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REVIEW

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A review of the methods for signal estimation in stochastic diffusion leaky integrate-and-fire neuronal models

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Abstract Parameters in diffusion neuronal models are divided into two groups; *intrinsic* and *input* parameters. Intrinsic parameters are related to the properties of the neuronal membrane and are assumed to be known throughout the paper. Input parameters characterize processes generated outside the neuron and methods for their estimation are reviewed here. Two examples of the diffusion neuronal model, which are based on the integrate-and-fire concept, are investigated—the Ornstein–Uhlenbeck model as the most common one and the Feller model as an illustration of state-dependent behavior in modeling the neuronal input. Two types of experimental data are assumed—intracellular describing the membrane trajectories and extracellular resulting in knowledge of the interspike intervals. The literature on estimation from the trajectories of the diffusion process is extensive and thus the stress in this review is set on the inference made from the interspike intervals.

Keywords Ornstein–Uhlenbeck · Statistical inference · Feller process · First-passage times · Maximum likelihood · Moment method · Laplace transform · Fortets integral equation · Interspike intervals

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1 Introduction

The integrate-and-fire neuronal models are probably the most common mathematical representations of a single neuron (Brunel and van Rossum 2008). These models have many variants and can even encompass other models which are not obviously of this type. Recently Burkitt (2006) reviewed the integrate-and-fire neuronal models and mathematical techniques to analyze them. All relevant references related to the history and treatment of the models can be found there. Our attention is restricted to a subclass of the integrate-and-fire models characterized by the terms *stochastic, diffusion* and *leaky*.

The interspike intervals (ISIs) recorded from different neuronal structures and under different experimental settings are very variable even under stable conditions. It suggests presence of stochastic variation in neuronal activity. Taking into account that the action potentials (spikes) from surrounding neurons are the input to the one under study, we may assume that there is a random component, generally denoted as noise, contained in the incoming signal. The other source of noise can be the neuron itself where a random force, due to the spontaneous opening and closing of ionic channels, acts and is added to the signal. From a mathematical point of view, an introduction of stochasticity into the description of the neuron represents an increase of model complexity. On the other hand, the random component of the neuronal activity can be considered a part of the signal transferred within neurons. This seems plausible since coding of information by randomness of ISIs is one possible variant of neuronal coding (Kostal et al. 2007a,b).

The stochastic integrate-and-fire neuronal models describe the membrane potential as a continuous-time stochastic process. Stochastic diffusion processes play a specific role in the theory of stochastic processes for their mathematical

tractability and simultaneous applicability in many different fields. They can be classified as continuous-time Markov processes with continuous trajectories, and since the introduction of the concept of integrate-and-fire neuronal model (Gerstein and Mandelbrot 1964; Johannesma 1968), many arguments have been given why this treatment of stochastic integrate-and-fire models is appropriate.

There are many variants of integrate-and-fire neuronal models (Burkitt 2006) and other generalizations were recently introduced aiming to improve flexibility of the model and its predictive power (Jolivet et al. 2006; Clopath et al. 2007). Leakage of the neuronal membrane, meaning that the current flows through the membrane due to its passive properties, was one of the first specifications of the integrate-and-fire neuron model. It is a crucial property and is inherent in practically all variants of the model.

The most common model of the leaky integrate-and-fire (LIF) type is the deterministic model, also known as the Lapicque model or RC-circuit (Tuckwell 1988),

$$\frac{\mathrm{d}x(t)}{\mathrm{d}t} = -\frac{x(t)-x_r}{\tau} + \mu(t), \quad x(0) = x_0, \tag{1}$$

where $x(t)$ represents the cell membrane voltage, x_0 is the initial voltage after spike generation, $\mu(t)$ is an input signal, and $RC = \tau > 0$ is a time constant governing the spontaneous decay of the voltage back to a resting level x_r. Here R is the membrane resistance and C is the capacitance. The solution of Eq. (1) includes an integral of the input signal $\mu(t)$ with exponentially decaying effect, which is the reason for calling the model by the name "leaky-integrator". The signal $\mu(t)$ appearing in (1) is a representation of an external signal transformed into an internal generator potential, a quantity having dimension of voltage per time. Due to the simplicity of model (1), the action potential generation is not an inherent part of the model like in more complex ones and the firing threshold S has to be imposed, where $S > x_0$. The model neuron fires whenever the threshold is reached and then the voltage $x(t)$ is reset to its initial value. The reset following the threshold crossing introduces a strong nonlinearity into the model. For a constant input $\mu(t) = \mu > S/\tau$, the neuron fires regularly, whereas for $\mu \leq S/\tau$, the model never reaches the threshold S and the neuron remains silent. This defines sub- and suprathreshold signal in model (1). Despite it is an abstraction, the parameters S, x_r, x_0 and τ characterize the neuronal membrane, and $\mu(t)$ characterizes the input signal.

Assume there is a random component contained in the incoming signal. A phenomenological way to introduce stochasticity into the deterministic leaky-integrator model is by introducing additional noise terms in (1),

$$\mathrm{d}X_t = \left(-\frac{X_t - x_r}{\tau} + \mu(t)\right)\mathrm{d}t + \sigma(X_t,t)\,\mathrm{d}F_t + a(X_t,t)\,\mathrm{d}P^+ + i(X_t,t)\,\mathrm{d}P^-, \quad X_0 = x_0, \tag{2}$$

where we use the notation $X(t) = X_t$, F_t represents a Wiener process with generalized derivative a δ-correlated Gaussian white noise with zero mean, and P^+ and P^- represent Poisson processes corresponding to excitatory and inhibitory synaptic inputs, respectively. The functions $\sigma(\cdot)$, $a(\cdot)$ and $i(\cdot)$ scale the noise terms. Similar to the deterministic model (1), also in the stochastic integrate-and-fire models, the firing is not an intrinsic part of the model and the firing threshold has to be imposed. The stochastic process X describing the membrane depolarization makes random excursions to the firing threshold S. When the threshold is reached, a firing event occurs and the membrane depolarization is reset. The ISIs are identified with the first passage time T of X across S. In numerous papers on stochastic LIF models, the properties of the random variable T are studied and compared by various methods with properties of ISIs.

Two interconnected problems, generally denoted as parameter identification, can be related to Eqs. (1) or (2). The first problem is identification of the model parameters (S, x_0, x_r, τ). This can be done by indirect electrophysiological methods, by deducing from the properties of other neurons, or from measuring the membrane potential fluctuations. If these parameters are known, one can check how well the model predicts spiking activity under the condition of an identical input with a real neuron (Jolivet et al. 2006, 2008; Clopath et al. 2007). The second problem, reviewed in this paper, is how to identify the signals impinging upon the neuron under the condition of stationarity and thus search for $\mu = \mu(t)$ and a constant parameter σ scaling the amplitude of the noise $\sigma(t)$. Knowledge of these two parameters can be used either to deduce an unknown signal arriving to a neuron, or to check if an artifically delivered signal can be read correctly.

To estimate the input signal, either data on the time-course of the membrane depolarization or ISIs have to be available. Obviously, from the trajectory of the membrane depolarization the length of the ISI can be deduced but not vice versa, and thus the former data contain more information. The literature on parameter estimation in diffusion models based on complete or partial knowledge of the trajectory is rather extensive (Prakasa Rao 1999; Kutoyants 2003), irrespective of the application field. On the other hand, we have failed to find any other application in which the parameters of the diffusion process are estimated from the knowledge of the first-passage times and the results in the neuronal context are quite limited. Therefore, we present only basic results on the estimation from intracellular recordings and concentrate on the problems arising in the procedures based on the ISIs. The properties of the models which are relevant for the estimation

procedures of the parameters are summarized in Sect. 2, and in Sect. 3 the methods are presented. The methods for estimation from ISI data have been widely verified and compared, both through simulation of artificial data and on experimental neuronal data in Ditlevsen and Lansky (2005, 2006, 2007, 2008) and Ditlevsen and Ditlevsen (2008).

2 Model

Stochastic diffusion In diffusion neuronal models, the changes in the membrane depolarization between two consecutive neuronal firings are represented by a scalar diffusion process $X = \{X_t;\ t \geq 0\}$ indexed by the time t, and given by the Itô-type stochastic differential equation

$$\mathrm{d}X_t = \nu(X_t, t)\ \mathrm{d}t + \sigma(X_t, t)\,\mathrm{d}W_t, \quad X_0 = x_0, \tag{3}$$

where $W = \{W_t;\ t \geq 0\}$ is a standard Wiener process and $\nu(\cdot)$ and $\sigma^2(\cdot)$ are real-valued functions (called the drift and the infinitesimal variance) of their arguments satisfying certain regularity conditions to ensure the existence of a unique solution to (3). The drift coefficient reflects the local average rate of displacement and local variability is represented by the infinitesimal variance. We will write $f(y, t|x)$ for the transition density function, i.e., the probability density function for the process X to be at y after time interval t given that the process was initially at x at time $t = 0$. For the theory of diffusion processes, see, e.g., Karlin and Taylor (1981).

First-passage-time is Interspike interval An action potential is produced when the membrane voltage X exceeds a voltage threshold for the first time, for simplicity assumed to be equal to a constant $S > x_0$. Formally, the ISI is identified with the first-passage time T of the threshold,

$$T = \inf\{t > 0 : X_t \geq S\}, \tag{4}$$

with probability density function $g(t|S, x_0)$. It follows from the model assumptions that for a time-homogeneous process X containing either a Poissonian or white noise only, the ISIs form a renewal process and the initial time following a spike can always be identified with zero. In Fig. 1 the random variable T is illustrated.

Renewal equation The renewal equation, also called Fortet's equation (Durbin 1971; Fortet 1943) relates the first-passage time density to the transition density $f(\cdot)$ for $x \geq S$,

$$f(x, t \mid x_0) = \int_0^t f(x, t-u \mid S) g(u \mid x_0, S)\,\mathrm{d}u. \tag{5}$$

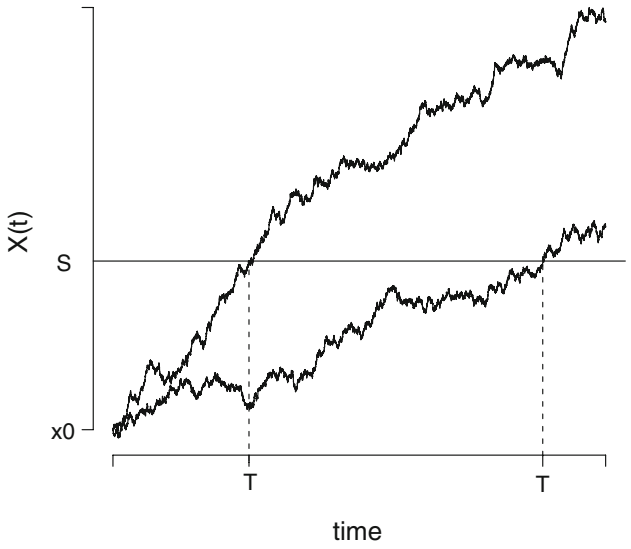

Fig. 1 Two realizations of the random variable T corresponding to two sample paths of X_t (membrane potential against time, arbitrary units)

We write $F(x, t-s \mid x_s) = \int^x f(v, t-s \mid x_s)\,\mathrm{d}v$ for the corresponding transition distribution function. For details see Ricciardi (1977).

First-passage time moments Assuming that the process X has an invariant distribution $\pi(x) = \lim_{t\to\infty} f(x, t|\cdot)$, such that if $X_0 \sim \pi$, then X is a stationary process with $X_t \sim \pi$ for all t, then the following recursion formula for the first-passage time moments can be obtained (Siegert 1951):

$$E[T^n] = n \int_{x_0}^{S} \frac{2}{\sigma^2(z)\pi(z)} \left(\int_{-\infty}^{z} \pi(y) E[T^{n-1}]\,\mathrm{d}y \right) \mathrm{d}z. \tag{6}$$

In particular, the mean is given by

$$E[T] = \int_{x_0}^{S} \frac{2}{\sigma^2(z)\pi(z)} \left(\int_{-\infty}^{z} \pi(y)\,\mathrm{d}y \right) \mathrm{d}z. \tag{7}$$

2.1 Ornstein–Uhlenbeck

The most common diffusion model proposed for nerve membrane behavior is the Ornstein–Uhlenbeck (OU) process. It is defined by Eq. (3) with infinitesimal moments

$$\nu(x) = -\frac{x}{\tau} + \mu,\ \sigma(x) = \sigma > 0, \tag{8}$$

where $\tau > 0$. Compared to Eqs. (1) or (2), it is seen that the resting potential is transformed to zero and the firing threshold and the reset value are relative to the resting level. This transformation is applied throughout the rest of the paper. The parameters appearing in (4) and (8) can be divided into two groups: parameters characterizing the input, μ and σ, and

intrinsic parameters, τ, x_0 and S, which describe the neuron, irrespective of the incoming signal (Tuckwell and Richter 1978). Note that compared with the deterministic LIF given by Eq. (1), an additional input parameter σ appears in Eq. (8). For a fixed time t, X_t given by (8) is a Gaussian random variable with mean

$$E[X_t] = x_0 e^{-t/\tau} + \mu\tau(1 - e^{-t/\tau}), \tag{9}$$

which is the solution of the deterministic model (1) for a constant input μ. The variance of X is

$$\mathrm{Var}[X_t] = \frac{\sigma^2\tau}{2}(1 - e^{-2t/\tau}). \tag{10}$$

Analogous to the deterministic LIF described in the Introduction, two distinct firing regimes, usually called sub- and suprathreshold, can be established for the OU model. In suprathreshold regime, the asymptotic mean depolarization $\mu\tau$ given by (9) is far above the firing threshold S and the ISIs are relatively regular (deterministic firing—which means that the neuron is active also in the absence of noise). In the subthreshold regime, $\mu\tau \ll S$ and firing is caused only by random fluctuations of the depolarization (stochastic or Poissonian firing). The term "Poissonian firing" indicates that when the threshold is far above the steady-state depolarization $\mu\tau$ (relative to σ), the firing achieves characteristics of a Poisson point process (Nobile et al. 1985; Wan and Tuckwell 1982). For our purposes, let us denote the third regime, when $\mu\tau \approx S$, as the threshold regime. Division of the firing regimes in three parts was already proposed in Wan and Tuckwell (1982).

The properties of the random variable T including its probability density function $g(t \mid x_0, S) = g(t)$ have been extensively studied (Ricciardi and Sacerdote 1979; Nobile et al. 1985; Ricciardi and Sato 1988; Ricciardi et al. 1999; Alili et al. 2005; Aalen and Gjessing 2004; Ditlevsen 2007). The distribution $g(t)$ is only known for the specific situation $\mu\tau = S$, where the first-passage time density of the OU process across the boundary S is (Bulsara et al. 1996; Ricciardi 1977):

$$g(t) = \frac{2S\exp(2t/\tau)}{\sqrt{\pi\tau^3\sigma^2}(\exp(2t/\tau) - 1)^{\frac{3}{2}}} \times \exp\left\{-\frac{S^2}{\sigma^2\tau(\exp(2t/\tau) - 1)}\right\}. \tag{11}$$

Note that the signal μ does not appear in this formula due to the threshold condition.

When $\mu\tau \neq S$ approximation techniques have been devised (Ricciardi et al. 1999), of which many are based on the renewal equation (5). Also the Laplace transform of T has been used to find characteristics of the first-passage time distribution $g(t)$. A representation for $k < 0$ is given by

$$E\left[e^{kT/\tau}\right] = \frac{\exp\left(\frac{(\mu\tau)^2}{2\tau\sigma^2}\right) D_k\left(\frac{\sqrt{2}\mu\tau}{\sqrt{\tau}\sigma}\right)}{\exp\left(\frac{(\mu\tau - S)^2}{2\tau\sigma^2}\right) D_k\left(\frac{\sqrt{2}(\mu\tau - S)}{\sqrt{\tau}\sigma}\right)} = \frac{H_k\left(\frac{\mu\tau}{\sqrt{\tau}\sigma}\right)}{H_k\left(\frac{(\mu\tau - S)}{\sqrt{\tau}\sigma}\right)}, \tag{12}$$

where $D_k(\cdot)$ and $H_k(\cdot)$ are parabolic cylinder and Hermite functions, respectively (Borodin and Salminen 2002; Lebedev 1972). Let $\lambda^{(k)}$ be the largest root of the kth Hermite polynomial. By defining suitable martingales and applying Doob's Optional-Stopping Theorem, Eq. (12) can be extended to $k > 0$ in the parameter subspace $(\mu, \sigma) = \theta \in \Theta^{(k)} = \{\theta \mid \mu\tau > S, \sqrt{\tau\sigma^2} < (\mu\tau - S)/\lambda^{(k)}\}$ to ensure that $E\left[e^{kT/\tau}\right] < \infty$ (Ditlevsen 2007). Thus, we have closed expressions for $E[e^{kT/\tau}]$, $k = 1, 2$, in suprathreshold regime and with certain restrictions on the size of σ,

$$E[e^{T/\tau}] = \frac{\mu\tau}{\mu\tau - S}, \tag{13}$$

$$E[e^{2T/\tau}] = \frac{2(\mu\tau)^2 - \tau\sigma^2}{2(\mu\tau - S)^2 - \tau\sigma^2}, \tag{14}$$

if $\sigma^2 < 2(\mu\tau - S)^2/\tau$ (Ditlevsen and Lansky 2005). The condition means that the asymptotic standard deviation of X is smaller than the distance between the threshold and the asymptotic mean of X, as follows from (9) and (10).

In Ricciardi and Sato (1988) moments of T were given, the first two being

$$E[T] = \tau\,(\phi_1(\eta) - \phi_1(\xi)), \tag{15}$$

$$E[T^2] = \tau^2\left(2\phi_1^2(\eta) - \phi_2(\eta) - 2\phi_1(\eta)\phi_1(\xi) + \phi_2(\xi)\right), \tag{16}$$

where

$$\xi = -\mu\tau\sqrt{2/\sigma^2\tau}, \quad \eta = (S - \mu\tau)\sqrt{2/\sigma^2\tau} \tag{17}$$

and

$$\phi_1(z) = \frac{1}{2}\sum_{n=1}^{\infty}\frac{(\sqrt{2}z)^n}{n!}\Gamma\left(\frac{n}{2}\right), \tag{18}$$

$$\phi_2(z) = \phi_1(z)(\psi(n/2) - \psi(1)), \tag{19}$$

and $\Gamma(\cdot)$ and $\psi(\cdot)$ denote the gamma and the digamma function, respectively.

It is sometimes convenient to reformulate model (4) and (8) to the equivalent dimensionless form

$$\mathrm{d}Y_s = (-Y_s + \alpha)\,\mathrm{d}s + \beta\,\mathrm{d}W_s, \quad Y_0 = 0, \tag{20}$$

where

$$s = \frac{t}{\tau}, \quad Y_s = \frac{X_t - x_0}{S - x_0}, \quad W_s = \frac{W_t}{\sqrt{\tau}},$$
$$\alpha = \frac{\mu\tau}{S - x_0}, \quad \beta = \frac{\sigma\sqrt{\tau}}{S - x_0}, \tag{21}$$

and $T/\tau = \inf\{s > 0 : Y_s \geq 1\}$. Note that the model now operates on the timescale of $s = t/\tau$, not on the original measured timescale. All observed ISIs thus have to be transformed by dividing by τ.

In strong suprathreshold regime, where $\alpha \gg 1$ and β is suitably small, i.e., the asymptotic mean of the membrane depolarization is far above the threshold compared to the asymptotic standard deviation, the time interval to cross the threshold will be nearly regular, and the distribution of T can be approximated by a Normal distribution, with mean and variance

$$E[T] \approx \log\left(\frac{\alpha}{\alpha - 1}\right) - \frac{\beta^2}{4}\left(\frac{2\alpha - 1}{\alpha^2\left((\alpha - 1)^2 - \beta^2/2\right)}\right), \tag{22}$$

$$\mathrm{Var}[T] \approx \frac{\beta^2}{2}\left(\frac{2\alpha - 1}{\alpha^2\left((\alpha - 1)^2 - \beta^2/2\right)}\right). \tag{23}$$

These moment approximations are valid if $\alpha > 1$ and $\beta < \sqrt{2}(\alpha - 1)$ (Ditlevsen and Lansky 2005). As mentioned, Poissonian behavior is induced in strong subthreshold regime, $\alpha \ll 1$, and the first-passage time density function can be approximated by an exponential distribution with mean

$$E[T] \approx \frac{S - \mu\tau}{\sigma\sqrt{\pi\tau}} \exp\left(\frac{(S - \mu\tau)^2}{\sigma^2\tau}\right), \tag{24}$$

(Nobile et al. 1985; Wan and Tuckwell 1982). In the region $\alpha \sim 1$ we may approximate the distribution of T by the known analytical result Eq. (11), valid for $\alpha = 1$. Thus, the behavior of the model is transparent in the entire parameter space.

2.2 Models with state-dependent infinitesimal variance

The change of the membrane depolarization by a synaptic input is independent of the actual value of X in the OU model, which results in an unrestricted state-space. In reality, the depolarization of the membrane caused by an excitatory postsynaptic potential decreases with decreasing distance of the membrane potential from the excitatory reversal potential, V_E. In the same manner, the hyper-polarization caused by inhibitory postsynaptic potential is smaller if the membrane potential is closer to the inhibitory reversal potential, V_I. A modified Eq. (2) with Poissonian input only is known as Stein's model with reversal potentials and it is given by the stochastic differential equation

$$\mathrm{d}X_t^* = -\frac{X_t^*}{\tau^*}\,\mathrm{d}t + a(V_E - X_t^*)\,\mathrm{d}P^+ + i(X_t^* - V_I)\,\mathrm{d}P^-,\ X_0^* = 0, \tag{25}$$

where $V_I < 0 < V_E$ are constants, and constants $-1 < i < 0 < a < 1$ reflect the fractional change of the membrane potential in response to an input pulse. In model (25) the jumps caused by the input are state-dependent and their magnitudes decrease linearly as X^* approaches the boundaries V_I or V_E. Hence, the process remains confined within these two boundaries.

Mathematical treatment of model (25) is complicated and therefore the diffusion variants have been examined (Hanson and Tuckwell 1983). There is a whole class of diffusion processes which can substitute model (25). All of them are characterized by the infinitesimal mean

$$\nu(x) = -\frac{x}{\tau^*} + \mu_1(V_E - x) + \mu_2(x - V_I) = -\left(\frac{1}{\tau^*} + \mu_1 - \mu_2\right)x + \mu_1 V_E - \mu_2 V_I \tag{26}$$

but with different infinitesimal variances (Lansky and Lanska 1987) (where $\mu_2 < 0 < \mu_1$ are constants). Here we consider one of the variants of the diffusion model with the infinitesimal variance

$$\sigma(x) = \sigma\sqrt{(x - V_I)}, \tag{27}$$

which stresses the relative importance of the inhibitory reversal potential.

The effect of the inclusion of reversal potentials into the diffusion models is apparent when comparing (26) or (27) with (8). Figure 2 shows simulations of X_t in absence of a threshold for the OU and the Feller process. For comparison, the same realization of the Wiener process is used in the two simulations. The OU process is symmetrically distributed around the asymptotic depolarization, whereas the Feller process is seen to stay above the inhibitory reversal potential and to reach larger values. From a qualitative point of view the infinitesimal variance in the Feller process becomes state-dependent, while the drift preserves its linearity. However, the interpretation of the drift term is entirely different. There is still the constant "leakage term", but now modified by the input parameters $\mu_1 - \mu_2$.

By the linear transformation $X = X^* - V_I$ the standard form of the Feller process is obtained (Feller 1951),

$$\mathrm{d}X_t = \left(-\frac{X_t}{\tau} + \mu\right)\mathrm{d}t + \sigma\sqrt{X_t}\,\mathrm{d}W_t, \quad X_0 = -V_I, \tag{28}$$

where $\tau = \tau^*/(1 + \tau^*(\mu_1 - \mu_2))$ and $\mu = \mu_1 V_E - (1/\tau^* + \mu_1)V_I$. Note that τ^* can be compared to the intrinsic time constant in (8), and that $\tau < \tau^*$. In contrast to the OU model, the leakage cannot be considered an intrinsic parameter but depends on the input, and should thus be estimated. The ISI is

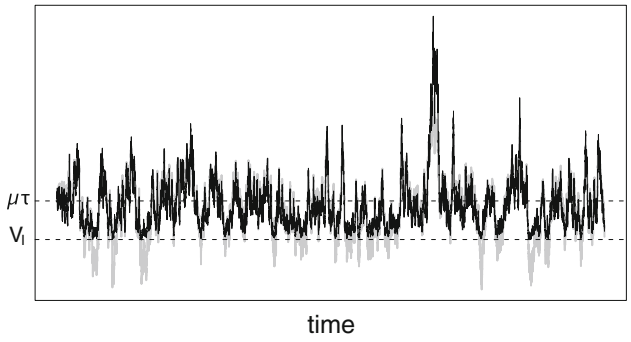

Fig. 2 Realizations of X_t (membrane potential against time, arbitrary units) for the OU process (*gray*) and the Feller process (*black*) in absence of a threshold. For comparison, the same realization of a Wiener process was used in the two simulations. The *dashed lines* are the asymptotic depolarization $\mu\tau$, which is equal for the two simulations, and the reversal potential V_I for the Feller process, respectively

now identified with the first-passage time T of the threshold $S - V_I$ by the process X. Note by comparison of Eqs. (8) and (28) that σ in (28) has not only different units, but also a different interpretation. Whereas in (8) it is the amplitude of the noise, in (28) it is only a proportion of the noise. Model (28) is called the Cox–Ingersoll–Ross process in the financial literature (Cox et al. 1985).

Sometimes it is convenient to reformulate model (28) to the equivalent dimensionless form

$$\mathrm{d}Y_s = (-Y_s + \alpha)\,\mathrm{d}s + \frac{\beta}{\sqrt{\alpha}}\sqrt{Y_s}\,\mathrm{d}W_s, \quad Y_0 = \frac{-V_I}{S - V_I}, \tag{29}$$

where

$$s = \frac{t}{\tau}, \quad Y_s = \frac{X_t}{S - V_I}, \quad W_s = \frac{W_t}{\sqrt{\tau}},$$
$$\alpha = \frac{\mu\tau}{S - V_I}, \quad \beta = \frac{\sigma\tau\sqrt{\mu}}{S - V_I}, \tag{30}$$

and $T/\tau = \inf\{s > 0 : Y_s \geq 1\}$. It is parameterized such that (20) and (29) have the same asymptotic mean and variance if α and β have the same values in the two models.

If $2(\alpha/\beta)^2 \geq 1$, or equivalently if $2\mu/\sigma^2 \geq 1$, the process stays positive, i.e., in Feller's terminology the boundary at zero is an entrance boundary defined as a boundary from which the process can start but not return to (Karlin and Taylor 1981, p. 234). Feller has shown that the transition probability distribution is a non-central χ^2-distribution with $\nu = 4(\alpha/\beta)^2$ degrees of freedom and with conditional mean

$$E(Y_s) = \alpha + (y_0 - \alpha)e^{-s} \tag{31}$$

and variance

$$\mathrm{Var}(Y_s) = \frac{\beta^2}{2}(1 - e^{-s})\left[1 + \left(\frac{2y_0}{\alpha} - 1\right)e^{-s}\right]. \tag{32}$$

The distribution is $F_{\chi^2}[a(s)y,\ \nu,\ \delta(s, y_0)]$, where $a(s) = 4\alpha/(\beta^2(1-e^{-s}))$ and $\delta(s, y_0) = (4\alpha y_0/\beta^2)(e^{-s}/(1-e^{-s}))$ is the non-centrality parameter, see, e.g., Cox et al. (1985). It is easily seen that since $\delta \to 0$ when $s \to \infty$, the asymptotic distribution is a gamma distribution.

In Ditlevsen and Lansky (2006) it is shown that for the model given by Eqs. (26) and (27)

$$E[e^{T/\tau}] = \frac{\mu\tau - x_0}{\mu\tau - S} \tag{33}$$

if $\mu\tau > S$, and

$$E[e^{2T/\tau}] = \frac{(\mu\tau - x_0)^2 + \tau\sigma^2(\mu\tau/2 - x_0)}{(\mu\tau - S)^2 + \tau\sigma^2(\mu\tau/2 - S)} \tag{34}$$

if $\tau\sigma^2(\sqrt{1 + 2\mu/\sigma^2} - 1)/2 < (\mu\tau - S)$. Expressions for the mean and variance of T were calculated in Giorno et al. (1988) and Lansky et al. (1995):

$$E[T] = \frac{S - x_0}{\mu} + \sum_{n=1}^{\infty} \frac{\tau\left(S^{n+1} - x_0^{n+1}\right)}{(n+1)\prod_{i=0}^{n}(\mu\tau + i\tau\sigma^2/2)}, \tag{35}$$

$$\mathrm{Var}[T] = \frac{2E[T]S}{\mu} + \sum_{n=1}^{\infty} \frac{2\tau E[T]\,S^{n+1}}{(n+1)\prod_{i=1}^{n}(\mu\tau + i\tau\sigma^2/2)} - 2\tau^2 \sum_{n=0}^{\infty} \frac{(S^{n+1} - x_0^{n+1})\left(\sum_{j=1}^{n}\frac{1}{j}\right)}{(n+1)\prod_{i=0}^{n}(\mu\tau + i\tau\sigma^2/2)} \tag{36}$$

in the case $2\mu \geq \sigma^2$. Define $k = 2\mu/\sigma^2$, then the assumption that 0 is entrance boundary implies $k \geq 1$. The moments were approximated in Ditlevsen and Lansky (2006)

$$E[T] \approx \frac{S - x_0}{\mu} - \frac{\tau}{k} - \frac{S}{(k+1)\mu} + \tau\left(\frac{\mu\tau}{kS}\right)^k \exp\left\{\frac{kS}{\mu\tau}\right\}\Gamma\left(\frac{kS}{\mu\tau}; k\right), \tag{37}$$

$$\mathrm{Var}[T] \approx 2E[T]\left(E[T] + \frac{x_0}{\mu}\right) + \frac{\tau S}{\mu} - \tau^2\left(\frac{\mu\tau}{kS}\right)^{k-1} \exp\left\{\frac{kS}{\mu\tau}\right\}\Gamma\left(\frac{kS}{\mu\tau}; k\right), \tag{38}$$

where $\Gamma(x; p) = \int_0^x t^{p-1}e^{-t}\,\mathrm{d}t$ is the incomplete Gamma function.

3 Parameter estimation

3.1 Intracellular recordings

Estimation when discrete observations of the trajectory of X given by (3) are available, can be done by the maximum likelihood method if the transition density is known and tractable. Assume X observed at equidistant time points $i\Delta$, where $i = 0, 1, \ldots, n$, for some $\Delta > 0$. Let X_i be the observation

of X at time $i\Delta$. Using the Markov property of X yields the likelihood function of the unknown parameter vector θ

$$L(\theta) = \prod_{i=1}^{n} f(X_i, \Delta | X_{i-1}; \theta). \tag{39}$$

The derivative of the log-likelihood yields the score functions, providing the maximum likelihood estimators.

3.1.1 Ornstein–Uhlenbeck model

The maximum likelihood estimators of μ and σ in (8) are given by the equations

$$\hat{\mu} = \frac{\sum_{i=1}^{n}(X_i - X_{i-1}e^{-\Delta/\tau})}{n(1-e^{-\Delta/\tau})\tau}, \tag{40}$$

$$\hat{\sigma}^2 = \frac{2\sum_{i=1}^{n}(X_i - \hat{\mu}\tau - (X_{i-1} - \hat{\mu}\tau)e^{-\Delta/\tau})^2}{n(1-e^{-2\Delta/\tau})\tau}, \tag{41}$$

see, e.g., Ditlevsen and Lansky (2008). In the case of high-frequency data, i.e., when Δ is small compared to τ, the likelihood equations can be simplified using that $e^{-\Delta/\tau} \approx 1 - \Delta/\tau$,

$$\begin{aligned}\hat{\mu} &\approx \frac{1}{\Delta n}\sum_{i=1}^{n}(X_i - X_{i-1}(1-\Delta/\tau)) \\ &= \frac{(X_n - X_0)}{\Delta n} + \frac{1}{\tau n}\sum_{i=1}^{n} X_{i-1},\end{aligned} \tag{42}$$

$$\hat{\sigma}^2 \approx \frac{1}{\Delta n}\sum_{i=1}^{n}\left(X_i - X_{i-1}(1-\Delta/\tau) - \Delta\hat{\mu}\right)^2. \tag{43}$$

This is relevant in intracellular recordings, where Δ typically is on the order of 0.1 ms and τ is on the order of 10 ms.

In the neuronal context, Lansky et al. (2006) used Eqs. (42) and (43) on intracellular data, where they also applied a moment method, with the estimators

$$\tilde{\mu} = \frac{\sum_{i=1}^{n} X_i - nX_0}{\tau\sum_{i=1}^{n}(1-e^{-i\Delta/\tau})}, \tag{44}$$

$$\tilde{\sigma}^2 = \frac{1}{\Delta n}\sum_{i=1}^{n}(X_i - X_{i-1})^2. \tag{45}$$

In Picchini et al. (2008) maximum likelihood estimation was used on a slightly extended model, where an additional variance parameter was introduced to model slow fluctuations in μ.

3.1.2 Feller model

Even if the transition density for this model is known, the expression is too complicated to make maximum likelihood estimation feasible. A useful alternative is martingale estimation functions. In Bibby and Sørensen (1996) the following estimators are proposed

$$\hat{\mu} = \frac{\sum_{i=1}^{n}(X_i - X_{i-1}e^{-\Delta/\tau})}{n\tau h_\Delta}, \tag{46}$$

$$\hat{\sigma}^2 = \frac{2\sum_{i=1}^{n} X_{i-1}^{-1}\left(X_i - \hat{\mu}\tau h_\Delta - X_{i-1}e^{-\Delta/\tau}\right)^2}{\sum_{i=1}^{n} X_{i-1}^{-1}\tau\left(\hat{\mu}\tau h_\Delta^2 + 2X_{i-1}h_\Delta e^{-\Delta/\tau}\right)}, \tag{47}$$

where $h_\Delta = (1-e^{-\Delta/\tau})$. Note that the estimator for μ is the same as in the OU case (40), since they have the same drift. Be aware, though, that the biological interpretation of the parameters is different in the two models. As before, when Δ is small compared to τ, also these likelihood equations can be simplified using that $e^{-\Delta/\tau} \approx 1 - \Delta/\tau$ and ignoring terms of order Δ^2,

$$\hat{\mu} \approx \frac{(X_n - X_0)}{\Delta n} + \frac{1}{\tau n}\sum_{i=1}^{n} X_{i-1}, \tag{48}$$

$$\hat{\sigma}^2 \approx \frac{1}{n\Delta}\sum_{i=1}^{n} X_{i-1}^{-1}\left(X_i - X_{i-1}(1-\Delta/\tau) - \hat{\mu}\Delta\right)^2. \tag{49}$$

Note that the simplified estimator for σ is similar to the simplified estimator in the OU model (43), except that each term in the sum is weighted by dividing by the state of the process.

3.2 Extracellular recordings

When first-passage times are the only data available, assume the ISI observations to be n independent realizations of the random variable $T : t_i, i = 1, \ldots, n$. In this case the attempts to solve the estimation problem are rare. When intracellular data are available, one can also estimate the intrinsic parameters, whereas for extracellular recordings, the membrane time constant is difficult to determine and has to be assumed, or otherwise estimated from other types of data. Some references of estimation of input parameters from ISI data are Brillinger (1988), Inoue et al. (1995), Shinomoto et al. (1999), Rauch et al. (2003), Paninski et al. (2004), Ditlevsen and Lansky (2005, 2006, 2007, 2008) and Ditlevsen and Ditlevsen (2008). All of these methods are based either on the moments, exponential moments, or the Fortet's equation. Recently Mullowney and Iyengar (2008) investigated the maximum likelihood method based on numerical inversion of the Laplace transform given by Eq. (12).

3.2.1 Ornstein–Uhlenbeck model

The Moment method In Inoue et al. (1995) it is proposed to equate the sample moments $m_1 = \frac{1}{n}\sum_{i=1}^{n} t_i$ and $m_2 = \frac{1}{n}\sum_{i=1}^{n} t_i^2$ with expressions (15) and (16), thus yielding estimates of η and ξ, which provides estimates of μ and σ through (17). However, Eqs. (18) and (19) are only useful for numerical calculations whenever $z \geq 0$ and $|z|$ is small. Otherwise approximations of (18) and (19) must be used.

These expressions have to be evaluated at $z = \xi$ and $z = \eta$. Note that ξ indicates the distance between reset value (here set to zero) and asymptotic mean, and η indicates the distance between the threshold and the asymptotic mean measured in units of the asymptotic standard deviation of the membrane potential. Here $\eta < 0$ corresponds to suprathreshold regime, and when $|\eta|$ is large the model is far away from threshold regime. Thus, this method works best in moderate subthreshold regime. In Inoue et al. (1995) tables are provided of the estimated parameters as functions of the sample first moment m_1/τ and the sample coefficient of variation (CV). The tables cover sample values of $0.5 \leq m_1/\tau \leq 50$ and $0.1 \leq \mathrm{CV} \leq 2$, and are calculated for $\tau = 5$ ms and $S - x_0 = 15$ mV. It is straightforward to transform the estimates from the tables to relevant values of the intrinsic parameters.

When η is large, the distribution of T is approximately symmetric, and Eqs. (22) and (23) can be used to estimate the input parameters. When η is small, the distribution is approximately exponential. Note that the exponential distribution is a one parameter distribution, and thus we can only estimate μ and σ up to the parameter function η given in (17). Assuming an exponential distribution yields the maximum likelihood estimating equation (Ditlevsen and Lansky 2005), see also Eq. (24)

$$\frac{\hat{\eta}}{\sqrt{2\pi}} \exp\left(\frac{\hat{\eta}^2}{2}\right) = \frac{1}{n}\sum_{i=1}^{n} t_i. \tag{50}$$

The Exponential moment method Straightforward estimators of $E[e^{T/\tau}]$ and $E[e^{2T/\tau}]$ are obtained from the empirical moments:

$$Z_1 = \hat{E}[e^{T/\tau}] = \frac{1}{n}\sum_{i=1}^{n} e^{t_i/\tau}, \tag{51}$$

$$Z_2 = \hat{E}[e^{2T/\tau}] = \frac{1}{n}\sum_{i=1}^{n} e^{2t_i/\tau}. \tag{52}$$

Moment estimators of the parameters, assuming that the data are in the allowed parameter region, are then obtained from Eqs. (33) and (34)

$$\hat{\mu} = \frac{SZ_1}{\tau(Z_1 - 1)}, \tag{53}$$

$$\hat{\sigma}^2 = \frac{2S^2(Z_2 - Z_1^2)}{\tau(Z_2 - 1)(Z_1 - 1)^2}, \tag{54}$$

(Ditlevsen and Lansky 2005). Note that the asymptotic depolarization will always be estimated to be suprathreshold ($\hat{\mu}\tau > S$), and that $0 < \hat{\sigma}^2 < 2(\hat{\mu}\tau - S)^2/\tau$.

The Integral Equation method In Ditlevsen and Ditlevsen (2008) it is proposed to apply the integral equation (5) in the following way. Define $\theta = (\alpha, \beta)$, where α and β are given by Eq. (21). The probability

$$P[X_t > S \mid X_0 = x_0] = 1 - F_\theta(S, t|x_0) \tag{55}$$

can alternatively be calculated by the transition integral

$$P[X_t > S|X_0 = x_0] = \int_0^t g_\theta(u)(1 - F_\theta(S, t - u|S))\,\mathrm{d}u. \tag{56}$$

For fixed θ, the probability expressed by the right-hand side of (55) is a function of t and can be calculated directly using that the transition density is normal with mean and variance given by Eqs. (9) and (10). For the same value of θ, the probability expressed by the right-hand side of (56) can be estimated at t from the sample by the average

$$\frac{1}{n}\sum_{i=1}^{n}(1 - F_\theta(S, t - t_i|S))\,1_{\{t_i \leq t\}}, \tag{57}$$

where 1_A is the indicator function of the set A, since it is the expected value of

$$1_{T\in[0,t]}\,(1 - F_\theta(S, t - T|S)) \tag{58}$$

with respect to the distribution of T. A statistical error measure is then defined as the maximum over t of the distance between (55) and (57), suitably normalized by dividing by $\omega(\theta) = \sup_{t>0}(1 - F_\theta(S, t|x_0))$ so that (55) will vary between 0 and 1 for all θ. To find the maximum over t a grid on the positive real line has to be chosen. A good choice for fixed θ is the set $\{t \in R_+ : (1 - F_\theta(S, t|x_0))/\omega(\theta) = i/N,\ i = 1, \ldots, N - 1\}$ for some reasonably large number N. The estimator of θ is finally obtained by minimizing this error function over the parameter space.

Let $\Phi(\cdot)$ be the normal cumulative distribution function. Combining Eq. (55) and Eqs. (9) and (10) and applying the transformations (20) and (21) we obtain

$$P[Y_s > 1 \mid Y_0 = 0] = \Phi\left(\frac{\alpha(1 - e^{-s}) - 1}{\sqrt{1 - e^{-2s}}\,\beta/\sqrt{2}}\right), \tag{59}$$

which we estimate from the sample using (57) by

$$\frac{1}{n}\sum_{i=1}^{n}\Phi\left(\frac{\alpha - 1}{\beta/\sqrt{2}}\sqrt{\frac{1 - e^{-(s-s_i)}}{1 + e^{-(s-s_i)}}}\right)1_{\{s_i \leq s\}}, \tag{60}$$

where $s_i = t_i/\tau$. The normalizing constant is given by $\Phi[(\alpha - 1)/(\beta/\sqrt{2})]$ for $\alpha \geq 0$ and $\Phi[-\sqrt{1 - 2\alpha}/(\beta/\sqrt{2})]$ for $\alpha < 0$. Then $\hat{\alpha}$ and $\hat{\beta}$ can be transformed to estimates of μ and σ through (21).

3.3 Feller model

The Exponential moment method Using the empirical moments (51) and (52) and Eqs. (33) and (34) we obtain the estimators

$$\hat{\mu} = \frac{SZ_1}{\tau(Z_1 - 1)}, \tag{61}$$

$$\hat{\sigma}^2 = \frac{2S^2(Z_2 - Z_1^2)}{\tau(Z_2 - 1)(Z_1 - 1)^2}, \tag{62}$$

assuming that the data are generated from the model operating in the allowed parameter region (Ditlevsen and Lansky 2006).

The Integral Equation method The integral equation (5) becomes

$$1 - F_{\chi^2}[a(s), \nu, \delta(s, y_0)] = \int_0^s f(u)\left(1 - F_{\chi^2}[a(s-u), \nu, \delta(s-u, 1)]\right) \mathrm{d}u, \tag{63}$$

$a(s) = 4\alpha/(\beta^2(1-e^{-s}))$, degrees of freedom $\nu = 4(\alpha/\beta)^2$, non-centrality parameter $\delta(s, y_0) = (4\alpha y_0/\beta^2)[e^{-s}/(1-e^{-s})]$, and normalizing constant $(1-F_{\chi^2}[4\alpha/\beta^2, \nu, 0])$.

4 Discussion

We have reviewed a range of methods for the estimation of parameters in stochastic diffusion neuronal models. The methods based on knowledge of the trajectories (intracellular recordings) are fairly developed and applied in many other fields. They are ignored in neuroscience probably due to the fact that when this type of data are available, then the researchers aim at more complex, biophysical models and do not expect to gain too much information from a simple model. Nevertheless, it might be interesting to judge the implications of reducing a biophysical model not only theoretically, as already done, but also in experimental conditions. References on estimation of input parameters from ISI data in stochastic diffusion neuronal models are few, especially when compared to the number of papers devoted to theoretical studies on these models. This is also in striking contrast with the enormous number of experiments in which ISIs have been collected. Here one can see wide possibilities not only in comparing the data with the models, but first of all in characterizing the data in a novel way. In addition to the traditional description of ISIs by the firing frequency, spiking variability and randomness, the methods offer quantification of the neuronal input and of the noise imposed on it. This can be an alternative when describing different regimens of neuronal activity.

The methods reviewed in this article should only be applied if the model assumptions are satisfied, i.e., the membrane potential fluctuations are well described by model (3) with specified drift and infinitesimal variance. Often, especially during stimulation, the assumption of time homogeneity of these two functions are violated and the data are not stationary. We have not studied the effect of the violation of the model assumptions on the quality of the estimates and it remains an open question. On the other hand, it is not required that the ISIs are collected continuously, as long as there are good reasons to believe that the model is valid in separate time windows. The data can then be taken from several neurons or several repetitions of the activity from the same neuron, analogous to Pawlas et al. (2008). Finally, the problem of noise with a specific temporal structure can appear, but that has not been solved up to now.

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