

Inference for the Diffusion Models of Neuronal Activity

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ABSTRACT

Diffusion models of neuronal-membrane potential behavior belong to the most frequently analyzed description of neuronal processes. However, attempts to compare these models with experimental data are rare, and they are always based on interspike-interval statistics only. In the present paper, statistical inference for both standard diffusion models is given under the assumption that the values of the membrane potential are available. The results are compared with the interspike-interval approach.

1. INTRODUCTION

The diffusion models of spontaneous neuronal activity have been discussed and analyzed many times; the papers concerning them form a fairly extensive list. A survey of these models and their properties can be found in Fienberg [10], Holden [14], Sampath and Srinivasan [26], Yang and Chen [35], and Goel and Richter-Dyn [12], and they serve as a primary example in the book of Ricciardi [24]. The properties of diffusion models with respect to the diffusion approximation of Stein's model [28] are summarized by Tuckwell and Cope [30].

Since almost all papers on diffusion models begin by giving the reasons for this type of neuronal activity description, we can directly start with the characterization of the models.

It is assumed that the interspike intervals are generated in accordance with a renewal process formed by the first-passage times of a membrane potential to a threshold potential S . The membrane potential is a one-dimensional diffusion process, the value of which is reset to a constant (usually the resting potential x_0) at the moment corresponding to the time of the previous spike generation. More formally, let $W = \{W_t, t \geq 0\}$ be a standard Wiener process, and let us suppose that $\mu(\cdot)$ and $\sigma(\cdot)$ are two continuous functions. Then the membrane potential $X = \{X_t, t \geq 0\}$ is defined as the solution of

the autonomous stochastic differential equation

$$\begin{aligned} dX_t &= \mu(X_t) dt + \sigma(X_t) dW_t, & t \geq 0, \\ X_0 &= x_0 < S \end{aligned} \quad (1)$$

and interspike intervals are independent realizations of the random variable

$$T_S = \inf\{t \geq 0; X_t \geq S\}. \quad (2)$$

The theory of stochastic differential equations (see [11]) immediately predicts that under general conditions on $\mu(x)$ and $\sigma(x)$ the transition probability density $f(x, t|x_0)$ of the process X is the solution of the Fokker-Planck equation

$$\frac{\partial f}{\partial t} = -\frac{\partial}{\partial x}[\mu(x)f] + \frac{1}{2} \frac{\partial^2}{\partial x^2}[\sigma^2(x)f] \quad (3)$$

with the initial condition $f(x, 0|x_0) = \delta(x - x_0)$.

Two basic mechanisms for the membrane-potential behavior are commonly taken into account. The first one is usually called the perfect integrator, and X is the Wiener process fulfilling (1) with

$$\mu(x) = \mu, \quad \sigma(x) = \sigma > 0. \quad (4)$$

The solution of (3) with the infinitesimal moments (4) is

$$f(x, t|x_0) = (2\pi\sigma^2 t)^{-1/2} \exp\left(-\frac{(x - x_0 - \mu t)^2}{2\sigma^2 t}\right). \quad (5)$$

To get the proper probability distribution of T_S we have to assume $\mu \geq 0$, for which the first-passage time probability density $p(t|S, x_0)$ is

$$p(t|S, x_0) = \frac{S - x_0}{\sigma(2\pi t^3)^{1/2}} \exp\left(-\frac{(S - x_0 - \mu t)^2}{2\sigma^2 t}\right). \quad (6)$$

The other extensively investigated neuronal diffusion model is not so simple as the previous one; it is known as the leaky integrator. In this case the infinitesimal moments are

$$\mu(x) = -\frac{x}{\tau} + \mu, \quad \sigma(x) = \sigma > 0, \quad (7)$$

where $\tau > 0$. Obviously $\tau \rightarrow \infty$ implies the coincidence of the two models.

The stochastic process X given by (1) with parameters (7) is the Ornstein-Uhlenbeck process, and its transition probability density, determined by Equation (3), is

$$f(x, t|x_0) = [\pi\sigma^2\tau(1 - e^{-2t/\tau})]^{-1/2} \exp\left(-\frac{[x - \mu\tau - (x_0 - \mu\tau)e^{-t/\tau}]^2}{\sigma^2\tau(1 - e^{-2t/\tau})}\right). \quad (8)$$

There has been great effort to compute the first-passage-time density of the Ornstein-Uhlenbeck process. The final result is the Laplace transform of $p(t|S, x_0)$,

$$p^*(\lambda|S, x_0) = \exp\left(\frac{x_0^2 - S^2}{2\sigma^2\tau} - \frac{\mu}{\sigma^2}(x_0 - S)\right) \times \frac{D_{-\lambda\tau}((2/\tau\sigma^2)^{1/2}(-x_0 - \mu\tau))}{D_{-\lambda\tau}((2/\tau\sigma^2)^{1/2}(-S - \mu\tau))}, \quad (9)$$

where

$$D_{-\lambda\tau}(x) = \frac{\exp(-x^2/4)}{\Gamma(\lambda\tau)} \int_0^\infty \exp\left(-xy - \frac{y^2}{2}\right) y^{\lambda\tau-1} dy.$$

The inversion of this transformation is not available, and the formula (5.18) of Yang and Chen [35] holds only for $S = \mu\tau$; for comparison see Ricciardi [24, (6.82)]. Thus numerical tables and some approximations were developed by Keilson and Ross [15], Mandl [20], Beekman [3], and others.

The model of Capocelli and Ricciardi [5] can be included in this class of neuronal models too. The infinitesimal moments introduced in their work are

$$\mu(x) = -\frac{x}{\tau} + \mu, \quad \sigma(x) = \sigma(S - x), \quad (10)$$

where $\tau > 0$, $\sigma > 0$. They obtain a slightly different version of the Fokker-Planck equation, using Stratonovich's approach, than is implied by (3). For suitable range of parameters, to make S a regular boundary, they compute $f(x, t|x_0)$ and $p(t|S, x_0)$ in a very complicated form.

As pointed out above, all the presented models have been extensively studied in a neurophysiological context and are highly useful for the description of neuronal activity. Nevertheless, attempts to identify their parameters have been exceptionally rare.

This parameter estimation is always based on interspike-interval statistics only. However, the interspike distribution is often so complicated (e.g. in the

case of the leaky integrator) that it makes this approach ineffective. The only way to overcome this difficulty is to consider the membrane potential sampled between consecutive neuronal firings. From the experimental point of view this is permitted by the application of intracellular techniques. Then, having parameter estimation at our disposal, the usual comparison with experimental interval histograms is possible. Therefore the present paper is devoted to the estimation of parameters of neuronal diffusion models under the assumption that the values of the membrane potential are available. Although the achieved results are only theoretical, they may stimulate attempts to obtain empirical validation of these types of models.

From the derivation of the models, namely through diffusion approximation, it is clear that μ and σ are input parameters and S , x_0 , and τ are characteristics of the neuron itself. We are not able to record the activity of all inputs, due to their intrinsic properties as well as to their extremely large number, so we have to base our inference on the membrane-potential behavior. The parameters S and x_0 can be easily identified, at least theoretically; see Griffith [13], Schmidt [27]. The identification of μ , τ , and σ is studied in this paper.

There exist very sophisticated methods for parameter estimation in stochastic processes, which are based on the theory of stochastic differential equation. For the survey of maximum-likelihood (m.l.) estimations in diffusion processes see e.g. Basawa and Prakasa Rao [2]. This approach assumes a continuous sampling of the analyzed stochastic process. On the other side, the classical m.l. method using the probability density function is more instructive and gives results in a form ready for direct numerical evaluation with discrete sampling. Thus, whenever possible, the transition densities are used. The results based on the stochastic differential representation are added for the evaluation of continuously recorded data.

2. THE PERFECT INTEGRATOR

Let us consider the model defined by (3) and (4) or directly by (5). The situation with this model is simple, as the first-passage-time density (6) is quite tractable. The moments of T_S can be easily computed, and the first two moments are

$$\begin{aligned} E(T_S) &= \frac{S - x_0}{\mu}, \\ \text{Var}(T_S) &= \frac{S - x_0}{\mu} \frac{\sigma^2}{\mu^2} \end{aligned} \tag{11}$$

for $\mu > 0$. Since for $\mu = 0$ the expected value of T_S is infinite, we will assume further that $\mu > 0$. On substituting $a = (S - x_0)/\mu$ and $b = (S - x_0)^2/\sigma^2$

into (6), we obtain the transformation of $p(t|S, x_0)$,

$$p(t|a, b) = \left(\frac{b}{2\pi t^3} \right)^{1/2} \exp\left(-\frac{b(t-a)^2}{2a^2 t} \right), \quad (12)$$

$a > 0, b > 0$. It follows from (11) that a is a measure of location while b is a reciprocal measure of dispersion. The density (12) is usually taken in the standard form of the inverse Gaussian distribution. Its statistical properties are well known, and they can be found in Tweedie [32, 33] and Roy and Wasan [25].

Denoting by $\epsilon_i, i = 1, 2, \dots, n$, the observed interspike intervals, the m.l. estimator of $(a, 1/b)$ are

$$\hat{a} = \frac{1}{n} \sum_{i=1}^n \epsilon_i = \bar{\epsilon}, \quad (13)$$

$$\frac{1}{\hat{b}} = \frac{1}{n} \sum_{i=1}^n \frac{1}{\epsilon_i} - \frac{1}{\bar{\epsilon}}. \quad (14)$$

The probability density of \hat{a} is $p(\hat{a}|a, b)$, and $1/\hat{b}$ is distributed in accordance with $\chi^2_{(n-1)}/bn$, where the symbol $\chi^2_{(n-1)}$ denotes the chi-square distribution with $n-1$ degrees of freedom. Let us also remark that the uniform minimum variance unbiased estimation of $1/b$ is $(n-1)^{-1} \sum_{i=1}^n (1/\epsilon_i - 1/\bar{\epsilon})$ (Roy and Wasan [25]), and the uniformly most powerful test of the hypothesis $1/b = 1/b_0$ is also given in that paper. The minimum-variance unbiased estimator of μ is derived by Brown and Hewitt [4]:

$$\tilde{\mu} = (S - x_0) E(T_S^{-1}) + \frac{1}{S - x_0},$$

and thus

$$\tilde{a} = \frac{(S - x_0)^2}{(S - x_0)^2 E(T_S^{-1}) + 1}.$$

All these results seem to have been ignored in neurophysiology. Pernier [23] suggests a gradient method for minimalizing the squared error between $p(t|S, t_0)$ and the histogram of experimental data. The parameters $(S - x_0)/\sigma$ and μ/σ are estimated there, and the sampling quantities $E^2(T_S)/\text{Var}(T_S)$ and $E(T_S)/\text{Var}(T_S)$ are taken as initial values.

Nilsson [21] rederives the m.l. estimates (13) and (14) and compares them with different algorithms for the least-squares method using the moment estimates as initial values again. The author favors the least-squares estimates

over the m.l. ones because the latter seem to be more biased by slight distortion of the model data.

Correia and Landolt [7] use numerical nonlinear curve fitting to compare their interval histograms with the perfect-integrator model output. They achieve agreement only exceptionally.

This disagreement leads, in the neurophysiologically oriented paper of Wise [34], to the modification of (6), but this approach is beyond the scope of the present paper. For the models leading to this modified inverse Gaussian distribution, see [1].

Up to now, we have assumed that only interspike intervals are available for the statistical inference. In the rest of the paper let us assume that the values of membrane potential X can be recorded at least at some time instants between consecutive spikes. We consider the process X in the time interval $\langle 0, T \rangle$ with spikes occurring at moments $\tau_0 \leq 0 < \tau_1 < \dots < \tau_n \leq T$, i.e. $\epsilon_i = \tau_i - \tau_{i-1}$, where $i = 1, \dots, n$. From the properties of both models we know that only a finite number of spikes appear in $\langle 0, T \rangle$ with probability one. Denote $N + n = \sum_{i=1}^n (m_i + 1)$ values of membrane potentials at instants t_{ij} , $0 = t_{11} < t_{12} < \dots < t_{1, m_1+1} \leq \tau_1 \leq t_{21} < \dots < t_{n, m_n+1} \leq \tau_n \leq T$, by the symbols x_{ij} . For $t_{i, m_i+1} = \tau_i$ we put $x_{i, m_i+1} = S$ and $x_{i+1, 1} = x_0$. The m.l. function for the perfect integrator follows from (5):

$$L(\mathbf{x}|\mu, \sigma^2) = \prod_{i=1}^n \prod_{j=1}^{m_i} f(x_{i, j+1}, h_{ij}|x_{ij}),$$

where $h_{ij} = t_{i, j+1} - t_{ij}$. Let us also denote $d_{ij} = x_{i, j+1} - x_{ij}$. Thus the log-likelihood function is

$$l(\mathbf{x}|\mu, \sigma^2) = \sum_{i=1}^n \sum_{j=1}^{m_i} \left(-\frac{1}{2} \log \sigma^2 - \frac{(d_{ij} - \mu h_{ij})^2}{2\sigma^2 h_{ij}} \right), \quad (15)$$

from which the equation for the estimation of μ is

$$\sum_{i=1}^n \sum_{j=1}^{m_i} (d_{ij} - \mu h_{ij}) = 0.$$

Solving this equation, we get

$$\hat{\mu} = \frac{\sum_{i=1}^n (x_{i, m_i+1} - x_{i1})}{T},$$

and for $t_{i,m_i+1} = \tau_i$ ($i=1, \dots, n$), $t_{11} = \tau_0$, we obtain

$$\hat{\mu} = \frac{S - x_0}{\bar{\varepsilon}}, \quad (16)$$

which is equivalent to (13). This result is not surprising, as it is the direct consequence of the fact that the first-passage time is sufficient for μ [4]. For the σ^2 estimation we have from (15) the equation

$$\sum_{i=1}^n \sum_{j=1}^{m_i} \left(-\frac{1}{2} \sigma^{-2} + \sigma^{-4} \frac{(d_{ij} - \mu h_{ij})^2}{2 h_{ij}} \right) = 0,$$

with the solution

$$\hat{\sigma}^2 = \frac{1}{N} \sum_{i=1}^n \sum_{j=1}^{m_i} \frac{(d_{ij} - \mu h_{ij})^2}{h_{ij}}. \quad (17)$$

Substituting $\hat{\mu}$ into this estimator, we have

$$\hat{\sigma}^2 = \frac{1}{N} \sum_{i=1}^n \sum_{j=1}^{m_i} \frac{d_{ij}^2}{h_{ij}} - \frac{1}{T} \left(\sum_{i=1}^n (x_{i,m_i+1} - x_{ij}) \right)^2,$$

and for the case described by (16),

$$\hat{\sigma}^2 = \frac{1}{N} \left(\sum_{i=1}^n \sum_{j=1}^{m_i} \frac{(d_{ij})^2}{h_{ij}} - \frac{n(S - x_0)^2}{\bar{\varepsilon}} \right). \quad (18)$$

Obviously, the estimator (18) is equivalent to (14) if the only observations of X are in the moments of the spike generation. The values of X recorded with increasing sampling rate improve the quality of σ^2 estimation, and finally a continuous record makes it possible to determine σ^2 exactly. More precisely, for any diffusion process (1) and for any interval $\langle 0, s \rangle$,

$$\lim_{n \rightarrow \infty} \sum_{j=1}^{2^n} (X_{js2^{-n}} - X_{(j-1)s2^{-n}})^2 = \int_0^s \sigma^2(X_t) dt \quad \text{a.s.}; \quad (19)$$

see [9]. Thus in the analyzed model, with appropriate subdivision of $\langle 0, T \rangle$,

$$\lim_{N \rightarrow \infty} \sum_{i=1}^n \sum_{j=1}^{m_i} (x_{i,j+1} - x_{ij})^2 = T \sigma^2 \quad \text{a.s.}$$

The term corresponding to the quadratic variation of X also dominates in the relationships (17) and (18).

Taking (19) into account, there is no need to analyze the asymptotic properties of σ^2 . For the parameter μ Fisher's information measure can be computed:

$$i(\mu) = E \left(\frac{f'(x_{i,j+1}, h_{ij}|x_{ij})}{f(x_{i,j+1}, h_{ij}|x_{ij})} \right)^2 = \frac{h_{ij}}{\sigma^2},$$

and hence the asymptotic distribution of

$$\sqrt{\sum_{i=1}^n \sum_{j=1}^{m_i} \frac{h_{ij}}{\sigma^2}} (\hat{\mu} - \mu) = \sqrt{\frac{T}{\sigma^2}} (\hat{\mu} - \mu)$$

is standard normal distribution from which an approximate confidence interval can be obtained, and with $T \rightarrow \infty$, $\hat{\mu}$ almost surely converges to μ [8].

3. THE LEAKY INTEGRATOR

The model given by (3) and (7), or by (8), is more complicated, as it contains an additional parameter τ . The distribution of T_S is known only in the form of the Laplace transform, and thus direct statistical inference based on interspike intervals is impossible. The formulae for moments of T_S are also complicated, and only numerical and approximation methods can be used [29, 30]. For these reasons there have not been any attempts to compare the model with the experimental data. The only exception is a note by Nillson [21], who mentions the possibility of some simulation method, but simultaneously rejects this proposal.

Let us assume the same sampling procedure on X as in the previous case. Using (8) and Taylor's expansion of e^{-x} , the log-likelihood function is

$$l(\mathbf{x}|\mu, \sigma^2, \tau) \sim -\frac{N}{2} \log \sigma^2 - \sum_{i=1}^n \sum_{j=1}^{m_i} \frac{(d_{ij} + (x_{ij}/\tau)h_{ij} - \mu h_{ij})^2}{2\sigma^2 h_{ij}}. \quad (20)$$

Thus, the m.l. equations are

$$\sum_{i=1}^n \sum_{j=1}^{m_i} \frac{d_{ij} + (x_{ij}/\tau)h_{ij} - \mu h_{ij}}{\sigma^2} = 0, \quad (21)$$

$$\sum_{i=1}^n \sum_{j=1}^{m_i} \frac{(d_{ij} + x_{ij}h_{ij}/\tau - \mu h_{ij})x_{ij}}{\sigma^2 \tau^2} = 0, \quad (22)$$

$$-\frac{N}{2} \frac{1}{\sigma^2} + \sum_{i=1}^n \sum_{j=1}^{m_i} \frac{[d_{ij} + (x_{ij}/\tau)h_{ij} - \mu h_{ij}]^2}{2h_{ij}\sigma^4} = 0, \quad (23)$$

which gives the estimates

$$\hat{\mu} = \frac{\sum_{i=1}^n \sum_{j=1}^{m_i} d_{ij} \sum_{i=1}^n \sum_{j=1}^{m_i} x_{ij}^2 h_{ij} - \sum_{i=1}^n \sum_{j=1}^{m_i} x_{ij} h_{ij} \sum_{i=1}^n \sum_{j=1}^{m_i} d_{ij} x_{ij}}{T \sum_{i=1}^n \sum_{j=1}^{m_i} x_{ij}^2 h_{ij} - \left(\sum_{i=1}^n \sum_{j=1}^{m_i} x_{ij} h_{ij} \right)^2}, \quad (24)$$

$$\hat{\tau} = \frac{\left(\sum_{i=1}^n \sum_{j=1}^{m_i} x_{ij} h_{ij} \right)^2 - T \sum_{i=1}^n \sum_{j=1}^{m_i} x_{ij}^2 h_{ij}}{T \sum_{i=1}^n \sum_{j=1}^{m_i} d_{ij} x_{ij} - \sum_{i=1}^n \sum_{j=1}^{m_i} d_{ij} \sum_{i=1}^n \sum_{j=1}^{m_i} h_{ij} x_{ij}} \quad (25)$$

and

$$\hat{\sigma}^2 = \frac{1}{N} \sum_{i=1}^n \sum_{j=1}^{m_i} \frac{(d_{ij} + x_{ij} h_{ij} / \hat{\tau} - \hat{\mu} h_{ij})^2}{h_{ij}} \quad (26)$$

If $x_{i, m_i+1} = S$, $x_{i1} = x_0$, $i = 1, \dots, n$, and $0 = \tau_0$, $T = \tau_n$, the estimators (24) and (25) can be rewritten

$$\hat{\mu} = \frac{\sum_{i=1}^n \sum_{j=1}^{m_i} x_{ij} h_{ij} \sum_{i=1}^n \sum_{j=1}^{m_i} d_{ij} x_{ij} - n(S - x_0) \sum_{i=1}^n \sum_{j=1}^{m_i} x_{ij}^2 h_{ij}}{\left(\sum_{i=1}^n \sum_{j=1}^{m_i} x_{ij} h_{ij} \right)^2 - T \sum_{i=1}^n \sum_{j=1}^{m_i} x_{ij}^2 h_{ij}} \quad (27)$$

and

$$\hat{\tau} = \frac{\left(\sum_{i=1}^n \sum_{j=1}^{m_i} x_{ij} h_{ij} \right)^2 - T \sum_{i=1}^n \sum_{j=1}^{m_i} x_{ij}^2 h_{ij}}{T \sum_{i=1}^n \sum_{j=1}^{m_i} d_{ij} x_{ij} - n(S - x_0) \sum_{i=1}^n \sum_{j=1}^{m_i} x_{ij} h_{ij}} \quad (28)$$

In $\hat{\sigma}$ the term $\sum_{i=1}^n \sum_{j=1}^{m_i} d_{ij}^2$ dominates again. As in the previous case, σ^2 can be determined from a continuous recording of X using (19). When a continuous recording is available, the estimators (27) and (28) may also be

modified by taking the limit $h_{ij} \rightarrow 0$. Then

$$\hat{\mu} = \frac{\sum_{i=1}^n \int_{\tau_{i-1}}^{\tau_i} X_t dt \sum_{i=1}^n \int_{\tau_{i-1}}^{\tau_i} X_t dX_t - n(S - x_0) \sum_{i=1}^n \int_{\tau_{i-1}}^{\tau_i} X_t^2 dt}{\left(\sum_{i=1}^n \int_{\tau_{i-1}}^{\tau_i} X_t dt \right)^2 - T \sum_{i=1}^n \int_{\tau_{i-1}}^{\tau_i} X_t^2 dt}, \quad (29)$$

$$\hat{\tau} = \frac{\left(\sum_{i=1}^n \int_{\tau_{i-1}}^{\tau_i} X_t dt \right)^2 - T \sum_{i=1}^n \int_{\tau_{i-1}}^{\tau_i} X_t^2 dt}{T \sum_{i=1}^n \int_{\tau_{i-1}}^{\tau_i} X_t dX_t - n(S - x_0) \sum_{i=1}^n \int_{\tau_{i-1}}^{\tau_i} X_t dt}, \quad (30)$$

where $\int_{\tau_{i-1}}^{\tau_i} X_t dX_t$ can be replaced by $\frac{1}{2} \{X_{\tau_i}^2 - X_{\tau_{i-1}}^2 - \sigma^2(\tau_i - \tau_{i-1})\}$, applying Ito's formula. Using the transition probability density (8), the information matrix for μ and τ can be computed [8]. For $h_{ij} \rightarrow 0$ it has the form

$$J = \begin{pmatrix} \frac{T}{\sigma^2} & \frac{1}{\sigma^2 \tau^2} \sum_{i=1}^n \int_{\tau_{i-1}}^{\tau_i} X_s ds \\ \frac{1}{\sigma^2 \tau^2} \sum_{i=1}^n \int_{\tau_{i-1}}^{\tau_i} X_s ds & \frac{1}{\tau^4 \sigma^2} \sum_{i=1}^n \int_{\tau_{i-1}}^{\tau_i} X_s^2 ds \end{pmatrix}, \quad (31)$$

and for the vector of estimations we have asymptotically

$$\sqrt{T}[(\hat{\mu}, \hat{\tau})' - (\mu, \tau)'] \sim N(0, J^{-1}).$$

The above results are based on the knowledge of the transition probability density and thus the formulae are obtained in the form applicable to data. However, a more sophisticated approach to the estimation of diffusion-process parameters is based on the stochastic differential equation [2, 17, 18, 19]. Using the cited method, the m.l. estimator for the diffusion model suggested by Capocelli and Ricciardi [5] can be computed in spite of the fact that the complicated form of the transition density makes the classical approach impractical. The model mentioned is given by (10), and the corresponding stochastic differential equation is

$$dX_t = \left(-\frac{1}{\tau} X_t + \mu \right) dt + \sigma \sqrt{S - X_t} dW_t; \quad (32)$$

its interpretation can be found in the cited paper.

For the estimation of the parameters of (32) we use the m.l. equation

$$0 = \int_0^T \sigma^{-2}(X_t) \frac{\partial}{\partial \Theta} [\mu(X_t | \Theta)] dX_t - \int_0^T \sigma^{-2}(X_t) \mu(X_t | \Theta) \frac{\partial}{\partial \Theta} [\mu(X_t | \Theta)] dt, \quad (33)$$

where Θ is an unknown parameter appearing only in $\mu(\cdot)$; see e.g. [24, Equation (5.8)]. Due to (19), we may consider a parameter involved in $\sigma(\cdot)$ as being known from a single realization, and so we put $\sigma^2 = 1$ in (32). For notational simplicity let us denote $Y_t = (S - X_t)^{-1}$. Substituting infinitesimal moments of (32) into (33), we obtain the following pair of equations for μ and τ :

$$0 = \int_0^T Y_t dX_t - \int_0^T \left(-\frac{1}{\tau} X_t + \mu \right) Y_t dt, \quad (34)$$

$$0 = \int_0^T \tau^{-2} X_t Y_t dX_t - \int_0^T \tau^{-2} \left(-\frac{1}{\tau} X_t + \mu \right) X_t Y_t dt. \quad (35)$$

Solving these equations, the m.l. estimators of μ and τ are

$$\hat{\mu} = \frac{\int_0^T Y_t dX_t + \int_0^T \tau^{-1} X_t Y_t dt}{\int_0^T Y_t dt} \quad (36)$$

and

$$\hat{\tau} = \frac{\int_0^T X_t^2 Y_t dt}{\int_0^T \mu X_t Y_t dt - \int_0^T X_t Y_t dX_t}, \quad (37)$$

and combining (36) and (37), we get another version more suitable for comparison with previous results:

$$\hat{\mu} = \frac{\int_0^T X_t Y_t dt \int_0^T X_t Y_t dX_t - \int_0^T Y_t dX_t \int_0^T X_t^2 Y_t dt}{\left(\int_0^T X_t Y_t dt \right)^2 - \int_0^T Y_t dt \int_0^T X_t^2 Y_t dt} \quad (38)$$

and

$$\hat{\tau} = \frac{\left(\int_0^T X_t Y_t dt \right)^2 - \int_0^T Y_t dt \int_0^T X_t^2 Y_t dt}{\int_0^T Y_t dt \int_0^T X_t Y_t dX_t - \int_0^T Y_t dX_t \int_0^T X_t Y_t dt}. \quad (39)$$

We can see that (38) and (39), with the function $Y_t = (S - X_t)^{-1}$ identically equal to one, coincide with (29) and (30) for $n=1$, $\tau_0=0$, $\tau_1=T$.

The whole procedure applied above assumes $T \leq \tau_1$; however, the generalization for $\tau_1 < T$ is straightforward.

4. REMARKS

As pointed out in the Introduction, there exist many generalizations of neuronal diffusion models. The most frequent one is based on the assumption of a time dependent threshold potential [6, 12, 16, 34]. To include this phenomenon in the derived statistical inference is only formal procedure which leaves most results untouched.

Another modification, with direct consequences for the real physiological interpretation, is spontaneous decay of X in the leaky integrator to some equilibrium value c . Then the infinitesimal mean value (7) is

$$\mu(x) = -\frac{x-c}{\tau} + \mu.$$

It is natural to expect $c = x_0$, and thus the estimates of μ given by (24), (27), (29), and (38) are in fact the estimates of $\mu + x_0/\tau$.

Any generalization leading to the diffusion model can be analyzed by methods described in the cited theoretical studies. The problem of testing a statistical hypothesis is closely related to the problem of parameter estimation. This question is only slightly touched on in this paper; however, the relevant results can be found in several cited papers [9, 17, 18, 19].

For the case of the perfect integrator the presented approach does not give any advantage over the interspike method. On the other hand, the leaky integrator given by (7) with $\mu=0$ is employed as an example in many theoretically oriented papers. In this connection, the results of Novikov [22] represent a powerful tool for more advanced statistical inference.

In almost any case it is possible to apply the method of Feigen [9], which includes the diffusion approximation, so relevant for neural modeling [30]. Then the results obtained can be compared with those of Tuckwell and Richter [31], who solved the problem of parameter estimation in the original Stein model.

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