Parameters of stochastic diffusion processes estimated from observations of first-hitting times: Application to the leaky integrate-and-fire neuronal model

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A theoretical model has to stand the test against the real world to be of any practical use. The first step is to identify parameters in the model estimated from experimental data. In many applications where renewal point data are available, models of first-hitting times of underlying diffusion processes arise. Despite the seemingly simplicity of the model, the problem of how to estimate parameters of the underlying stochastic process has resisted solution. The few attempts have either been unreliable, difficult to implement, or only valid in subsets of the relevant parameter space. Here we present an estimation method that overcomes these difficulties, is computationally easy and fast to implement, and also works surprisingly well on small data sets. The method is illustrated on simulated and experimental data. Two common neuronal models—the Ornstein-Uhlenbeck and Feller models—are investigated.

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The first-hitting time to a constant threshold of a diffusion process has been in focus for stochastic modeling of problems where a hidden random process only shows when it reaches a certain level that triggers some observable event. Applications come from various fields: e.g., biology, survival analysis, mathematical finance, and others. The application in this paper originates from neuronal modeling. Neurons transfer information by emitting electrical pulses (spikes), and diffusion models describe the underlying dynamics of the interspike intervals (ISIs). They represent the time evolution of the neuronal membrane depolarization, modeled by a scalar process X_t given by an Itô stochastic differential equation

$$dX_t = \nu(X_t,\theta)dt + \sigma(X_t,\theta)dW(t), \quad X_0 = x_0, \tag{1}$$

where ν and σ are real-valued functions (the infinitesimal drift and variance), θ is a p-dimensional parameter, and $W(t)$ is a standard Wiener process (Brownian motion). An alternative description to Eq. (1) is the Fokker-Planck equation for the transition density $f_\theta(x,t|x_0,0)$ [1].

Firing of spikes is not an intrinsic part of model (1), so a firing threshold has to be imposed. A firing event occurs when the membrane voltage X_t exceeds a voltage threshold for the first time, here assumed to be a constant $S>x_0$. After a spike, the membrane depolarization is reset to the initial value. Formally, the ISIs are identified with the first-passage time (hitting time) of X_t across S,

$$T = \inf\{t \geqslant 0: X_t \geqslant S | X_0 = x_0 < S\}. \tag{2}$$

Thus, we assume the ISIs form a renewal process—i.e., that they are independent and identically distributed. The properties of the random variable T including its probability density function $g_\theta(t|x_0,S)=g_\theta(t)$ have been extensively studied. The distribution $g_\theta(t)$ is only known for a few simple models, and approximation techniques have been devised [2], of which many are based on the renewal equation, the so-called Fortet's equation [3,4] relating the first-passage-time density and the transition density $f_\theta(\cdot)$ for $x \geqslant S$,

$$f_\theta(x,t|x_0,0) = \int_0^t f_\theta(x,t|S,\tau) g_\theta(\tau|x_0,S) d\tau. \tag{3}$$

We write $F_\theta(x,t-s|x_s)=\int^x f_\theta(u,t|x_s,s)du$ for the corresponding transition distribution function.

Estimation of θ has been extensively studied; see e.g., [5–8], or [9–11] in the neuronal context. All these methods are based on complete or partial observations of the trajectory of $X(t)$. However, if only first-passage times are available, attempts to solve the estimation problem are rare; some references are [12–14]. We proposed Laplace-transform moment estimators for two specific diffusion models [15,16]; see also the cited papers therein. These estimators have certain drawbacks: e.g., they are only valid in a subspace of the parameter space [17] and the variance parameter is poorly determined. Recently we proposed a method based on an integral equation applicable to any one-dimensional diffusion process with known transition density [18], which we will apply in this paper.

Parameter estimation. Consider the sample $t_1,\ldots,t_n$ of n independent observations of T from which θ will be estimated. The method applies the integral equation (3) as described in the following; see also [18]. The probability

$$P[X_t > S | X_0 = x_0] = 1 - F_\theta(S,t|x_0) \tag{4}$$

can alternatively be calculated by the transition integral

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$$P[X_t > S|X_0 = x_0] = \int_0^t g_\theta(u)[1 - F_\theta(S,t-u|S)]du. \quad (5)$$

For fixed θ, Eq. (4) is a function of t and can be calculated directly. The value of Eq. (5) can be estimated at t from the sample by the average

$$\frac{1}{n}\sum_{i=1}^{n}[1 - F_\theta(S,t-t_i|S)]1_{\{t_i \leqslant t\}}, \quad (6)$$

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

$$1_{T\in[0,t]}[1 - F_\theta(S,t-T|S)], \quad (7)$$

with respect to the distribution of T for fixed θ. A statistical error measure is then defined as the maximum over t of the distance between (4) and (6), suitably normalized by dividing by $\omega(\theta)=\sup_{t>0}[1-F_\theta(S,t|x_0)]$ so that (4) 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 $\{t\in\mathbb{R}_+:[1-F_\theta(S,t|x_0)]/\omega(\theta)=i/N, i=1,\ldots,N-1\}$ for some reasonably large number N. In the applications below $N=100$. The estimator of θ is finally obtained by minimizing this error function over the parameter space. The estimate is denoted $\hat{\theta}$.

Ornstein-Uhlenbeck neuronal model. A phenomenological way to introduce stochasticity into the deterministic leaky-integrator model $dx(t)/dt=-x(t)/\tau+\mu$ is by assuming an additional term of Gaussian white noise. This model is a special case of model (1) for which

$$\nu(x) = -\frac{x}{\tau} + \mu, \quad \sigma(x) = \sigma > 0, \quad x_0 = 0, \quad (8)$$

where $\tau>0$ is the membrane time constant and μ and σ are constants characterizing neuronal input. Model (8) is the Ornstein-Uhlenbeck (OU) process [1,15,19–22]. The transition density function is Gaussian,

$$f_\theta(x,t) = (2\pi V_t)^{-1/2}\exp\{-(x-M_t)^2/(2V_t)\}, \quad (9)$$

where $M_t=\mu\tau(1-e^{-t/\tau})$ and $V_t=\sigma^2\tau(1-e^{-2t/\tau})/2$. Despite many efforts, an analytical solution for the first-passage-time density has only been found for $S=\mu\tau$ [20,23,24].

Two types of parameters appear: the intrinsic parameters and the parameters characterizing the input [25]. The intrinsic parameters are constants given prior to the verification of the model: the firing threshold S, the initial depolarization x_0, and the membrane time constant τ reflecting spontaneous voltage decay in absence of input. The input parameters are related to the signal coded by the neuron: μ characterizes the depolarization of the membrane between spikes, and σ characterizes the random variability in the depolarization process.

It is convenient to reformulate models (1) and (8) to the equivalent dimensionless form

$$dY_s = (-Y_s + \alpha)ds + \beta dW_s, \quad Y_0 = 0, \quad (10)$$

where

$$s = \frac{t}{\tau}, \quad Y_s = \frac{X_t}{S}, \quad W_s = \frac{W_t}{\sqrt{\tau}}, \quad \alpha = \frac{\mu\tau}{S}, \quad \beta = \frac{\sigma\sqrt{\tau}}{S}, \quad (11)$$

and $T/\tau=\inf\{s>0:Y_s\geqslant 1\}$. It shows that only two parameters are identifiable from ISI data, in contrast to when sample trajectories of the process are available. Therefore, without loss of generality, all considerations in the following will be related to the dimensionless process Y_s and its first crossing of the level 1. Note, however, that the model now operates on the time scale of $s=t/\tau$, not on the original measured time scale. All observed ISIs thus have to be transformed by dividing by τ. The membrane time constant has to be assumed or otherwise estimated from other types of data. Increasing α results in shorter ISIs. Increasing β when $\alpha>1$ increases the ISI variability, whereas in the subthreshold regime [26] showed that the coefficient of variation was nonmonotone as a function of the noise level.

Let $\Phi(\cdot)$ be the normal cumulative distribution function. Combining (4) and (9) we obtain

$$P[Y_s > 1|Y_0 = 0] = \Phi\left(\frac{\alpha(1-e^{-s})-1}{\sqrt{1-e^{-2s}}\beta/\sqrt{2}}\right), \quad (12)$$

which we estimate from the sample using (6) by

$$\frac{1}{n}\sum_{i=1}^{n}\Phi\left(\frac{\alpha-1}{\beta/\sqrt{2}}\sqrt{\frac{1-e^{-(s-s_i)}}{1+e^{-(s-s_i)}}}\right)1_{\{s_i\leqslant s\}}, \quad (13)$$

where $s_i=t_i/\tau$. The normalizing constant is given by $\Phi[(\alpha-1)/(\beta/\sqrt{2})]$ for $\alpha\geqslant 0$ and $\Phi[-\sqrt{1-2\alpha}/(\beta/\sqrt{2})]$ for $\alpha<0$. Then $\hat{\alpha}$ and $\hat{\beta}$ can be transformed to physically interpretable quantities of μ and σ through (11).

Simulated data. Trajectories of the OU process were simulated according to the Euler scheme for four different combinations of parameter values: $(\alpha,\beta)=(0.8,1)$, (1,0.1), (2,0.1), and (2,1), respectively. The process was run until the trajectory reached the threshold where the time was recorded. We generated 1000 samples with 10 observations each for each combination of parameter values. This was repeated for sample sizes of 50, 100, and 500, respectively. On all samples α and β were estimated; estimation results are summarized in Fig. 1, where the densities of the estimates for different sample sizes are plotted. The estimators behave well even for sample sizes of only 50 observations. Thus, we expect the method to be reliable if the data are well described by the OU model. As appears from Fig. 1, the estimators seem asymptotically well described by a normal distribution, which can be used to construct confidence intervals. In Table I mean and standard deviations of the samples of 1000 estimates are reported for all combinations of parameter values and sample sizes. A reasonable confidence interval would then be the estimate ±2 times the standard deviation. As would be expected, the standard deviation of the estimator seems approximately proportional to β and inversely proportional to the square root of the sample size.

Auditory thalamic neurons in guinea pigs. The first two sets of experimental ISI data were recorded intracellularly from the auditory system of a guinea pig (for details of the

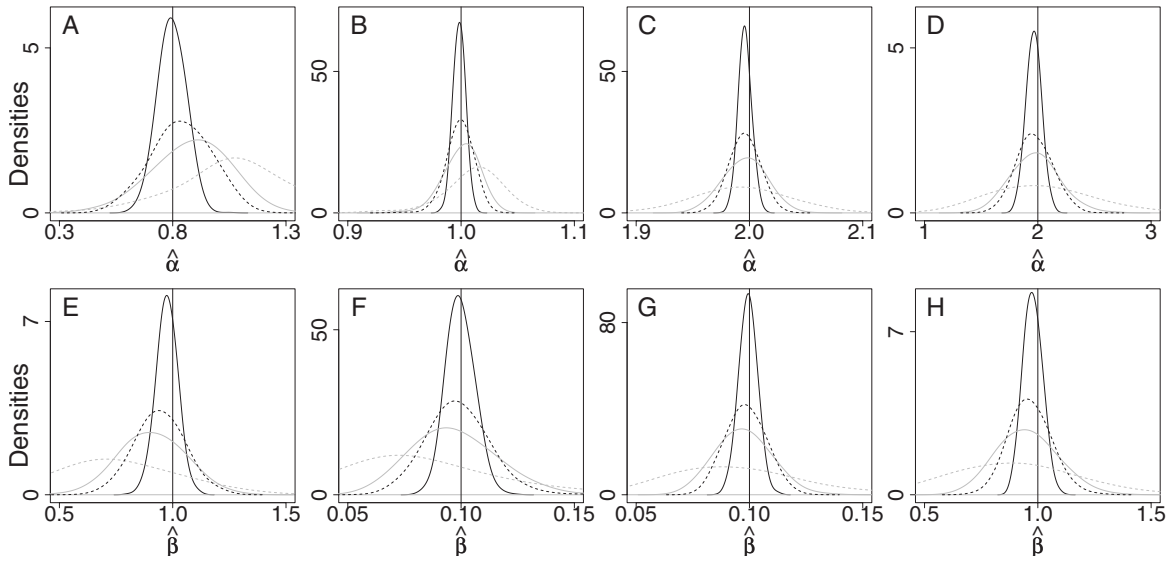

FIG. 1. Densities of estimates for simulated data based on 1000 estimates. Upper panels: estimates of α. Lower panels: estimates of β. Solid black lines: sample sizes of 500. Dashed black lines: sample sizes of 100. Solid gray lines: sample sizes of 50. Dashed gray lines: sample sizes of 10. Vertical lines: true values used in the simulations: (A), (E) $(\alpha,\beta)=(0.8,1)$; (B), (F) $(\alpha,\beta)=(1,0.1)$; (C), (G) $(\alpha,\beta)=(2,0.1)$; (D), (H) $(\alpha,\beta)=(2,1)$. Note different scales.

stimulation protocol, data acquisition, and processing see [27]). The first set contains ISIs during the spontaneous activity, and being based on the intracellular data (not only the ISIs), the parameters were also estimated by standard procedures [10]. This permits us to evaluate the new estimation procedure. Moreover, intracellular data gives "exact" information about the threshold value, the reset value, and the membrane time constant. The second set, obtained from the same neuron, contains the first ISIs within the stimulation period. The intrinsic parameters were considered to be the same as for the spontaneous activity.

TABLE I. Summary of estimates from data simulated from model (10). The last two columns are sample mean±sample standard deviation (SSD) of estimates.

Parameter value (α,β)	Sample size	Estimates of α mean±SSD	Estimates of β mean±SSD
(0.8, 1)	10	1.086±0.276	0.759±0.255
(0.8, 1)	50	0.881±0.164	0.910±0.141
(0.8, 1)	100	0.838±0.127	0.943±0.107
(0.8, 1)	500	0.796±0.061	0.975±0.046
(1, 0.1)	10	1.011±0.084	0.027±0.034
(1, 0.1)	50	1.000±0.016	0.097±0.018
(1, 0.1)	100	0.999±0.012	0.099±0.013
(1, 0.1)	500	0.998±0.005	0.100±0.006
(2, 0.1)	10	1.992±0.043	0.097±0.039
(2, 0.1)	50	1.996±0.018	0.097±0.012
(2, 0.1)	100	1.996±0.013	0.098±0.009
(2, 0.1)	500	1.996±0.006	0.099±0.004
(2, 1)	10	2.035±0.441	0.899±0.268
(2, 1)	50	1.978±0.206	0.953±0.129
(2, 1)	100	1.973±0.151	0.967±0.090
(2, 1)	500	1.965±0.065	0.977±0.040

The spontaneous record consists of 312 ISIs. In [10] the intrinsic parameters were estimated to $S-x_0=11$ mV and $\tau=39$ ms. Transforming the observed ISIs by dividing by this τ, the dimensionless parameters were estimated to $\hat{\alpha}=0.852$ and $\hat{\beta}=0.094$. Using (11) we obtain the following estimates for the input parameters: $\hat{\mu}=0.240$ V/s and $\hat{\sigma}=0.005$ V/$\sqrt{\text{s}}$. In [10] the median values for these were 0.285 V/s for μ with most estimates falling in the range 0.1–0.45 V/s, and 0.014 V/$\sqrt{\text{s}}$ for σ with most estimates falling in the range 0.01–0.016 V/$\sqrt{\text{s}}$. Note that since we base the estimation on the hitting times, we obtain only one set of estimates for the entire record, whereas in [10] the estimation is based on intracellular observations and different sets of estimates for the input parameters are obtained for each ISI. Both parameters estimated only with the information contained in the hitting times were of the same order of magnitude as the estimations using all the information in the data set. A mean parameter is easier to estimate than a variance parameter, and accordingly μ appears precisely determined judged by the estimation from the intercellular recording.

The stimulated record consists of 83 ISIs. Using the intrinsic parameters estimated from the spontaneous part, we estimated $\hat{\alpha}=4.79$ and $\hat{\beta}=0.625$, obtaining $\hat{\mu}=1.351$ V/s and $\hat{\sigma}=0.035$ V/$\sqrt{\text{s}}$. Note that the value of μ, which reflects intensity of stimulation, is 5-6 times larger than for the spontaneous activity.

To check the adequacy of the OU model with the estimated parameter values for these data, Eq. (12) and the empirical equation (13) are compared in Fig. 2, after dividing by $\Phi[(\hat{\alpha}-1)/(\hat{\beta}/\sqrt{2})]$. Especially the stimulated record shows a good fit.

Feller neuronal model. In many applications the OU process is unrealistic because it is unbounded. Introducing an

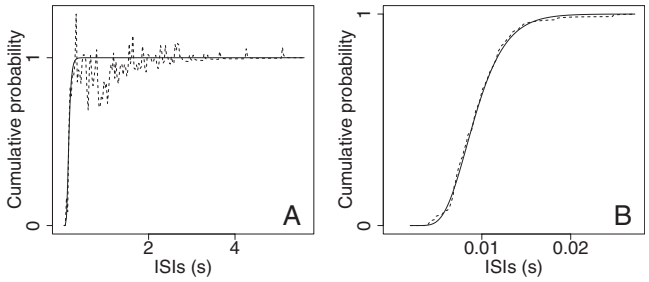

FIG. 2. Auditory neurons. Comparison of the (normalized) right-hand side of Eq. (12) (solid curves) to the (normalized) empirical equation (13) (dashed curves), calculated with estimated parameters. Vertical axes can be interpreted as a cumulative probability; horizontal axes are ISIs (s). (A) Spontaneous record: $\hat{\alpha}=0.85$, $\hat{\beta}=0.09$. (B) Stimulated record: $\hat{\alpha}=4.8$, $\hat{\beta}=0.63$. Note different time axes.

inhibitory reversal potential $V_I<x_0<S$ leads to model (1) with

$$\nu(x)=-\frac{x}{\tau}+\mu, \quad \sigma(x)=\sigma\sqrt{x-V_I}, \tag{14}$$

where $2\mu\geqslant\sigma^2$. In dimensionless form it becomes

$$dY_s=(-Y_s+\alpha)ds+(\beta/\sqrt{\alpha})\sqrt{Y_s}dW_s, \quad 0<y_0<1, \tag{15}$$

$$2(\alpha/\beta)^2\geqslant 1,$$

where

$$Y_s=(X_t-V_I)/(S-V_I),$$

$$\alpha=(\mu\tau-V_I)/(S-V_I),$$

and

$$\beta=\sigma\sqrt{\tau}\sqrt{\mu\tau-V_I}/(S-V_I).$$

Model (15) is known as the Feller process [16,28,29], or the CIR process in mathematical finance [30]. The transition density follows a noncentral χ^2 distribution $F_{\chi^2}[\cdot]$ [30]. The integral equation becomes

$$1-F_{\chi^2}[a(s),\nu,\delta(s,y_0)] = \int_0^s f(u)\{1-F_{\chi^2}[a(s-u),\nu,\delta(s-u,1)]\}du, \tag{16}$$

with $a(s)=4\alpha/[\beta^2(1-e^{-s})]$, degrees of freedom $\nu=4(\alpha/\beta)^2$, and noncentrality parameter

$$\delta(s,y_0)=(4\alpha y_0/\beta^2)[e^{-s}/(1-e^{-s})].$$

The normalizing constant is given by

$$(1-F_{\chi^2}[4\alpha/\beta^2,\nu,0]).$$

Spontaneous firing of olfactory receptor neurons in rats. The next sets of ISIs were obtained during spontaneous activity of normally breathing and tracheotomized rats (for details see [31,32]). No information on intrinsic parameters was available, and we could find no values in the literature for this specific type of neurons. In [33] (p. 56) the values of the membrane time constant are given as ranging from 10 to 50 ms. We assume that sensory neurons, despite different modalities, have similar membrane time constants, and we therefore used the values from the previous application of 39 ms. There were 24 data records containing between 27 and 1907 ISIs in each record. Both the OU model and the Feller model were fitted. Summaries are given in Table II.

TABLE II. Summary of estimates from olfactory neurons for $S-x_0=11$ mV, $\tau=39$ ms, and $x_0-V_I=11$ mV.

	Median[a]	Range[a]	Median[b]	Range[b]
$\hat{\mu}$ [V/s]	0.030	−0.059–0.218	−0.007	−0.108–0.212
$\hat{\sigma}$[c]	0.041	0.017–0.078	0.208	0.085–0.722

[a]OU model, all 24 olfactory neurons.
[b]Feller model, 18 olfactory neurons.
[c]Units: $[V/\sqrt{s}]$ (OU), $[\sqrt{V/s}]$ (Feller).

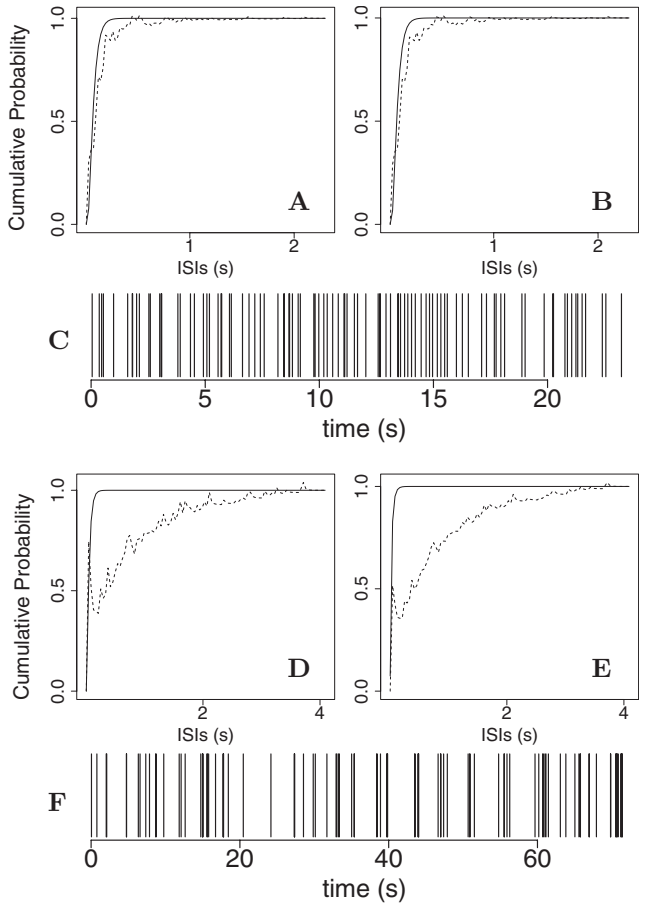

FIG. 3. Olfactory neurons. (A), (B), (C) Neuron that fits the models. (D), (E), (F) Neuron that did not fit the models. (A), (D) OU model, normalized comparison of the right-hand side of Eq. (12) (solid lines) to the empirical equation (13) (dashed lines), calculated with estimated parameters. Vertical axes can be interpreted as a cumulative probability; horizontal axes are ISIs (s). (B), (E) Likewise for the Feller model. (C), (F) Corresponding spike trains consisting of 100 spikes. Note different time axes.

Some neurons showed an acceptable fit to both models, and some did not fit at all; see Fig. 3 for examples. For six neurons the Feller model could not be fitted. The ISIs do not contain enough information to distinguish between the two models, and the choice of model has to be based on physical reasons or other types of data: e.g., intracellular recordings. To appreciate the qualitatively different behavior of the neurons that fit and did not fit, respectively, in the lower part of Fig. 3 are typical patterns of activity (spike trains) pictured for the same two neurons. Only the first 100 spikes of the records are plotted, such that both time series contain the same number of spikes. Typically, the neurons that did not fit had a tendency to clustering of spikes with bursts and relatively long periods of silence. The bursting type of activity of these neurons was already mentioned in [31]. When neurons show bursting behavior, the assumption of independent and identically distributed ISIs is obviously violated. In this case more elaborate models taking account of the autocorrelation should be considered. Moreover, neither the OU nor Feller model can produce this combination of many short ISIs with a heavy tail of long ISIs in the distribution.

In conclusion, we have presented a method to compare stochastic diffusion models with experimental data of first-hitting times, providing seemingly good estimators for physical quantities previously considered very difficult to obtain. Also a diagnostic tool for model evaluation is provided.

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