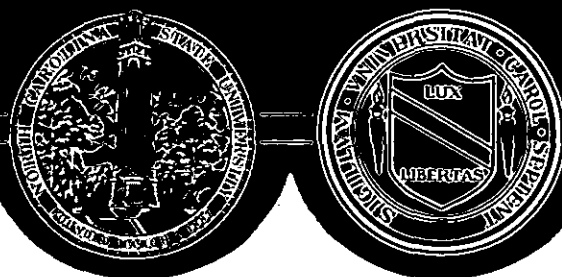


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IN NEURAL FIRST-PASSAGE-TIME MODELS

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ABSTRACT

The effect of a random initial value is examined in several stochastic integrate-and-fire neural models with a constant threshold and a constant input. The three models considered are approximations of Stein's model, namely: (1) a leaky integrator with deterministic trajectories, (2) a Wiener process with drift, and (3) an Ornstein Uhlenbeck process. For model (1) different distributions for the initial value lead to commonly observed interspike interval distributions. For model (2) a discrete and a uniform distribution for the initial value are examined along with some parameter estimation procedures. For model (3) with a truncated normal distribution for the initial value, the coefficient of variation is shown to be greater than one and as the threshold becomes large, the first passage time distribution approaches an exponential distribution. The relationship among the models and to previous models is also discussed, along with the robustness of the model assumptions and methods of their verification. The effects of a random initial value are found to be most pronounced at high firing rates.

potentials respectively. The fact that N^+ and N^- are homogeneous processes reflects a time invariant input; that is, the model is appropriate for spontaneous activity or activity due to a constant stimulus of long duration. The amplitude of the postsynaptic potentials is denoted by a for the excitatory ones and by l for the inhibitory ones. The membrane constant, τ , describes the rate at which the membrane potential decays to the resting potential in the absence of any synaptic input.

In all the papers where (1.1) or its generalizations have been studied, the initial value of X was considered to be a constant, usually equal to the resting potential. However, this assumption is sometimes biologically unrealistic, e.g., the effect of cumulative afterhyperpolarization (Smith and Goldberg, 1986). In order to get some feeling for the effect of relaxing this assumption, here we assume that the initial value, X_0 , is either a discrete r.v. with distribution $(p_i, i=1,2)$ or a continuous one with probability density function (p.d.f.) $w(x_0;S)$. Some support for this assumption comes from O'Neill et al. (1986), who measured X_0 as the minimum potential of the action potential waveform as it is reset after a spike. Their figure 5 gives a histogram of these values in snail visceral ganglia neurons. Suga (1984) suggested that a non-fixed initial value may partially account for doublet impulses in spike trains.

In studying neuronal models, we are mainly interested in the properties of the r.v., T_s , which is the first passage time (FPT) of the process X to the threshold S . T_s is identified with interspike interval (ISI) and is defined by the relationship

$$T_s = \inf\{ t \geq 0; X(t) > S \} . \quad (1.2)$$

The agreement of experimentally obtained distributions of ISI's with common families

of probability distributions is often unsatisfactory (Correia and Landolt, 1977; Lánský and Radil, 1987) which also suggests that some more complicated mechanism is responsible for spike generation, e.g., a random initial value.

Any characterization of T_S for X given by (1.1) is extremely complicated and practically only numerical and approximation results are available (e.g., Tuckwell, 1975; Tuckwell, 1976; Tuckwell and Richter, 1978; Tuckwell and Cope, 1980; Wan and Tuckwell, 1982; Wilbur and Rinzel, 1982; 1983; Smith and Smith, 1984). Therefore the process (1.1) is usually approximated by another, more mathematically tractable, stochastic process having similar properties (e.g., Gluss, 1967; Johannesma, 1968; Roy and Smith, 1969; Capocelli and Ricciardi, 1971; Ricciardi, 1976; Ricciardi and Sacerdote, 1979; Tuckwell and Cope, 1980; Sato, 1982; Ricciardi et al., 1983; Kallianpur, 1983). Not only the approximation itself, but also the properties of the limiting process are studied in these papers. Lánský (1984) has shown that under appropriate conditions the distribution of T_S converges to the distribution of limiting process's FPT as well. The deterministic limit of X was also considered there. In this paper, the following three types of models are analyzed:

(1) The model with deterministic trajectories, where stochasticity is introduced solely by the random initial value X_0 ,

$$X(t) + \frac{1}{\tau} \int_0^t X(s) ds = \mu t + X_0 \quad (1.3)$$

Equation (1.3) is a limit of (1.1) under the condition $\nu_0 \sim O(a^{-1})$, $\nu_1 \sim O(i^{-1})$, where ν_0 and ν_1 are the intensities of the corresponding input processes N^+ and N^- . In this case, X is also sometimes called a singular process. To ensure the firing of neuron we also have to assume $\mu\tau > S$, i.e. the solution $X(t)$ crosses S . The

asymptotic level $X(\infty) = \mu\tau$ is sometimes called the mean excitation level (Harvey, 1978).

(2) The Wiener process model given by the equation

$$X(t) = \mu t + \sigma W(t) + X_0, \quad \mu > 0, \quad (1.4)$$

where $W = \{W(t); t \geq 0\}$ is a standard Wiener process, $\sigma > 0$ is a constant.

(3) The Ornstein Uhlenbeck process model defined in the following way

$$X(t) + \frac{1}{\tau} \int_0^t X(s) ds = \mu t + \sigma W(t) + X_0 \quad (1.5)$$

Both models (1.4) and (1.5) can be viewed as diffusion approximations of (1.1) when the input processes go in some limiting sense to a Wiener process with drift. The difference between the two models is that for finite τ we obtain (1.5) and as $\tau \rightarrow \infty$ we have (1.4).

All the models (1.3) - (1.5) are similar in that they perform a certain type of integration of the input signal. For a fixed initial condition, the analysis of (1.3) usually has been performed separately from that of (1.4) and (1.5). The reason for this is twofold. The first one is a formal reason, as (1.3) represents the deterministic approach in contrast to (1.4) and (1.5) which are of stochastic nature. The second reason is a biological one. Model (1.3), with perhaps small perturbations added, is adequate to describe many regularly discharging neurons, while neurons with an irregular spacing of action potentials require a stochastic description such as (1.4) and (1.5). There have been only a few attempts to bring both types of models together (e.g., Angelini et al., 1982).

In addition to studying the properties of the FPT, some methods for model

verification are also proposed. Despite its equivalent importance, this part of neural modeling is not as extensive as the modeling itself. The papers by Pernier (1972), Nilsson (1977), Tuckwell and Richter (1978), Lánský (1983), Lánský et al. (1988) are exceptions in that they offer procedures for parameter estimation in the neuronal model. A different approach to verification in an integrate-and-fire model was applied by O'Neill et al. (1986). Segundo (1986) gives a critical review of the integrate-and-fire models from a neurophysiological point of view. A time series approach (e.g., Brillinger and Segundo, 1979) represents yet another useful method for model verification.

The inference methods proposed in this paper require both ISI measurements, which are routinely recorded, and measurements of initial values of the membrane potential, which are technically more difficult to record (O'Neill et al., 1986). Inference methods based solely on intracellular membrane trajectories (Lánský, 1983; Lánský et al., 1988) with random initial condition will be considered in another paper.

Using the terminology of Tuckwell and Richter (1978), there are two types of parameters appearing in our models. The first ones are so-called neuroanatomical parameters, which can be measured directly by intracellular recordings and correspond to S , x_0 and τ above. Said another way, they are a property of the neuron rather than of its inputs.

The second type of parameters are input parameters, which have to be estimated in any case. They tend to be less stable in time, with respect to external and internal conditions, than the neuroanatomical parameters. Here, they are: μ in models (1.3)-(1.5) and σ in models (1.4) and (1.5).

The amount of literature on the models (1.3) - (1.5) with a fixed initial value is quite large. Many of these results can be generalized to the case of a random initial value. Therefore the list of references in this paper, which is far from a

complete survey, is nevertheless an extensive one and may serve as a limited review of these models and their analysis.

2. Deterministic model with random initial value.

Equation (1.3) has frequently been used to model inhibitory feedback (e.g., Knight, 1972; Fohlmeister, 1973; Fohlmeister et al., 1974; Ascoli et al., 1977) and phase-locking (e.g., Poppele and Chen, 1972; Scharstein, 1979; Angelini et al., 1984) in neurons. However, all these papers assumed a degenerate distribution for X_0 , i.e. , $P(X_0=x_0) = 1$. The random initial value of the membrane potential may bring some improvement in the situations where the original fixed-initial-condition model fails.

The solution of (1.3) can be written as

$$X(t) = \mu\tau(1 - e^{-t/\tau}) + X_0e^{-t/\tau} \quad (2.1)$$

and solving the FPT problem for (2.1), we obtain an ISI of length

$$T_S = \tau \ln \left(\frac{\mu\tau - X_0}{\mu\tau - S} \right) \quad (2.2)$$

The input-output relationship, in the form μ versus t_s^{-1} (firing rate), is often plotted for the deterministic model (2.1) with fixed initial value $X_0=x_0$ (see the above cited papers). Such a plot can also be accomplished for (2.1) by substituting $E(T_S^{-1})$ for t_s^{-1} . As a first approximation we could instead substitute $E(T_S)^{-1}$, but

this will give an underestimate of the slope since $E(T_S^{-1}) \geq E(T_S)^{-1}$. On the other hand, the firing rate is also often defined as $E(T_S)^{-1}$ (e.g., Stein, 1967).

Using the transformation (2.2) on the random variable X_0 we can derive the p.d.f. $g(t;S)$ of T_S in terms of an arbitrary p.d.f. for the initial value, $w(\cdot;S)$, i.e.

$$g(t;S) = \frac{\mu\tau - S}{\tau} e^{t/\tau} w(\mu\tau - (\mu\tau - S)e^{t/\tau};S). \quad (2.3)$$

The form of (2.2) suggests using a lognormal distribution for X_0 to produce ISI's that are normally distributed with a mean m and standard deviation σ , i.e., $T_S \sim N(m, \sigma^2)$. With the constraint that parameters m and σ have values that ensure that the probability of a negative ISI is negligible. The assumption may not be unreasonable since ISI's with roughly a normal distribution have been reported several times (e.g., for tonic receptor neurons - Werner and Mountcastle, 1965; Walloe, 1970; Schreiner et al., 1978; Fuller and Williams, 1983). In particular, for these regularly firing neurons where only small fluctuations of ISI's are present, this model may be a suitable approximation. From (2.2) we have

$$\frac{-\tau \ln(\mu\tau - S) - m}{\sigma} + \frac{\tau}{\sigma} \ln(\mu\tau - X_0) \sim N(0,1) \quad (2.4)$$

Note that $(-X_0)$ has a lognormal distribution on $(-\mu\tau, \infty)$ with parameters

$$\zeta = \ln(\mu\tau - S) + \frac{m}{\tau}, \quad \sigma' = \frac{\sigma}{\tau} \quad (2.5)$$

(for particulars on the lognormal distribution see, e.g., Johnson and Kotz, 1970, chpt.

14). Clearly the probability $P(S \leq X_0 < \mu\tau)$ is negligible as it is equal to $P(T_S < 0)$. Using the well known properties of the lognormal distribution; the mean, variance and p.d.f. of X_0 become

$$E(X_0) = \mu\tau - (\mu\tau - S) \exp\left(\frac{m}{\tau} + \frac{1}{2} \left(\frac{\sigma}{\tau}\right)^2\right), \quad (2.6)$$

$$\text{Var}(X_0) = (\mu\tau - S)^2 \exp\left(2\frac{m}{\tau} + \left(\frac{\sigma}{\tau}\right)^2\right) (\exp\left(\left(\frac{\sigma}{\tau}\right)^2\right) - 1) \quad (2.7)$$

and

$$w(x_0;S) = [(\mu\tau - x_0)\sqrt{2\pi\sigma/\tau}]^{-1} \exp\left\{-\frac{1}{2} \left[\ln\left(\frac{\mu\tau - x_0}{\mu\tau - S}\right) - \frac{m}{\tau} \right]^2 / \left(\frac{\sigma}{\tau}\right)^2\right\} \quad (2.8)$$

for $x_0 < \mu\tau$.

Probably more useful than (2.3) would be an equation for $w(x_0;S)$ under the condition that the p.d.f. for ISI is known. Known in the sense that histogramming (p.d.f. estimation) is a common technique in ISI analysis (e.g., Rodieck et al., 1962; Perkel et al., 1967; Sanderson and Kobler, 1976; Anderson and Correia, 1977; Landolt and Correia, 1978; Abeles, 1982). So from (2.2) the p.d.f. of X_0 becomes

$$w(x_0;S) = \frac{\tau}{\mu\tau - x_0} g\left(\tau \ln\left[\frac{\mu\tau - x_0}{\mu\tau - S}\right]; S\right) \quad (2.9)$$

An exponential or a shifted exponential distribution has also been used to describe some ISI distributions, (e.g., Škvařil et al. 1971; Walsh et al. 1972;

MacGregor et al. 1975) and can be obtained from model (1.3) as outlined below. As will be seen later, the exponential distribution arises naturally from the model (1.5) as well. For $t > 0$,

$$g(t;S) = \lambda e^{-\lambda t} \quad (2.10)$$

the distribution of X_0 is calculated from (2.9) to be

$$w(x_0;S) = \frac{\lambda \tau (\mu \tau - S)^{\lambda \tau}}{(\mu \tau - x_0)^{\lambda \tau + 1}} \quad , \quad x_0 < S \quad . \quad (2.11)$$

Using the transformation $y = \mu \tau - x_0$, (2.11) becomes

$$w(y;S) = \frac{\lambda \tau (\mu \tau - S)^{\lambda \tau}}{y^{\lambda \tau + 1}} \quad , \quad y \geq \mu \tau - S \quad (2.12)$$

which is the usual form for a Pareto distribution. It follows that the first two moments are given by

$$E(X_0) = \frac{\tau(\lambda S - \mu)}{\lambda \tau - 1} \quad , \quad \lambda \tau > 1 \quad (2.13)$$

$$E(X_0^2) = \frac{\tau(\lambda \tau - 1)\lambda S^2 - 2\mu\tau(\lambda S - \mu)}{(\lambda \tau - 1)(\lambda \tau - 2)} \quad , \quad \lambda \tau > 2 \quad (2.14)$$

(for further details see Johnson and Kotz, 1970, chpt. 19).

For other types of commonly used distributions for ISI's, the formula for $w(x_0;S)$ is not a simple one. For example if we assume that the ISI's are gamma distributed (e.g., Correia and Landolt, 1977),

$$g(t;S) = \frac{t^{\alpha-1}e^{-t/\beta}}{\beta^\alpha \Gamma(\alpha)} \quad (2.15)$$

then upon substituting (2.15) into (2.9), the distribution for the initial value becomes

$$w(x_0;S) = \left(\frac{\tau}{\beta}\right)^\alpha \frac{(\mu\tau - S)^{\tau/\beta}}{(\mu\tau - x_0)^{\tau/\beta+1}} \frac{1}{\Gamma(\alpha)} \left[\ln \left(\frac{\mu\tau - x_0}{\mu\tau - S} \right) \right]^{\alpha-1} \quad (2.16)$$

Note that when the shape parameter α of the gamma distribution has a value of 1, then as expected, (2.16) coincides with (2.11).

The problem of the identification and verification of the model (1.3) is now considered. From the form of $g(t;S)$ given by (2.3) we can deduce that the mode of this distribution corresponds to the mode of the distribution of X_0 . In the framework of this model if we measure realizations of T_S denoted by $(t_i, i=1, \dots)$, then we indirectly specify the values of the r.v. X_0 ($x_{0,i}; i=1, \dots$) by using (2.2). Said another way, a histogram of values for T_S gives a histogram of values for X_0 . Unfortunately this transformation method requires that the parameters, S , μ and τ , of model (1.3) are known.

Two different situations can occur in measuring ISI's. If nothing is assumed about the functional form of $g(t;S)$, then it has to be estimated (by histogramming or a number of other methods for density estimation). In any case, it does not help with the identification of $w(x_0;S)$ because even if τ and S are known, μ is still unspecifiable. A different situation arises when some parametric form of ISI distribution is assumed, as it is usually done. Then an estimate of the input parameter μ can be computed and the estimate $\hat{g}(t;S)$ can be transformed into a corresponding estimate $\hat{w}(x_0;S)$.

Recall that the model (1.3) is most suitable for neurons with firing patterns that are "regular" in the sense that the variation in ISI's is small relative to their mean. Sciabassi (1976) studied model (1.3) with randomness introduced in slightly different way. He assumed that the mean excitation level $X(\infty) = \mu\tau$ is a r.v. and is redrawn after each firing from a Gaussian distribution with a fixed mean and variance. The main drawback of his model seems to be its lack of physiological interpretation, namely why should μ change instantaneously from one spike to the next.

3. Wiener process model

The solution of the FPT problem for the diffusion process X given by (1.4) under the condition $P(X_0 = x_0) = 1$ has been known for very long time and for $\mu = 0$ even longer. Nevertheless, it was not until the 1950's that it was widely used in applications (e.g., in stochastic dynamical systems, for a general survey and historical references see Folks and Chhikara, 1978). While including a random initial condition into this model does not make solving the FPT problem much more

difficult, there are complications in applying statistical methods and in interpreting the results physically.

For a constant initial value condition x_0 , the p.d.f. of T_S is

$$g(t;S,x_0) = \frac{S-x_0}{\sigma\sqrt{2\pi t^3}} \exp \left\{ -\frac{(S-x_0-\mu t)^2}{2\sigma^2 t} \right\}. \quad (3.1)$$

Several different names have been assigned to this distribution in the past, but the name inverse Gaussian distribution (IGD) is now commonly used. The assumption made in (1.4) that $\mu > 0$ ensures that the mean FPT is finite, however, the case when $\mu = 0$ has also been suggested as a description of neuronal activity. The reason is that when $\mu = 0$ (3.1) is a stable law (Feller, 1966) and there have been several reports on preserving the shapes of histograms when the adjacent ISI's are summed (e.g., Rodieck et al, 1962; Holden, 1975; Holden and Ramadan, 1982). Several different parameterizations are available for p.d.f. (3.1). The most common one in the statistical literature uses the parameters

$$a = (S - x_0)/\mu, \quad b = (S - x_0)^2/\sigma^2 \quad (3.2)$$

which turns (3.1) into

$$p(t;S,x_0) = \sqrt{\frac{b}{2\pi t^3}} \exp \left\{ -\frac{b(t-a)^2}{2a^2 t} \right\}. \quad (3.3)$$

However, we will use (3.1) as the physical interpretation is clearer when the underlying mechanism is the FPT of a Wiener process.

Before proceeding to the case of a random initial condition, we will review some of the basic characteristics of (3.1) which will be used later. The moment generating function, defined for a r.v. Y as $h(\theta) = E(\exp(\theta Y))$, corresponding to (3.1) is

$$h(\theta; S, x_0) = \exp \left\{ \frac{(S - x_0)\mu}{\sigma^2} \left[1 - \sqrt{1 - \frac{2\theta\sigma^2}{\mu^2}} \right] \right\} \quad (3.4)$$

and from it, the moments of T_{S, x_0} can be computed. The mean, variance and square of the coefficient of variation (CV) are

$$E(T_{S, x_0}) = \frac{S - x_0}{\mu}, \quad (3.5)$$

$$\text{Var}(T_{S, x_0}) = \frac{S - x_0}{\mu} \frac{\sigma^2}{\mu^2}, \quad (3.6)$$

$$\text{CV}^2(T_{S, x_0}) = \frac{\sigma^2}{\mu(S - x_0)}, \quad (3.7)$$

which show 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

$$\beta_1 = 9 \frac{\sigma^2}{\mu(S - x_0)} = 9 CV^2(T_{S,x_0}) > 0, \quad (3.8)$$

$$\beta_2 = 3 + 15 \frac{\sigma^2}{\mu(S - x_0)} = 3 + 15 CV^2(T_{S,x_0}) > 0 \quad (3.9)$$

which gives the linear relationship

$$\beta_2 = 3 + \frac{5}{3} \beta_1. \quad (3.10)$$

Plotting sample values of β_1 and β_2 may serve as a preliminary indication via (3.10) as to whether the sample is from the IGD family of distributions. Also note that as $x_0 \rightarrow -\infty$ the IGD tends to a normal one, while increasing x_0 increases the skewness and kurtosis of the p.d.f.

As a first step, let us assume that X_0 can take just two different values $x_{0,1}$ and $x_{0,2}$ with probability p_1 , and $p_2 = 1 - p_1$, respectively. Now the ISI distribution is a mixture of IGD's with a p.d.f.

$$g(t;S) = \sum_{i=1}^2 p_i \frac{S - x_{0,i}}{\sigma \sqrt{2\pi t^3}} \exp \left\{ - \frac{(S - x_{0,i} - \mu t)^2}{2\sigma^2 t} \right\} \quad (3.11)$$

The moment generating function for (3.11) follows directly from (3.4)

$$h(\theta; S, x_{0,1}, x_{0,2}) = \sum_{i=1}^2 p_i \exp \left\{ \frac{(S - x_{0,i})\mu}{\sigma^2} \left(1 - \sqrt{1 - \frac{2\theta\sigma^2}{\mu^2}} \right) \right\} \quad (3.12)$$

from which the moments can be derived. We have

$$\begin{aligned} E(T_S) &= p_1 \frac{S - x_{0,1}}{\mu} + p_2 \frac{S - x_{0,2}}{\mu} = \frac{1}{\mu} (S - (p_1 x_{0,1} + p_2 x_{0,2})) = \quad (3.13) \\ &= E(T_S, E(X_0)) \end{aligned}$$

$$\begin{aligned} \text{Var}(T_S) &= \frac{\sigma^2}{\mu^3} (S - (p_1 x_{0,1} + p_2 x_{0,2})) + \frac{p_1 p_2}{\mu^2} (x_{0,2} - x_{0,1})^2 \geq \quad (3.14) \\ &\geq \text{Var}(T_S, E(X_0)) \end{aligned}$$

$$\begin{aligned} \text{CV}^2(T_S) &= \frac{\sigma^2}{\mu} (S - (p_1 x_{0,1} + p_2 x_{0,2}))^{-1} + p_1 p_2 \frac{(x_{0,2} - x_{0,1})^2}{(S - (p_1 x_{0,1} + p_2 x_{0,2}))^2} \geq \\ &\geq \text{CV}^2(T_S, E(X_0)) \quad (3.15) \end{aligned}$$

That is, the mean of the mixture has the same value as that in the model (3.1) with x_0 being the mean initial value. On the other hand, the variance and CV^2 for the mixture are larger than their counterpart in (3.1).

The parameters in (3.11) can be estimated by the method of moments by using (3.12) to compute the first five moments. Unfortunately, this procedure is not very practical due to the large sample size required. However, as noted in the previous section if S is assumed to be known, then the estimation problem is more promising and can be pursued in several ways. If in addition to ISI's measurements, $x_{0,1}$ and $x_{0,2}$ can be measured directly, then p_1 can be estimated as the relative proportion of $x_{0,1}$ and only μ and σ remain to be estimated. They could be estimated simply by say the method of moments using (3.13) and (3.14).

On the other hand if only ISI's are measured and simultaneously $x_{0,1} \approx x_{0,2}$, then for some range of values of μ and σ the problem of parameter estimation will be complicated. While in this case the estimation problem becomes complicated, the actual FPT distribution may be well approximated by the model with a fixed initial condition. If $x_{0,1}$ and $x_{0,2}$ are distinctly different, again relative to μ and σ , then the problem of estimating the proportion p_1 can be performed in an analogous way to that used for a mixture of normals (Johnson and Kotz, 1970).

Another feature of the model is the serial dependence between ISI's. For the model (3.1), c.f. (1.4), the renewal process is always postulated, however, the model (3.11) can be recognized as the marginal distribution of ISI's in a two-state semi-Markov neuronal model (see e.g., Cox and Lewis, 1966) or its generalizations (Ekholm, 1972; De Kwaadsteniet, 1982). In the last cited paper the model is called a semi-alternating renewal process and methods for its verification are extensively studied there, including the estimation of IGD components. This model appears to be a reasonable description for neurons with a clustered firing pattern (Thompson and Gibson, 1981). A more complicated scheme would follow from the approach of Sugaan (1984). There the resting potential in his integrate-and-fire model is also non-fixed with its value determined by the previous interval's final membrane potential just

before firing. Clearly this assumption leads to Wold's Markov process as a neuronal model.

A more realistic model, and therefore also less mathematically tractable than the previous one, can be based on the assumption of a continuously distributed X_0 . This creates a compound (randomized) IGD as the ISI distribution and to our knowledge this distribution has not been analyzed. For this model the p.d.f. of T_S can be computed from the relationship

$$g(t;S) = \int_{-\infty}^S g(t;S,x_0)w(x_0;S)dx_0 . \quad (3.18)$$

where $g(t;S,x_0)$ is given by (3.1).

At first we consider the situation when X_0 is uniformly distributed over an interval $(x_{0,\min}, S)$, where $x_{0,\min}$ represents minimal attainable hyperpolarization,

$$w(x_0;S) = (S - x_{0,\min})^{-1} \quad (3.19)$$

Substituting (3.19) into (3.18) we obtain

$$g(t;S) = \left[t (S - x_{0,\min}) \right]^{-1} E(Y) , \quad (3.20)$$

where $Y \sim N(\mu t, \sigma^2 t)$, truncated at 0 and $(S - x_{0,\min})$ and is not renormalized to be a p.d.f. on this interval. Deriving (3.20) we used the relationship between the IGD and normal distribution

$$\int_{-\infty}^S g(t;S,x_0)dx_0 = \frac{1}{t} \int_0^{\infty} \frac{x}{\sigma\sqrt{2\pi t}} \exp\left\{-\frac{(x - \mu t)^2}{2\sigma^2 t}\right\} dx \quad (3.21)$$

Another distribution for ISI's can be obtained by assuming X_0 to be exponentially distributed on $(-\infty, S)$,

$$w(x_0; S) = \omega e^{-\omega(S - x_0)} \quad (3.22)$$

Using the same procedure as for the derivation of (3.20) we get

$$g(t; S) = \frac{\lambda}{t} \exp\left\{\frac{1}{2}t\lambda(2\mu + \sigma^2\lambda)\right\} \int_0^\infty \frac{x}{\sigma\sqrt{2\pi t}} \exp\left\{-\frac{(x - \mu t - \lambda\sigma^2 t)^2}{2\sigma^2 t}\right\} dx \quad (3.23)$$

For more details see Schneider (1986), where the methods for obtaining (3.20), (3.21) and (3.23) can be found.

The maximum likelihood estimates of the parameters of the IGD given by (3.1) are available when the data consists of the pairs $(x, t) = (x_{0,i}, t_i, i=1, \dots, n)$, which are the initial hyperpolarization and corresponding ISI in n independent intervals. The likelihood function takes the form

$$L(\mathbf{x}, \mathbf{t} | \mu, \sigma^2) = \prod_{i=1}^n g(t_i; S, x_{0,i}) \quad (3.24)$$

where the p.d.f g is given by (3.1). Thus the log-likelihood function is

$$l(\mathbf{x}, \mathbf{t} | \mu, \sigma^2) = \sum_{i=1}^n \left(-\frac{1}{2} \log \sigma^2 - \frac{(S - x_{0,i} - \mu t_i)^2}{2\sigma^2 t_i} \right) \quad (3.25)$$

from which the equation for the estimation of μ is found to be

$$\sum_{i=1}^n (S - x_{0,i} - \mu t_i) = 0 \quad (3.26)$$

Solving this equation, we get

$$\hat{\mu} = \frac{\sum_{i=1}^n (S - x_{0,i})}{\sum_{i=1}^n t_i} = \frac{\overline{S - x_0}}{\bar{t}}, \quad (3.27)$$

where bar denotes the first sample moment. For the estimation of σ^2 we have from (3.25) the equation

$$\sum_{i=1}^n \left(-\frac{1}{2}\sigma^{-2} + \frac{(S - x_{0,i} - \mu t_i)^2}{2\sigma^4 t_i} \right) = 0 \quad (3.28)$$

with the solution

$$\hat{\sigma}^2 = \frac{1}{n} \sum_{i=1}^n \frac{(S - x_{0,i})^2}{t_i} - \frac{(\overline{S - x_0})^2}{\bar{t}} = \overline{\left(\frac{S - x_0}{t} \right)^2} - \frac{(\overline{S - x_0})^2}{\bar{t}} \quad (3.29)$$

where $\hat{\mu}$ was substituted for μ in (3.28). The estimates (3.27) and (3.29) corresponds to those obtained by Lánský (1983) for the model with a fixed initial condition, however, they were derived there using the transition density. This equivalence of the form of the estimators was noticed by Dawid (1978).

If there is no variability in x_0 , the maximum likelihood estimate of μ is known to be biased, which follows directly from the integration by parts of (3.1), (Brown and Hewitt, 1975). The bias is $\sigma^2(S-x_0)^{-1}$. Using the same procedure for (3.27), this estimator is found to have a bias of an analogous form

$$E(\hat{\mu}) - \mu + \sigma^2 E_{X_0} \left(\frac{1}{S-X_0} \right) \geq \mu + \sigma^2 (E_{X_0} (S-X_0))^{-1} . \quad (3.30)$$

Note the bias in the estimation of μ depends linearly on σ^2 and thus for large values of σ^2 , the bias may be several times greater than the value of the estimated parameter itself.

4. Ornstein Uhlenbeck process model

When the membrane potential is described by equation (1.5) the methods of the previous section are not applicable due to the lack of an analytical expression for the FPT distribution. There have been many attempts to solve this problem numerically, either by the direct inversion of the Laplace transformation of the FPT p.d.f. (e.g., Keilson and Ross, 1975) or by application of a renewal equation and its generalizations (Cerbone et al., 1981; Ricciardi and Sato, 1983; Ricciardi et al., 1984; Buonocore et al., 1987). A review of the Ornstein Uhlenbeck process with an emphasis on its use in neuronal modeling can be found in Ricciardi and Sacerdote

(1979).

In view of this mathematical difficulty we will consider only one particular distribution for the initial value of the membrane potential in model (1.5). This distribution is derived from the well known stationary distribution of the Ornstein Uhlenbeck process. The normalization ($\tau=1, \mu=0, \sigma=\sqrt{2}$) produces a stationary distribution that is normal with zero mean and unit variance, as well as normalizes the time scale (Keilson and Ross, 1975).

The Fokker-Planck equation for the transition density corresponding to (1.5) is

$$\frac{\partial f}{\partial t} = \frac{\partial}{\partial x} \left[\left(\frac{x}{\tau} - \mu \right) f \right] + \frac{1}{2} \frac{\partial^2}{\partial x^2} [\sigma^2 f] \quad (4.1)$$

The transformation required to normalize (4.1) is

$$x \leftarrow \frac{(x - \mu\tau)\sqrt{2}}{\sigma\sqrt{\tau}}, \quad t \leftarrow \frac{t}{\tau}, \quad (4.2)$$

where the new variables are on the left hand side. The threshold S is transformed in the same way as x and this transformed threshold is denoted by P .

The distribution used for the initial condition is the truncated normal,

$$w(x_0; P) = \frac{A}{\sqrt{2\pi}} \exp\left\{ -\frac{x_0^2}{2} \right\}, \quad x_0 < P, \quad (4.3)$$

where $A^{-1} = \frac{1}{\sqrt{2\pi}} \int_{-\infty}^P \exp\left\{ -\frac{x^2}{2} \right\} dx = \Phi(\bar{P})$,

and $\Phi(P)$ is the cumulative distribution function (c.d.f.) of the normal distribution with zero mean and unit variance. Except for the truncation, the distribution (4.3) is the stationary probability distribution of the process (1.5) transformed by (4.2). The transition density $f(x,t;x_0)$ of the transformed, and restricted, process X has to satisfy the Fokker-Planck equation

$$\frac{\partial f}{\partial t} = \frac{\partial}{\partial x}(xf) + \frac{\partial^2 f}{\partial x^2} \quad (4.4)$$

with the boundary condition $f(P,t;x_0) = 0$ at P , a natural boundary at $-\infty$ and the initial condition (4.3).

The method of eigenfunction expansions can be used to solve Fokker-Planck equations with imposed boundaries (e.g., Lindenberg et al., 1975). Details of using the methods of eigenfunctions to solve boundary- and initial-value problems can be found, for example, in Denne Meyer (1968). In order to obtain bounds on the FPT distribution and its moments, we will use the eigenfunction representation of the transition p.d.f. given by Mandl (1962), rather than the one that uses Hermite polynomials,

$$f_p(x,t) = \frac{A}{\sqrt{2\pi}} \sum_{k=0}^{\infty} \exp(-n_k t) \int_{-\infty}^P z_k(y) z_k(x) dy \quad (4.5)$$

where $z_k(y) = h_k(y) \exp\{-\frac{y^2}{4}\}$, and $\{h_k(y)\}_0^{\infty}$ is an orthonormal system of eigenfunctions in L^2 , square integrable functions (Feller, 1966), satisfying the equation

$$\frac{d^2h}{dy^2} + \left(n + \frac{1}{2} + \frac{1}{4}y^2 \right) h = 0 \quad (4.6)$$

and $\{n_k\}_0^\infty$ is the corresponding system of eigenvalues with $0 < n_k < n_{k+1}$. It follows from the properties of the solution of (4.4) (Mandl, 1962, eqn. 7) that $k < n_k$.

Now from the definition of the transition density $f_p(x,t)$ it is clear that the c.d.f., denoted by $G(t;P)$, of the FPT becomes

$$G(t;P) = 1 - \int_{-\infty}^P f_p(x,t) dx = 1 - \sum_{k=0}^{\infty} \exp(-n_k t) a_k \quad , \quad (4.7)$$

where $a_k = \frac{A}{\sqrt{2\pi}} \left(\int_{-\infty}^P z_k(y) dy \right)^2$. From the properties of n_k and a_k and using (4.7)

we can deduce that

$$a_0 e^{-n_0 t} \leq 1 - G(t;P) \leq a_0 e^{-n_0 t} + e^{-t}(1 - a_0) \quad . \quad (4.8)$$

Using the expressions for computing the moments of positive r.v.'s, we obtain from (4.8)

$$\frac{a_0}{n_0} \leq E(T_p) = \sum_{k=0}^{\infty} \frac{a_k}{n_k} \leq \frac{a_0}{n_0} + 1 - a_0 \quad (4.9)$$

and

$$\frac{2a_0}{n_0^2} \leq E(T_P^2) \leq \frac{2a_0}{n_0^2} + 2(1 - a_0) \quad (4.10)$$

Combining (4.9) and (4.10) yields bounds for the variance

$$\frac{2a_0}{n_0^2} - \left[\frac{a_0}{n_0} + (1 - a_0) \right]^2 \leq \text{Var}(T_P) \leq \frac{a_0}{n_0^2} (2 - a_0) + 2(1 - a_0) \quad (4.11)$$

Returning to equation (4.7) and differentiating it with respect to t , we find that the p.d.f. of the FPT satisfies the following inequality

$$(-1)^n \frac{d^n}{dt^n} g(t;P) \geq 0, \quad n = 1, 2, \dots \quad (4.12)$$

which is the relationship defining a completely monotone function on $(0, \infty)$, see, for example, Feller (1966, p. 439). The property (4.12) can be used (Keilson, 1979) to further characterize the FPT distribution. By using the Bernstein theorem, the completely monotonic character of $g(t;P)$ implies that it can be written in the form

$$g(t;P) = \int_0^\infty e^{-\lambda t} dF(\lambda) = \int_0^\infty e^{-\lambda t} \lambda dU(\lambda), \quad (4.13)$$

where $dF(\lambda) = \lambda dU(\lambda)$. Since T_P is a proper r.v., it follows that

$$1 = \int_0^\infty \int_0^\infty e^{-\lambda t} \lambda dt dU(\lambda) = \int_0^\infty dU(\lambda) \quad (4.14)$$

and we see $U(\lambda)$ is a c.d.f. Then due to (4.13) $g(t;P)$ can be considered to be a

compound exponential distribution. T_p can thus be written as the product of two independent r.v.'s, i.e. $T_p = YZ$, where Y is exponentially distributed r.v. (2.10) with the mean equal to one ($\lambda = 1$). One consequence is that $E(T_p) = E(Z)$, which leads to a bound for the CV of T_p (c.f. Keilson, 1979, p. 68), namely

$$CV^2(T_p) = \frac{E(T^2) - (E(T))^2}{(E(T))^2} = \frac{2E(Z^2) - (E(Z))^2}{(E(Z))^2} = \frac{2\text{Var}(Z)}{(E(Z))^2} + 1 \geq 1 \quad (4.15)$$

Before estimating the difference between the exponential c.d.f. and the c.d.f. of the FPT, we need a bound for the p.d.f. $g(t;P)$. From (4.7), for $t \geq 0$,

$$g(t;P) \leq \sum_{k=0}^{\infty} n_k a_k \leq \left[\sum_{k=0}^{\infty} a_k / n_k \right]^{-1} = E(T_p)^{-1} = \lambda \quad (4.16)$$

where the mean FPT is denoted by λ^{-1} . This result will be used in the same way as by Keilson (1979) by applying the following theorem (see Feller, 1966; p 512). Let F be the c.d.f. of a r.v. with mean λ^{-1} and characteristic function ϕ and suppose that G is the c.d.f. of another r.v. with the same mean and with characteristic function γ and with a bounded p.d.f., that is $g \leq m$, where m is a constant. Then for all t and $T \geq 0$

$$|G(t;P) - F(t)| \leq \frac{1}{\pi} \int_{-T}^T \left| \frac{\phi(t) - \gamma(t)}{t} \right| + \frac{24m}{\pi T} \quad (4.17)$$

Using the complete monotonicity property again, we have $T_p = Y'Z'$, where now $E(Z') = 1$ and $P(Y' \leq y) = 1 - e^{-\lambda y}$, i.e. Y' is exponentially distributed. Which implies

$$|\phi(t) - \gamma(t)| \leq |t| \lambda^{-1} E|Z' - 1| \quad (4.18)$$

and substituting this into (4.17) and using (4.16) we achieve the desired bound

$$|G(t;P) - (1 - e^{-\lambda t})| \leq \frac{2T}{\pi} \lambda^{-1} E|Z' - 1| + \frac{24\lambda}{\pi T} \leq \quad (4.19)$$

$$\leq \frac{8\sqrt{3}}{\pi} \sqrt{E|Z' - 1|} \leq \frac{8\sqrt{3}}{\pi} \sqrt{E(Z' - 1)^2} = \frac{8\sqrt{3}}{\pi} \sqrt{\frac{CV^2(T_p) - 1}{2}}.$$

This result is similar to that of Nobile et al. (1985) which states that for a fixed x_0

$$g(t;P, x_0) = \lambda e^{-\lambda t} + o(\lambda e^{-\lambda t}) \quad (4.20)$$

For other choices of $w(x_0;S)$ it does not appear that analytical results for $g(t;S)$ will be easily obtained. However, expressions for the moments, which are often used in spike train analysis, can be computed via the conditional expectation formulas

$$E(T_s) = E_{X_0}(E(T_s|x_0)) \quad (4.21)$$

$$\text{Var}(T_s) = E_{X_0}(\text{Var}(T_s|x_0)) + \text{Var}_{X_0}(E(T_s|x_0)) \quad (4.22)$$

and using the known results on the FPT moments for the Ornstein Uhlenbeck process with a fixed initial condition (e.g., Keilson and Ross, 1975; Thomas, 1975; Sato, 1978; Cerbone et al., 1981; Ricciardi and Sato, 1988).

Finally a remark about the conditional means of the process and of the FPT. While the conditional mean, $E(X(t)|X_0)$, of models (1.3) and (1.5) are the same, the conditional mean of the FPT, $E(T_s|X_0)$, of (1.3) is not that of model (1.5). On the other hand, in the limit as $\tau \rightarrow \infty$, the conditional means of both the processes and the FPT's are the same in models (1.3) and (1.4), c.f., (2.2) and (3.5).

5. Discussion

In this section we will discuss some generalizations and modifications of the models considered above and the robustness of some of the model assumptions.

The three models (1.3)-(1.5) are just a small part of the many neural models which address the FPT problem. A random initial condition could be introduced in these other models as well. For example, a simple variant of (1.1) is produced by assuming $\tau \rightarrow \infty$, $i = 0$. Then T_s is gamma distributed (2.14), where $\alpha-1$ is number of jumps necessary to reach the threshold S , i.e. $\lceil (S-x_0)/a \rceil$, which would become a r.v. since x_0 is a r.v. The ISI distribution now becomes the compound gamma distribution (Feller, 1966).

Other models which are similar to the models discussed above are the diffusion approximations of Stein's model with reversal potentials, (Hanson and Tuckwell, 1983; Smith and Smith, 1984; Lánský and Lánská, 1987; Giorno et al., 1988). The main characteristic of these models is that the membrane potential X is now confined between two boundaries called the excitatory and inhibitory reversal potentials. For some of these models the FPT problem is solved and the random initial value of resting potential can be introduced by applying formula (3.18); however, the value of x_0 cannot be lower than the value of the inhibitory reversal potential.

The model proposed recently by van den Boogaard and Johannesma (1984) for the interval distribution of a neuron's spontaneous activity in neural interaction studies can be reinterpreted in the terms of the model discussed in section 2. The model (1.3) is generalized by them in this way: The initial value x_0 is determined by the length of the previous ISI. Since the previous ISI is a r.v., the initial value for the following ISI will also be a r.v. To see this, let the r.v. X_0 's value on a given interval be x_0 , then the subsequent ISI is equal to the sum of two components; $t_1 = T_{S,x_0}$ given by (2.2), which they interpret as a random dead time, and t_2 which is a realization of an exponentially distributed r.v. specified by p.d.f. (2.10). A value of $X(t_1+t_2)$, given by (2.1), is now computed and the initial value X_0 for the next ISI is $X(t_1+t_2) - w$, where w is a positive constant. To ensure positive values of the dead time t_1 it is necessary that $w \geq (\mu\tau - S)$. The value of initial hyperpolarization is thus a transformation of an exponential r.v. and longer ISI's will produce an initial value closer to the threshold. The ISI's are obviously not independent r.v.'s in this model.

The introduction of dead times does not, however, preclude a renewal process for the ISI's. For example, the dead time model of Teich et al. (1976) can also be

cast in the framework of model (1.3). The dead time is t_1 , as above but the initial condition is now a r.v. that independent of the previous ISI's, and t_2 comes from an exponential distribution as above. The r.v. T_1 is assumed by them to be normally distributed, which we showed in section 2 can be produced by a lognormal distribution for X_0 .

As was the case in these two dead time models, the ISI's can either be a renewal process or there can be some type of serial dependence between intervals (see reviews cited in Introduction). Even under constant stimulus conditions, some significant serial dependence is often found experimentally for some types of neurons and stimulus conditions. Furthermore this dependence may not be detected in some cases due to the sensitivity to small sample sizes of the statistical methods used (e.g., Correia and Landolt, 1977; Lansky and Radil, 1987). Interpreting an observed serial dependence in the output spike train can also be difficult, as it may be due to cellular mechanisms, such as afterhyperpolarization, or due to dependency in the input processes (Goldberg et al., 1964). In any case, modeling the ISI distribution can still play a relevant role if the serial dependency is also properly modeled. As an example, suppose the marginal distribution of ISI's is a mixture of IGD's. In section 3, parameter estimation for this mixture was seen to be a complicated task. If the ISI's are a semi-alternating renewal or a psuedo-Markov process (de Kwaadsteniet, 1982; Ekholm, 1972), then the estimation problem can be significantly simplified by also using the autocorrelations. Modeling the marginal ISI distribution is also important in other approaches to spike train analysis, such as a 1-memory intensity function description for auditory brainstem neurons (Johnson et al., 1986).

Amoh (1984) studied the mixture of two IGD's in a different way than in Section 3. His approach can be interpreted as follows: x_0 and μ are constants, and

σ^2 takes on two different values. The resulting distribution is then derived from (1.4) by assuming that both the initial condition x_0 and drift μ are fixed but σ^2 takes the two different values σ_1^2 and σ_2^2 . While the distribution considered by Amoh always has a unimodal p.d.f. and its mean is same as the mean of each of its components, the model (3.11) can have a bimodal p.d.f. with a mean somewhere between the means of its components. Sufficient conditions for bimodality have been considered for normally distributed components (see Johnson and Kotz, 1970). For mixtures of IGD's a similar analysis may also be possible. A multimodal distribution similar to a mixture of IGD's was presented by Cobb et al. (1983) and was viewed as the stationary distribution of a diffusion process. They examined conditions for bimodality in generalized normal distributions but not for IGD's. Amoh (1985) solved the problem of discrimination between both components in a mixture of IGD's under the condition that the parameters or at least the mixing proportions are known.

As the threshold becomes large, the FPT distribution for the Ornstein Uhlenbeck process with a fixed initial condition approaches a limiting exponential form. This has been shown in various ways (see Smith, 1987 for a survey and references). The introduction of a random initial condition did not alter this result. The other main result for the Ornstein Uhlenbeck process with a random initial condition was that the CV is bounded below by 1, which is the CV of an exponential distribution. For a fixed initial value equal to the resting potential, this result can be deduced from tables (Keilson and Ross, 1975; Cerbone et al., 1981) or from series expansion (Smith and Sato, in preparation). Values of the CV > 1 have also been seen in some other related neuronal models (Tuckwell, 1979; Wilbur and Rinzel, 1983).

Studying the effect of varying the parameters in neuronal models can provide some practical insight as well as provide some type of sensitivity analysis. Some

relevant examples in Stein's model and its diffusion approximations are Ricciardi and Sacerdote (1979), Tuckwell (1979), Wilbur and Rinzel (1983), Smith and Smith (1984). For the models we have examined in this paper, the modeling assumptions are most appropriate when the intensities of input processes tend to be in the upper range and the effective size of postsynaptic potentials in the low range of values considered in the above examples.

This leads to a remark about the model parameters and the relation between the models. As σ becomes small with the other parameters fixed, the behaviour of (1.5) approaches that of (1.3). The FPT of model (1.4) may also approximate the FPT of model (1.5) in the case that the mean excitation level is well above threshold. (Smith, 1987). This can occur in two ways. As mentioned in the Introduction and at the end of Section 4, when $\tau \rightarrow \infty$ the process described model (1.5) approaches that of model (1.4). The other way is when τ is small but $\mu\tau$ is still sufficiently large. Since this is the scenario that produces high firing rates it will be the region where the effect of a random initial condition is most pronounced.

In most of the numerical studies on models (1.3) and (1.5) the value of τ is identified with value of passive membrane time constant and with a value of around 5 ms. Angelini et al. (1982) have discussed this question for the model (1.3) and they have warned against the direct identification of τ with the whole neuron membrane time constant. Other evidence suggests that the value of τ is more variable and ranges in value from 1 to 20 ms (Kandel and Schwartz, 1985, p. 69). The smoothing of the postsynaptic potential due to spatial properties of the neuron, e.g., effective cable length, is another confounding factor in making accurate measurements of τ (Jack et al., 1983, p. 168).

The final point to be discussed concerns the need for including a random, rather than fixed, initial condition in neural models. There is some experimental

evidence that the range of variation of x_0 is not large (e.g., O'Neill et al., 1986) and the fixed initial condition versions of (1.3)-(1.5) have worked reasonably well for some neuronal systems. Both of these facts suggest that the introduction of a random initial condition should be viewed as an attempt to produce a better fit of the ISI's and provides a more realistic understanding of the physiological mechanisms particularly at high firing rates. A caveat should be added though concerning the modeling of the distribution of X_0 . The upper limit is maximally S and biologically there is also a lower bound, due to say a reversal potential. For this reason we have to be extremely careful with all the models in which X_0 is distributed on $(-\infty, S)$ and the probability of an extreme hyperpolarization is not negligible.

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