogeneous and thus the functions μ and σ appearing in (1.1), (1.3) and (1.4) do not depend explicitly on t , i. e., $\mu(x, t) = \mu(x)$, $\sigma(x, t) = \sigma(x)$, and thus $f(x, t | x_0, t_0) = f(x, t - t_0 | x_0)$. Time non-homogeneous diffusion models have been mentioned by Matsuyama et al., (1974), Matsuyama, (1976), Ricciardi (1982), Lánský (1984). Since very few analytical results are available, simulation methods are required here.

In addition to assuming temporal homogeneity for X , we shall initially also assume that the threshold potential is constant, i.e., $S = \text{const}$. Results for non-constant threshold potentials, which model a relative refractory period, are considered later.

The Fokker-Planck equation (1.3) and the backward Kolmogorov equation (1.4) are second-order parabolic partial differential equations. To solve them we need an initial condition, for example like that given above, and boundary conditions at the ends of the interval on which X is constrained. The first boundary condition follows immediately from the requirement that the process is terminated when the membrane potential X reaches the

threshold potential S . Thus we impose here the absorbing boundary condition

$$f(S, t | x_0) = 0 \quad (1.6)$$

The other boundary conditions are specific to the different models and will be introduced as they are encountered. Three common techniques for solving (1.3) are: Laplace transform, eigenvalue expansion and direct numerical evaluation.

The functional or numerical solutions of the FPT problem are usually based on the analysis of the equations (1.3) or (1.4). The usefulness of the knowledge of the transition density for the FPT problem follows immediately from the relationship

$$g_S(t | x_0) = - \frac{\partial}{\partial t} \int_{\nu}^S f(x, t | x_0) dx, \quad (1.7)$$

where ν stands for lower boundary of the state space for the membrane potential (in the case of unrestricted state space we have $\nu = -\infty$).

The renewal equation for the unrestricted process X (without the absorption condition (1.6)) gives the following result for $x > S$

$$f(x, t | x_0) = \int_0^t f(x, t-s | S) g_S(s | x_0) ds. \quad (1.8)$$

Together with the backward Kolmogorov equation (1.4), (1.8) serves as the basis for the derivation of Siegert's equation for the Laplace transform $g_S(\lambda | x_0)$ of p.d.f. $g_S(t | x_0)$,

$$\mu(x_0) \frac{\partial g_S(\lambda | x_0)}{\partial x_0} + \frac{1}{2} \sigma^2(x_0) \frac{\partial^2 g_S(\lambda | x_0)}{\partial x_0^2} - \lambda g_S(\lambda | x_0) = 0 \quad (1.9)$$

with the initial condition given above and an additional condition $g_S(\lambda | x_0) < \infty$ for each $x_0 \in (\nu, S)$. From this equation and from the known relationship between the Laplace transform of the p.d.f. and its moments, a recursion relation is available for the moments of r.v. T_S ,

$$\mu(x_0) \frac{\partial M_n(S | x_0)}{\partial x_0} + \frac{1}{2} \sigma^2(x_0) \frac{\partial^2 M_n(S | x_0)}{\partial x_0^2} = -n M_{n-1}(S | x_0) \quad (1.10)$$

for $n = 1, \dots$, and $M_0(S|x_0) = 1$.

The assumption of a fixed initial condition in the models considered here represents an oversimplification which was noticed as early as 1964 by Stevens (1964) in his comments about the paper by Gerstein and Mandelbrot (1964). To avoid this simplification we can assume that the initial value of the membrane potential is a r.v. X_0 taking its values in the state space of X . Under the assumption that its p.d.f $w(x_0)$ exists, we may write the p.d.f of the FPT in the form of a randomized distribution with respect to the parameter x_0 , (e.g., Feller, 1966),

$$g_S(t) = \int_{\nu}^S g_S(t|x_0) w(x_0) dx_0. \quad (1.11)$$

While for a discrete distribution of the initial value, a mixture of the distributions $g_S(t|x_0)$ is obtained (Lánský and Smith, 1989).

2. WIENER PROCESS

The simplest diffusion neuronal model is the Wiener process with a positive drift and defined by the constant infinitesimal moments

$$\mu(x) = \mu > 0, \quad \sigma(x) = \sigma > 0 \quad (2.1)$$

with the state space $(-\infty, S)$. The boundary $-\infty$ is a natural one and hence

$$f(-\infty, t|x_0) = 0, \quad (2.2)$$

using this together with (1.6) we can solve (1.9) to obtain the p.d.f. of T_S

$$g_S(t|x_0) = \frac{S-x_0}{\sigma\sqrt{2\pi t^3}} \exp \left\{ -\frac{(S-x_0-\mu t)^2}{2\sigma^2 t} \right\}. \quad (2.3)$$

Several different names have been assigned to this distribution in the past, but the name inverse Gaussian distribution (IGD) is now commonly accepted (for a survey of its properties see Chhikara and Folks, 1989). The assumption made in (2.1) that $\mu > 0$ ensures that the

mean FPT is finite, however, the case with $\mu = 0$ is also of interest for neural modeling. The reason is that when $\mu = 0$, (2.3) is a stable law (Feller, 1966) and there have been several reports on preserving the shapes of histograms when the adjacent interspike intervals are summed (e.g., Rodieck et al., 1962; Gerstein and Mandelbrot, 1964; Holden, 1975). Several different parameterizations are available for p.d.f. (2.3). The most common one in the statistical literature uses the parameters

$$a = (S - x_0)/\mu \quad , \quad b = (S - x_0)^2/\sigma^2 \quad (2.4)$$

which turns (2.3) into

$$g_S(t|x_0) = \sqrt{\frac{b}{2\pi t^3}} \exp \left\{ -\frac{b(t-a)^2}{2a^2 t} \right\} . \quad (2.5)$$

We now give some of the basic characteristics of (2.3). The moment generating function, defined for a r.v. Y as $h(\theta) = E(\exp(\theta Y))$ provided it exists, corresponding to (2.3) is

$$h_S(\theta|x_0) = \exp \left\{ \frac{(S - x_0)\mu}{\sigma^2} \left(1 - \sqrt{1 - \frac{2\theta\sigma^2}{\mu^2}} \right) \right\} \quad (2.6)$$

and from it, the moments of T_S can be computed. The mean, variance and square of the coefficient of variation (CV) are

$$E(T_S) = \frac{S - x_0}{\mu} , \quad (2.7)$$

$$\text{Var}(T_S) = \frac{S - x_0}{\mu} \frac{\sigma^2}{\mu^2} , \quad (2.8)$$

$$\text{CV}^2(T_S) = \frac{\sigma^2}{\mu(S - x_0)} , \quad (2.9)$$

which shows that as $x_0 \rightarrow S$ the CV is not only greater than one but it increases without bound. The skewness and kurtosis (Pearson's β_1 and β_2 , respectively) are

$$\beta_1 = 9 \frac{\sigma^2}{\mu(S - x_0)} = 9 \text{ CV}^2(T_S) > 0, \quad (2.10)$$

$$\beta_2 = 3 + 15 \frac{\sigma^2}{\mu(S - x_0)} = 3 + 15 \text{ CV}^2(T_S) > 0 \quad (2.11)$$

which gives the linear relationship

$$\beta_2 = 3 + \frac{5}{3} \beta_1 \quad (2.12)$$

Plotting sample values of β_1 and β_2 may serve as a preliminary indication via (2.12) as to whether the sample is from the IGD family of distributions. (e.g. Correia and Landolt, 1977; Lánský and Radil, 1987). Also note that as $x_0 \rightarrow -\infty$ the IGD tends to a normal one, while an increase of x_0 increases the skewness and kurtosis of the p.d.f. (2.3). The positive skew of (2.3) is also indicated by the position of the mode,

$$t_{\text{mode}} = \left((E(T_S))^2 + \left(\frac{3\sigma^2}{2\mu^2} \right)^2 \right)^{\frac{1}{2}} - \left(\frac{3\sigma^2}{2\mu^2} \right) < E(T_S) \quad (2.13)$$

Several generalizations have been made of the Wiener process as a neuronal model. Assuming that X_0 takes two different values $x_{0,1}$ and $x_{0,2}$ with probability p_1 , and $p_2 = 1 - p_1$, respectively, the interspike interval distribution becomes a mixture of IGD's with a p.d.f.

$$g(t;S) = \sum_{i=1}^2 p_i \frac{S-x_{0,i}}{\sigma\sqrt{2\pi t^3}} \exp \left\{ -\frac{(S-x_{0,i}-\mu t)^2}{2\sigma^2 t} \right\} \quad (2.14)$$

This and the other generalizations with non-constant initial value are analyzed by Lánský and Smith (1989). Some parameter estimation problems for the distribution (2.14) were examined by Amoh (1984).

Another generalization of this model of interspike intervals was proposed by Wise (1981) in which the p.d.f. (2.3) is modified such that

$$g(t) = At^{-Q} \exp(-\phi(t/\alpha + \alpha/t)) \quad (2.15)$$

is obtained; A is a normalizing constant, $Q \neq 3/2$ is a constant. The p.d.f. (2.15) coincides with (2.3) for $Q = 3/2$ and it is a special case of generalized IGD,

$$g(t) = \frac{(\psi/\chi)^{\frac{\lambda}{2}}}{2K_{\lambda}(\sqrt{\chi\psi})} t^{\lambda-1} \exp\left\{-\frac{1}{2}(\chi t^{-1} + \psi t)\right\} \quad (2.16)$$

where K_{λ} is the modified Bessel function of the third kind with index λ ; the domain of variation of the parameter (λ, ψ, χ) in (2.16) is

$$\chi \geq 0, \psi > 0 \text{ for } \lambda > 0; \quad \chi > 0, \psi > 0 \text{ for } \lambda = 0; \quad \chi > 0, \psi \geq 0 \text{ for } \lambda < 0;$$

for a survey of its properties see Jorgensen (1982). He also reanalyzed a neural data set considered by Cox and Lewis (1966) and concluded that “the fit of the generalized IGD appears excellent”. Pearson’s β_1 and β_2 for this family of distributions describe a region bounded by the lines corresponding to the gamma and reciprocal gamma distributions and also correspond to the results of the many experimental interspike interval distributions. It is again supporting the proposition to characterize interspike intervals by (2.16). Barndorff-Nielsen et al., (1978) found time-homogeneous diffusion process for which (2.16) is the FPT density. The role of this generalized diffusion model has not been studied in a neurophysiological context.

There are at least two reasons for considering a time-varying threshold in the Wiener process neuronal model. One is a direct modeling of relative refractory period by a time varying boundary with the membrane potential being approximated by a Wiener process. The other, which occurs frequently, arises when there is a constant threshold potential and the membrane potential is described by some other diffusion process. By transforming that process into the Wiener process (see the next Section), the boundary then becomes time dependent. Methods for the solution of the FPT problem for the Wiener process in the presence of a time-varying threshold have been extensively studied. Most analytical results are available for the square root boundary, however the biophysical interpretation here appears to be difficult. The other boundaries seem to require a numerical solution, which are in general based on the equation (1.8). This equation with the substitution of the transition density of the Wiener

process is a Volterra equation of the first kind with a singularity at $t = s$. Methods for its solution as applied to the FPT problem have been presented by Durbin (1971), Smith (1972), Anderssen et al. (1973). Park and Schuurmann (1976) derived a different integral equation for the cumulative distribution function of Wiener process FPT. The same authors (Park and Schuurmann, 1980) also proposed a new algorithm for the time evaluation of the FPT probability on large intervals. As we will see in the next sections, this is appropriate for neural models. Another solution method for FPT's to time varying boundaries was recently developed by Buonocore et al. (1987) for a more general class of processes than above. Another generalization is to allow the threshold potential to also be a stochastic process. Stochastic barriers for the Wiener process were studied by Park and Beekman (1983).

There are several objections against using the Wiener process as a model of neuronal membrane potential: the model does not reflect some basic physiological properties of the neuron such as the state space is not restricted from below, for others see Tuckwell (1988). Also the distribution (2.3) is not a proper one when $\mu < 0$. The objections just mentioned could both be removed imposing a reflecting boundary at some $\nu < x_0$. The analytical results for the FPT problem under this condition are well known in the stochastic process literature but apparently have not been used in neural modeling.

3. ORNSTEIN-UHLENBECK PROCESS

The most common diffusion model proposed for nerve membrane behavior is the Ornstein-Uhlenbeck process, and can be viewed as an extension of the Wiener process model. This model can be defined by (1.1) with infinitesimal moments

$$\mu(x) = -\frac{x}{\tau} + \mu, \quad \sigma(x) = \sigma \quad (3.1)$$

where $\tau > 0$, $\sigma > 0$ and μ are constants. As in the previous section the state space of the process is not restricted from below and thus the boundary condition (2.2) holds. The process (3.1) itself as well as its FPT problem have been analyzed extensively. The difference between the models (2.1) and (3.1) is that, for finite τ , the drift term $\mu(x)$ is linearly state dependent rather than a constant. We obtain (2.1) as $\tau \rightarrow \infty$ in (3.1). Unlike the Wiener process model, here the threshold crossing is a certain event, $\text{Prob}(T_S < \infty) = 1$, independent of the value of μ .

The transition density of the unrestricted process is obtained by solving the Fokker-

Planck equation,

$$f(x,t|x_0) = \sqrt{\frac{1}{2\pi V(t)}} \exp\left(-\frac{(x-x_0 e^{-t/\tau} - \mu\tau(1-e^{-t/\tau}))^2}{2V(t)}\right) \quad (3.2)$$

with $V(t) = \sigma^2\tau(1-e^{-2t/\tau})/2$, which shows that at time t , $X(t)$ is a Gaussian r.v. with mean and variance

$$E(X(t)) = x_0 e^{-t/\tau} + \mu\tau(1 - e^{-t/\tau}) \quad (3.3)$$

$$\text{Var}(X(t)) = V(t) = \frac{\sigma^2\tau}{2} (1 - e^{-2t/\tau}).$$

The stationary p.d.f., mean and variance can be computed from (3.2) and (3.3) by letting $t \rightarrow \infty$.

An analytical solution for the FPT density has not been found with the exception of when $S = \mu\tau$ by using symmetry arguments (Siebert, 1969; Sugiyama et al., 1970, Ricciardi, 1977). It is a very special choice of the threshold, namely, the asymptotic value of $E(X(t))$.

The general expression for the Laplace transform of the FPT p.d.f. is

$$g_S(\lambda|x_0) = \exp\left\{\frac{(\mu-x_0)^2 - (\mu-S)^2}{2\sigma^2\tau}\right\} \frac{D_{-\lambda\tau}((\mu-x_0)\sqrt{2/\sigma^2\tau})}{D_{-\lambda\tau}((\mu-S)\sqrt{2/\sigma^2\tau})}, \quad (3.4)$$

where $D_{-\lambda}(z)$ is the Weber function, given by the following integral representation

$$D_{-\lambda}(z) = \frac{\exp(-z^2/4)}{\Gamma(z)} \int_0^\infty \exp\left(-\frac{z-zx^2}{2}\right) x^{\lambda-1} dx, \quad \lambda > 0.$$

An alternative expression for $g_S(\lambda|x_0)$ can be found in Nobile et al., (1985a), namely

$$g_S(\lambda|x_0) = \frac{1 + \sum_{k=1}^{\infty} \lambda^k \tau^k \chi_k\left(\frac{x_0+\mu}{\sigma\sqrt{\tau}}\right)}{1 + \sum_{k=1}^{\infty} \lambda^k \tau^k \chi_k\left(\frac{S+\mu}{\sigma\sqrt{\tau}}\right)}, \quad (3.5)$$

where

$$\chi_1(z) = \sqrt{\pi} \int_0^z \exp(t^2) dt + \sum_{n=0}^{\infty} \frac{2^n}{(n+1)(2n+1)!!} z^{2n+2},$$

and

$$\chi_i(z) = 2 \int_0^z \exp(y^2) \int_{-\infty}^z \exp(-u^2) \chi_{i-1}(u) du dy, \quad i=2,3,\dots$$

The first three moments of T_S were computed by differentiating (3.4) in Sato (1978) and in Cerbone et al. (1981). A more compact form for them is given in Nobile et al., (1985a) by a direct application of Siegert's relation for the moments. The mean of the FPT is

$$\begin{aligned} E(T_S) &= 2\sqrt{\pi} \left(\frac{\mu-x_0}{\sigma} \Phi\left(\frac{1}{2}, \frac{3}{2}; \left(\frac{\mu-x_0}{\sigma}\right)^2\right) - \frac{\mu-S}{\sigma} \Phi\left(\frac{1}{2}, \frac{3}{2}; \left(\frac{\mu-S}{\sigma}\right)^2\right) \right) \\ &+ \sum_{k=0}^{\infty} \frac{2^k}{(2k+1)!!(k+1)} \left(\left(\frac{\mu-S}{\sigma}\right)^{2k+2} - \left(\frac{\mu-x_0}{\sigma}\right)^{2k+2} \right), \end{aligned} \quad (3.6)$$

where Φ is the confluent hypergeometric function of the first kind

$$\Phi(a, c; x) = 1 + \sum_{n=1}^{\infty} \frac{a(a+1)\dots(a+n-1)}{c(c+1)\dots(c+n-1)} \frac{x^n}{n!}$$

The formulas for the higher order moments are notationally complicated to be presented here. A simpler form for these moments can be found in Ricciardi and Sato (1988). The relationship between skewness and kurtosis is close to that of the gamma distribution (Smith and Sato, 1989) and does not overlap with the region specified by the generalized IGD.

The process (3.1) may be transformed into the basic form ($\mu(x) = -x$, $\sigma(x) = \sqrt{2}$), which has a stationary distribution that is Gaussian with zero mean and unit variance. Keilson and Ross (1975) have calculated extensive numerical tables for this normalized p.d.f. and for its first two moments. They use numerical techniques for the inversion of (3.4), i. e., they compute the poles λ_j and residues β_j in the expansion

$$g_S(t|x_0) = \sum_{j=0}^{\infty} \beta_j \exp(\lambda_j t)$$

Thomas (1975) gives the first two moments when $\mu = 0$, $x_0 = 0$, in terms of the normal integral and approximates the integral by polynomials.

Newell (1962), Mandl (1968), Beekman (1975), Sato (1978, 1982), Nobile et al., (1985a) have examined the exponential trend for large thresholds of the FPT for the Ornstein-Uhlenbeck process. The main result is that

$$g_S(t|x_0) = m^{-1} \exp(-t/m) + o(m^{-1} \exp(-t/m)), \quad (3.7)$$

where $m = E(T_S)$. This convergence to the exponential distribution for an increasing threshold is accompanied by a large increase in the mean FPT. Experimentally it is reassuring that the interspike intervals for some neurons become increasingly more like an exponential distribution as the firing rate decreases (e.g., Škvařil et al., 1971).

The other way to treat this model is to transform it into the standard Wiener process W and to use the results available for it. The transformation is

$$x' = \sqrt{\frac{2}{\sigma^2}} [x e^{t/\tau} - \mu\tau(e^{t/\tau} - 1)], \quad t' = \tau(e^{2t/\tau} - 1), \quad (3.8)$$

$$f'(x', t'|0) = f(x, t|x_0) \left| \frac{dx}{dx'} \right|.$$

However, the constant threshold S is also transformed into a time varying one $S'(t')$,

$$S'(t') = \sqrt{\frac{2}{\sigma^2}} [\mu\tau + (S - \mu\tau) \sqrt{\frac{t'}{\tau} + 1}] \quad (3.9)$$

which complicates the analysis and requires the previously mentioned methods for the FPT problem of the Wiener process with a time varying boundary. Clearly the role of large time intervals is important here, due to the exponential transformation of time given by (3.8), and is examined by Park and Schuurmann (1980). A related transformation method was developed by Ricciardi and Sato (1983) for a class of diffusion processes with time varying boundaries.

Sugiyama et al. (1970) examined the numerical solution of the Fokker-Planck equation (1.3) specified by (3.1) with the absorbing boundary condition (1.6) and found it to be a

convenient method for solving the FPT problem. They used a finite-difference method to evaluate the transition density function and then by summation approximated the integral in (1.7). The differences between successive sums represent the FPT p.d.f.

Time dependent thresholds in neural modeling aim to simulate various aspects of the time varying behavior of the neuron, e. g. the relative refractory period. These thresholds need to have a high initial value (or infinity) which decays with time to the constant value S_0 . An example of such a threshold is

$$S(t) = S_0 + S_1 e^{-t/\gamma}, \text{ for } S_1 > 0, \quad (3.10)$$

other forms for time dependent thresholds can be found in Tuckwell (1988). Here again the value of $S_0 = \mu\tau$ plays a special role. Because for this asymptotic threshold and when $\gamma = \tau$, an analytic solution of the FPT problem exists, for details see (Clay and Goel, 1973; Ricciardi, 1977). Otherwise numerical methods appear necessary. The indirect method, described above, of transforming to a Wiener process has some numerical problems associated with it. Some direct numerical procedures suitable for computational purposes in the FPT problem through time-dependent thresholds have been recently developed in the series of papers by Ricciardi and his coworkers (Ricciardi et al., 1984; Balossino et al., 1985; Buonocore et al., 1987; Giorno et al., 1988a). In their approach, $g_S(t|x_0)$ can be obtained as the solution of a Volterra integral equation of the second kind.

Tuckwell and Wan (1984) proposed a new method for the computation of the moments of the FPT in the presence of a moving barrier. They considered a vector process whose components are the process itself and the barrier. The theory of multi-dimensional processes was used to obtain a partial differential equation for the moments of the FPT. For several values of the parameters for the process and the barrier, the mean FPT of the Ornstein-Uhlenbeck process to the exponentially decaying boundary (3.10) was computed.

The FPT problem for stationary Gaussian processes with a linear threshold was analyzed in a neural context by Kostyukov, (1978) and Kostyukov et al., (1981).

Wan and Tuckwell, (1982) studied the first two moments of T_S and their dependence on the model parameters for the case of a small infinitesimal variance. They transformed the original process (3.1), by normalizing the parameters μ and σ , into the form where $\tau = 1$ (time is then measured in the units of τ) and $S = 1$. When the mean asymptotic value of X , which follows from (3.3), is much higher the threshold, $\mu\tau \gg S$, the mean FPT becomes

$$E(T_S) \cong \ln \left(\frac{\mu'}{\mu' - 1} \right) - \frac{1}{4} \sigma'^2 \left(\frac{2\mu' - 1}{(\mu' - 1)^2 \mu'^2} \right), \quad (3.11)$$

where μ' and σ' are the normalized parameters of the model. On the other hand, when the asymptotic value of X is small with respect to the threshold, $\mu\tau \ll S$, then

$$E(T_S) \cong \frac{\sigma' \sqrt{\pi}}{1 - \mu'} \exp \left(\frac{(1 - \mu')^2}{\sigma'^2} \right) \quad (3.12)$$

They also give an expression for the mean of T_S when the asymptotic value of X is close to the threshold, however, its form as well as the form for the second moments in these three different situations are notationally slightly more complicated. An alternative way to obtain the leading order terms in their perturbation results in the first case is by using Stein's approximation procedure (Smith, 1989). This method is also applicable for neural models with a mixed Poisson and Wiener input (Smith and Smith, 1984).

By imposing a reflecting boundary at $\nu < x_0$, a drawback of the model can be remedied, namely an unbounded membrane hyperpolarization. This has been considered by Matsuyama et al., (1974), Pacut and Dabrowski, (1988). In the first of these papers, a time dependent threshold was used and the latter one analyzed the exponential trend of this process for large thresholds. For the other theoretical results on the Ornstein-Uhlenbeck process confined between one absorbing and one reflecting boundary see, e.g., Goel and Richter-Dyn (1974); Lindenberg et al. (1975).

4. MODELS WITH A NON-CONSTANT INFINITESIMAL VARIANCE

The models considered in the two previous sections do not reflect some basic physiological features of real neurons. It is therefore not surprising that some additional types of diffusion neuronal models have been proposed. However, further analysis of the FPT problem for these new models is needed. The papers of Capocelli and Ricciardi, (1973), Hanson and Tuckwell, (1983), Giorno et al., (1988a, b) on FPT properties are exceptions. There are also several nondiffusion type models, e. g., Poisson driven differential equations, that attempt to more realistically model the physiology, but are beyond the scope of this review (see Tuckwell, 1988, 1989).

Capocelli and Ricciardi (1973) proposed a model in which the effect of the noise, that influences the membrane potential, decreases as the membrane potential gets closer to the threshold. Their model can be defined on $(-\infty, S)$ by

$$\mu(x) = -ax + \mu, \quad \sigma(x) = \sigma\sqrt{(S-x)} \quad (4.1)$$

where a , μ and $\sigma > 0$ are constants. Many analytical results are derived for the model (4.1) in this paper, however, the role of the model seems to be limited by the biological assumptions leading to the form of the infinitesimal variance in (4.1).

Matsuyama (1976) examined shunting inhibition in neural models by studying the stochastic diffusion model defined on (ν, S) by the moments

$$\mu(x) = -ax + \mu, \quad \sigma(x) = \sqrt{\sigma_1^2 + \sigma_2^2(S-x)^2} \quad (4.2)$$

where a , μ , $\sigma_1 > 0$ and $\sigma_2 > 0$ are constants and where the boundary $\nu < x_0$ is reflecting. Using numerical methods for the solution of the FPT problem via Fokker-Planck equation, the FPT's of model (4.2) was compared with that of the Ornstein-Uhlenbeck model.

The other models reviewed in this sections are known as the models with reversal potentials. The main reason for their introduction was a biological restriction of the state space of the process X and the nonlinear summation of synaptic input. They were firstly suggested by Johannesma, (1968) but their analysis appeared later. Hanson and Tuckwell, (1983) considered two reversal potential diffusion models; the first is given by

$$\mu(x) = -\frac{x}{\tau} + \mu(V_E - x), \quad \sigma(x) = \sigma(V_E - x) \quad (4.3)$$

where τ , μ and $\sigma > 0$ are constant and where V_E is a constant called the excitatory reversal potential for which $V_E > S$ holds. The model (4.3) is studied in the cited paper either without any additional boundary or being restricted from below. In the restricted version, the reflecting boundary condition had been imposed at the resting potential.

The second model proposed and analysed by these authors was defined by the infinitesimal moments

$$\mu(x) = -\frac{x}{\tau} + \mu_1(V_E - x) + \mu_2(x - V_I),$$

(4.4)

$$\sigma(x) = \sqrt{\sigma_1^2 (V_E - x)^2 + \sigma_2^2 (x - V_I)^2}$$

where $\tau, \mu_1, \mu_2, \sigma_1 > 0$ and $\sigma_2 > 0$ are constants and where $V_I < x_0$ is an additional constant called the inhibitory reversal potential. The role of V_E is same as that in model (4.3). As above, the lower boundary was taken to be either $-\infty$ or a constant, here V_I , and V_I was a reflecting boundary. For both the models (4.3) and (4.4) the first two moments of X and the stationary density were derived in the absence of the threshold S . Using the equation (1.10), the first two moments of the FPT through S were computed. They used numerical and asymptotical methods for the evaluation of the integrals appearing in the solution of (1.10).

The diffusion processes (4.3) and (4.4) are characterized by a linear infinitesimal mean $\mu(x)$. The above notation stresses the contribution of each term in $\mu(x)$. The form of the infinitesimal variance $\sigma(x)$ does not permit a simple interpretation of the model in the sense that there is no value of the membrane potential for which the infinitesimal variance is zero. Therefore an additional boundary condition has to be imposed. This issue has motivated the development of additional diffusion neuronal models. Giorno et al., (1988a,b) thoroughly analysed the diffusion neuronal model given by

$$\mu(x) = -ax + \mu, \quad \sigma(x) = \sigma\sqrt{(x - V_I)} \quad (4.5)$$

where $\sigma > 0, \mu > 0$ and a are constants. The coefficient of x in the infinitesimal mean term is denoted by a to distinguish it from that in the above models as the interpretation here is different. Now the boundary V_I is either regular, for $\mu < \sigma^2$, or entrance for $\mu \geq \sigma^2$ and in the latter case may be interpreted as a reset mechanism. When the process is restricted from below at V_I , the transition density of X , its limiting p.d.f. and the first two moments were determined. For the FPT problem, the first three moments were derived in an analytical form. An extension of the approach developed by Buonocore et al., (1987), for the Wiener and Orstein-Uhlenbeck process, was used for the numerical evaluation of the p.d.f for the FPT problem. They also calculated the probability distribution of the firing frequency, i. e., the probability distribution and mean and variance of having n firings in the time interval $(0, t]$ under the condition that there is a spike at zero. The exponential behavior of the p.d.f. for large values of the threshold in this model follows as a special case of the result by Nobile et

al., (1985b). This implies that the frequency description of the model behaves in a Poisson-like manner. Finally the joint distribution is derived for the number of firings together with the value of the membrane potential.

Two other diffusion models with reversal potential have been introduced by Lánský and Lánská, (1987) of the form

$$\mu(x) = -ax + \mu, \quad \sigma(x) = \sigma(x - V_I) \quad (4.6)$$

and

$$\mu(x) = -ax + \mu, \quad \sigma(x) = \sigma(V_E - x)(x - V_I) \quad (4.7)$$

where the constants and the reversal potentials are denoted as in the previous cases. The properties of (4.6) and (4.7) have not been studied previously in a neuronal context, however they have been used in other applications of stochastic diffusion processes. For example, for (4.7) by transforming the interval (V_I, V_E) into the interval $(0,1)$ we obtain a process that is well known in genetic applications (see, e.g., Karlin and Taylor, 1981). One difference from the genetic applications is that now the transformed threshold S' lies somewhere inside the interval $(0,1)$, instead of at the boundaries zero or one.

From a modeling point of view, the variety of forms for the infinitesimal variance and the linear form of the infinitesimal mean are not unexpected. These models are trying to reflect by an "equivalent" noisy ordinary differential equation, the properties at a single spatial location, the trigger zone, on a spatially distributed neuron with noisy inputs, i. e., a stochastic partial differential equation. The linear mean term models the passive electrical circuit properties of the membrane at the trigger zone and also the mean effect of the noisy input. The infinitesimal variance, on the other hand, must not only take into account the diversity of spatial configurations for different neurons, but the location and type of synaptic input on that neuron as well. Hence, a variety of forms for this term in the diffusion equation are appropriate.

5. REMARKS

In addition to studying the properties of the models themselves, methods for model verification are also important, yet not as extensively studied. However, for diffusion models,

some results are available (Pernier, 1972; Nilsson, 1977; Tuckwell and Richter, 1978; Lánský, 1983; Lánský et al., 1988). Also noteworthy are Segundo's (1986) neurophysiologically oriented, critical review of the integrate-and-fire models and the thorough comparison between experimental and simulation results in the stochastic after-hyperpolarization model of Smith and Goldberg (1986).

Matsuyama et al., (1974) applied numerical methods and computer simulations of the Ornstein-Uhlenbeck process with time dependent infinitesimal moments to describe the stimulated activity of neuron. They assumed a non-homogeneous periodic input for the model in order to produce a multimodal p.d.f. of the FPT. They also studied the behavior of a connected pair of neurons. A multimodal p.d.f. of the FPT can also be produced in other ways, e.g. by having a periodic threshold function (Giorno et al., 1989). However, the biological interpretation is not as straightforward as that for a time varying input. This raises a modeling problem that has not been resolved in the literature, namely how to distinguish among a time varying boundary, a time varying input and time varying coefficients in (1.1).

The neuronal behavior described by the stochastic diffusion models assume directly or indirectly that the output is a renewal process (intervals between threshold crossing are independent and identically distributed). Recently Frigessi and Den Hollander, (1989) introduced a model aimed at simulating the clustering effect in spike generation. Their model is based on the Ornstein-Uhlenbeck process with a threshold of two different values and the dynamics of the resultant output can be expressed in the terms of a semi-Markov process. Serial dependence among interspike intervals has also been modeled in other ways, e.g., by adjusting the reset value after each spike in the Ornstein-Uhlenbeck process (Geisler and Goldberg, 1966).

Stochastic neuronal models are also used for the description of more complex neuronal structures. Holden (1978) used the Wiener and Ornstein-Uhlenbeck processes for the study of information transfer in a chain of neurones. The papers by Brannan and Boyce (1981), Brannan (1982), Kryukov (1984) Buhman and Schulten (1987) are among the few examples where stochastic diffusion models are used to study the dynamics of neural nets. The networks studied in these papers consist of neuronal units which are modeled by an Ornstein-Uhlenbeck process with a constant or time-varying threshold. A recent critical review of deterministic and stochastic approaches to the analysis of neural networks can be found in Cowan and Sharp (1988). A review of several specific neuronal systems and networks, together with simulation programs and an extensive bibliography can be found in the recent book by MacGregor (1987).

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