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Input parameters in a one-dimensional neuronal model with reversal potentials

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Abstract

An equation for a stochastic neuronal model describing the initiation of action potentials is studied for the case in which the depolarization of the membrane potential is restricted by the reversal potentials. It is assumed that the values of the membrane potential can be continuously recorded between consecutive spikes. Under this assumption, the estimators of the model parameters are derived and the methods for testing the model are proposed. The objective of the methods presented in this contribution is to provide neuroscientists with quantitative means in order to estimate parameters of stochastic neuronal models.

Keywords: Stochastic neuronal model; Reversal potential; Diffusion process; Estimation of parameters; Continuous recording

1. Introduction

Neuronal models of single cells reflect the electrical properties of the membrane via electric circuit description. Such circuit models can be written in terms of differential equations for the membrane voltage. Complexity of the models ranges from realistic description (Hodgkin–Huxley model) to simplified integrate-and-fire schemes. All these models neglect morphological properties of a neuron and characterize its features in a single point (trigger zone). For simple integrate-and-fire models the firing is not an intrinsic property of the model and a firing threshold has to be imposed. An action potential (spike) is produced when the accumulated voltage reaches the threshold and then the voltage is instantaneously reset to its initial value. Time intervals between action potentials are identified with experimentally observable interspike intervals. The importance of interspike intervals follows as a consequence of generally accepted hypothesis that the information transferred within the nervous system is encoded by the timing of action potentials. In this contribution we analyze one specific single-point, integrate-and-fire model.

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An apparent variability in activity of neurons exists and it holds for neurons from very different structures and under very different experimental conditions. One approach to reproduce this variability in firing timing is to use the theory of stochastic processes. There randomly timed inputs to the cell are considered and the above mentioned differential equations describing the membrane voltage have a 'noisy' input. Their solutions are random processes with discontinuous trajectories (jumps), where the jumps mimic appearance of excitatory and inhibitory postsynaptic potentials. Again, as for the deterministic models, an action potential is produced when the membrane voltage exceeds the voltage threshold and it corresponds to the first passage time for the associated stochastic process. To solve the first-passage-time problem for models with discontinuous trajectories is rather complicated task. Therefore these models are commonly approximated by diffusion (continuous trajectory) models having statistically the same properties but being mathematically more tractable (Ricciardi, 1977; Hanson and Tuckwell, 1983; Lánský, 1984). Many papers have been published on this type of neuronal models over last thirty years and their review can be found in Tuckwell (1988), Ricciardi (1994) and Lánský and Sato (1998).

Whereas many papers have been published analyzing the models, the papers devoted to their verification are relatively rare. This is true at least for two reasons, the first of which being the mathematical complexity of the problem. The task is easily solvable only for the simplest model–the Wiener process. However, the Wiener process, which is a stochastic counterpart of the perfect-integrator, is such a simplified model that any successful fit to the data must be interpreted with an utmost care. The model can be used as a statistical descriptor characterizing activity of a specific neuron under specific conditions, but it contains no information about biophysical mechanism responsible for spike generation. The second reason for lack of attempts to verify the stochastic models are enormous difficulties caused by implementation of real experimental data into the theoretical schemes. Indeed, such data in general do not comply with the ideal requirements posed by the mathematics underlying the considered methods, such as large samples or renewal character.

Verification of any model has to start with estimation of its parameters. Then the model should be compared with the data and the last step is testing hypotheses about the values of the parameters. To derive estimation methods based on interspike interval statistics for any model that is more complex than the one provided by the Wiener process is a difficult task. This was shown recently by Inoue et al. (1995), where the parameters for the Ornstein–Uhlenbeck neuronal model (stochastic counterpart of the leaky-integrator) were estimated. The Ornstein–Uhlenbeck model is practically the most frequently proposed stochastic neuronal model; however, some of its features, such as unlimited membrane potential fluctuation or state-independent changes of the voltage, are questionable. For other models, which are hardly distinguishable from the Ornstein–Uhlenbeck model on the basis of interspike intervals (Lánský et al., 1995), different methods have to be developed. For that reason, simultaneously with the effort to estimate the parameters from interspike intervals, methods for their estimation based on continuous or discrete sampling of the membrane potential between spikes have been proposed (Lánský, 1983; Habib and Thavaneswaran, 1990).

The aim of the present contribution is to derive methods of parameter estimation in one of the single-point neuronal models with Poisson driven inputs under the conditions that the intensities of these input processes are sufficiently high, while the effects caused by them are relatively small. Verification of the proposed methods and their comparison based on the estimation from the simulated trajectories of the diffusion processes will be presented elsewhere.

2. The model

In the following, a stochastic process X represents changes in the membrane potential between two consecutive neuronal firings. The reference level for the membrane potential is usually taken

to be the resting potential. The initial voltage (the reset value following a spike) is often assumed to be equal to the resting potential, $X(0)=x_0=0$, and we will use this assumption throughout this contribution. An action potential is produced when the membrane voltage X exceeds for the first time a voltage threshold, for simplicity assumed to be equal to a constant $S>0$. It follows from the model assumptions, that for time-unstructured input containing either Poissonian or white noise only, the interspike intervals form a renewal process.

The stochastic model proposed by Tuckwell (1979) is an integrate-and-fire model with membrane potential passive decay and non-linear summation of discrete excitatory and inhibitory synaptic inputs driven by time-homogeneous Poisson processes. The transmitter action at the synaptic junction is controlled by two reversal potentials, whose main effect is to bound the membrane potential fluctuations. This is done by decreasing the amplitudes of the postsynaptic potentials induced by the input signals, in accordance to how close the membrane potential gets to the reversal potential. The model is expressed by the stochastic differential equation

$$\mathrm{d}X = -\gamma X\mathrm{d}t + a(V^+ - X)\mathrm{d}N^+(t) + i(X - V^-)\mathrm{d}N^-(t), \qquad (2.1)$$

where $\gamma>0$, $-1<0<a<1$ are constants; $N^+ = \{N^+(t), t\geq 0\}$, $N^- = \{N^-(t), t\geq 0\}$ are two independent homogeneous Poisson processes with $N^+(0)=N^-(0)=0$ and intensities λ^+, λ^- resp.; $V^-<0$ is a constant representing the inhibitory reversal potential and $V^+>S$ stands for another constant; the excitatory reversal potential. We assume that the constants V^- and V^+ are known. In Eq. (2.1) the jumps caused by the input are state-dependent in such a way that their magnitude decreases linearly as X approaches the boundaries V^- and V^+, respectively. In between the jumps the membrane potential decays exponentially to the resting level (zero) with the time constant $\gamma(\gamma^{-1}=\mathrm{RC}$ in RC circuit representation of the model).

Eq. (2.1) has discontinuous trajectories which causes complications in its mathematical treatment. Therefore it is convenient to substitute it by a diffusion processes with statistically similar properties. The original model is replaced by a more tractable diffusion process. A scalar diffusion process $X=\{X(t);\ t\geq 0\}$

$$\mathrm{d}X(t) = \mu(X(t),t)\mathrm{d}t + \sigma(X(t),t)\mathrm{d}W(t), \qquad (2.2)$$

where $W=\{W(t);\ t\geq 0\}$ is a standard Wiener process and μ and σ are real-valued functions of their arguments called the infinitesimal mean and standard deviation. Diffusion process (Eq. (2.2)) is specified by its infinitesimal mean

$$\mu(x) = -\gamma x + \mu(V^+ - x) + v(x - V^-), \qquad (2.3)$$

where $\mu>0$ and $v<0$ are new constants relating the input intensities λ^+ and λ^- and jump sizes (a and i), and by infinitesimal variance

$$\sigma^2(x) = \sigma^2(V^+ - x)(x - V^-), \qquad (2.4)$$

where $\sigma>0$ is a constant, a diffusion counterpart of (Eq. (2.1)). The construction of the diffusion approximation leading to the infinitesimal moments (Eqs. (2.3) and (2.4)) can be found in Lánský and Lánská (1987). Lánská et al. (1994) investigated the model in detail. For notational reasons, let us study the process (Eqs. (2.3) and (2.4)) transformed linearly into a new process X defined on the interval (0,1) using the transformation $x\rightarrow(x-V^-)/(V^+-V^-)$. This leads to the drift

$$\mu(x) = -\alpha x - V^-/(\tau(V^+ - V^-)) + \mu = -\alpha x + \beta, \qquad (2.5)$$

where $\alpha=\gamma+\mu-v>0$, and the infinitesimal variance

$$\sigma^2(x) = \sigma^2(1-x)x. \qquad (2.6)$$

3. The parameters

The parameters appearing in (2.1) can be easily divided into two groups: parameters characterizing the input frequencies λ^+ and λ^-, and the rest of the parameters which are of intrinsic character as they describe the neuron irrespectively of the incoming signal (Tuckwell and Richter, 1978). Unfortunately, this distinction disappears due to

the diffusion transformation of (Eq. (2.1)). We have shown, in Section 2, that the model can be analyzed in its basic form

$$dX(t) = (-\alpha X(t) + \beta)dt + \sigma(X(t)(1-X(t))^{1/2}dW(t), \quad (3.1)$$

where $\alpha > \beta > 0$ and $\sigma > 0$. For (Eq. (3.1)) the parameters α and β depend on the input frequencies. The parameter σ may either reflect the input variability or it can represent an internal noise produced by the neuron. Thus, from, modeling point of view, its role is more complicated. On the other hand, the nature of diffusion allows us to evaluate σ exactly, given a continuous record, from the formula

$$\sum_{j=1}^{2^n} (X_{js2^{-n}} - X_{(j-1)s2^{-n}})^2 = \int_0^s \sigma^2(X(t))dt. \quad (3.2)$$

as pointed out by Brown and Hewitt (1975). Thus, for the sake of simplicity, we set $\sigma = 1$ and further we set $\sigma^2(X(t)) = [X(t)(1-X(t))]$. The problem of σ estimation will be studied separately together with a study on the role of discontinuous sampling of X. Here we propose several methods for estimation of unknown parameters α and β on the basis of the observations of the process X during the time $\mathcal{T}$. The observations of the process are described by the following schema. Time $\mathcal{T}$ is composed of N subintervals, interspike intervals,

$$\varepsilon_i = (\tau_{i-1}, \tau_i),$$

$$i = 1, \ldots, N, \text{ where } \tau_0 = 0 \text{ and } \tau_N = \mathcal{T} = \sum_{i=1}^{N} \varepsilon_i.$$

The observed process X governed by (Eq. (3.1)) is always continuous inside ε_i. At the points where it reaches the threshold and the spikes are generated, there X is reset to the initial value, so at these points τ_i are discontinuities, $X_{\tau_i+} = 0$ and $X_{\tau_i-} = S$

3.1. Maximum likelihood method

The log-likelihood function for the continuous sampling of the process X driven by (Eq. (3.1)) on the interval $\varepsilon_i = (\tau_{i-1}, \tau_i)$ is given by

$$l_i(\alpha,\beta) = \int_{\tau_{i-1}}^{\tau_i} \frac{(-\alpha X(s) + \beta)}{\sigma^2(X(s))} dX(s) - \frac{1}{2}\int_{\tau_{i-1}}^{\tau_i} \frac{(-\alpha X(s) + \beta)^2}{\sigma^2(X(s))} ds. \quad (3.3)$$

To get the maximum-likelihood (ML) estimators one has to maximize (Eq. (3.3)) with respect to α and β. This can be achieved by solving the following system of equations,

$$\frac{\partial}{\partial\alpha} l_i(\alpha,\beta) = 0, \quad \frac{\partial}{\partial\beta} l_i(\alpha,\beta) = 0. \quad (3.4)$$

Taking into account the type of the observations being at disposal, we get

$$\sum_{i=1}^{N}\left[-\int_{t_{i-1}}^{\tau_i} \frac{dX(s)}{1-X(s)} + \beta \int_{\tau_{i-1}}^{\tau_i} \frac{ds}{1-X(s)} - \alpha \int_{\tau_{i-1}}^{\tau_i} \frac{X(s)ds}{1-X(s)}\right] = 0$$

$$\sum_{i=1}^{N}\left[\int_{t_{i-1}}^{\tau_i} \frac{dX(s)}{(1-X(s))X(s)} - \beta \int_{\tau_{i-1}}^{\tau_i} \frac{ds}{(1-X(s))X(s)} + \alpha \int_{\tau_{i-1}}^{\tau_i} \frac{X(s)ds}{1-X(s)}\right] = 0$$

Let us use the following notation for $i = 1, \ldots, N$:

$$A_i = \int_{\tau_{i-1}}^{\tau_i} \frac{dX(s)}{1-X(s)}, \quad B_i = \int_{\tau_{i-1}}^{\tau_i} \frac{dX(s)}{(1-X(s))X(s)},$$

$$C_i = \int_{\tau_{i-1}}^{\tau_i} \frac{ds}{1-X(s)}, \quad D_i = \int_{\tau_{i-1}}^{\tau_i} \frac{X(s)ds}{1-X(s)},$$

$$E_i = \int_{\tau_{i-1}}^{\tau_i} \frac{ds}{(1-X(s))X(s)}.$$

Then, for the ML estimators $\hat{\alpha}_N$ and $\hat{\beta}_N$

$$\hat{\alpha}_N = \frac{\sum B_i \sum C_i - \sum A_i \sum E_i}{\sum D_i \sum E_i - \left(\sum C_i\right)^2}$$

$$\hat{\beta}_N = \frac{\sum B_i \sum D_i - \sum A_i \sum C_i}{\sum D_i \sum E_i - \left(\sum C_i\right)^2}, \quad (3.5)$$

where Σ stands for $\Sigma_{i=1}^{N}$. If we denote $\Sigma_{i=1}^{N} = l_i(\alpha,\beta) = l(N,\alpha,\beta)$, then the second order partial derivatives are computed directly as:

$$\frac{\partial^2}{\partial\alpha^2} l(N,\alpha,\beta) = \sum D_i, \quad \frac{\partial^2}{\partial\beta^2} l(N,\alpha,\beta) = \sum E_i,$$

$$\frac{\partial^2}{\partial\alpha\partial\beta} l(N,\alpha,\beta) = \frac{\partial^2}{\partial\beta\partial\alpha} l(N,\alpha,\beta) = -\sum C_i.$$

Since the matrix of second order partial derivatives is negative definite, $l(N,\alpha,\beta)$ is concave. Therefore, the maximum of $l(N,\alpha,\beta)$ is a global maximum. Under the condition

$$0 < \mathrm{E}C_i = c < \infty,$$
$$0 < \mathrm{E}D_i = \mathrm{d} < \infty,\ 0 < \mathrm{E}E_i = e < \infty, \tag{3.6}$$

the estimates given by (Eq. (3.5)) are strongly consistent, which means that $\hat{\alpha}_N \to \alpha_0$ and $\hat{\beta}_N \to \beta_0$ almost surely as $N \to \infty$, where (α_0,β_0) is a true value of the vector of unknown parameters. Moreover, $\sqrt{N}[(\hat{\alpha}_N,\hat{\beta}_N)' - (\alpha_0,\beta_0)']$ has asymptotically multivariate normal distribution with mean $(0, 0)'$ and the covariance matrix Σ^{-1}, where

$$\sum = \begin{bmatrix} d & -c \\ -c & e \end{bmatrix}. \tag{3.7}$$

The matrix Σ does not depend on (α,β) and is positive definite.

The statistical properties (asymptotical distributions) of the ML estimates are known and this can be well used in the testing hypotheses about the parameters (for example, $\mathrm{H}_0{:}\alpha = \alpha_0$ versus the alternative $H_1{:}\alpha \neq \alpha_0$).

3.2. Bayes method

This method requires certain prior information upon the unknown parameters. On the other hand, if available, such information can improve the result of the procedure. We shall assume that the prior distribution of the vector of unknown parameters $(\alpha,\beta)'$ is two dimensional Gaussian distribution, with $E(\alpha) = a$, $E(\beta) = b$, $\mathrm{Var}(\alpha) = \sigma_a^2$, $\mathrm{Var}(\beta) = \sigma_b^2$ and $\mathrm{Cov}(\alpha,\beta) = \rho_{ab}$. Then the posterior density distribution function has the form

$$f(\alpha,\beta|X) = C \exp\left(-\frac{1}{2(1-\rho_{ab}^2)} \left[\frac{(\alpha-a)^2}{\sigma_a^2} - 2\rho_{ab}\frac{(\alpha-a)(\beta-b)}{\sigma_a\sigma_b} - \frac{(\beta-b)^2}{\sigma_b^2} \right] \right) \exp\left(l(N,\alpha,\beta)\right), \tag{3.8}$$

where C is a constant such that $f(\alpha,\beta|X)$ is a probability density function. Thus the posterior means are considered as the estimators of the unknown parameters. In our case the estimates for α and β are denoted by $\hat{\alpha}_B$ and $\hat{\beta}_B$. They have similar form to ML estimates (Eq. (3.5)), where the following substitution has to be done:

$\sum A_i$ is replaced by

$$\left(\sum A_i - \frac{a}{(1-\rho_{ab}^2)\sigma_a^2} + \frac{b\rho_{ab}}{(1-\rho_{ab}^2)\sigma_a\sigma_b} \right),$$

$\sum B_i$ is replaced by

$$\left(\sum B_i + \frac{b}{(1-\rho_{ab}^2)\sigma_b^2} + \frac{a\rho_{ab}}{(1-\rho_{ab}^2)\sigma_a\sigma_b} \right),$$

$\sum C_i$ is replaced by

$$\left(\sum C_i + \frac{\rho_{ab}}{(1-\rho_{ab}^2)\sigma_a\sigma_b} \right),$$

$\sum D_i$ is replaced by

$$\left(\sum D_i + \frac{1}{(1-\rho_{ab}^2)\sigma_a^2} \right),$$

$\sum E_i$ is replaced by

$$\left(\sum E_i + \frac{1}{(1-\rho_{ab}^2)\sigma_b^2} \right).$$

For this case of prior knowledge about the parameters of the model, the asymptotic properties of the estimates are the same as for ML case. Moreover, for $-\infty < a < \infty$, $-\infty < b < \infty$, $\sigma_a^2 \to \infty$ and $\sigma_b^2 \to \infty$ we get ML estimators.

3.3. Minimum contrast method

This estimation method (MC) is based on minimization, with respect to the unknown parameters, of a contrast function $f(x, \alpha, \beta)$, which has to fulfill the condition

$$-\infty < \int_0^1 f(x,\alpha_0,\beta_0)\mathrm{d}m_0(x) < \int_0^1 f(x,\alpha,\beta)\mathrm{d}m_0(x) < \infty, \tag{3.9}$$

where $m_0(x)$ is the stationary distribution of the process for true values of the parameters. For the

model specified by (Eqs. (2.3) and (2.4)) as shown by Lánská et al. (1994) the stationary distribution is a beta distribution linearly transformed on the interval (V^-,V^+). The ML method can be treated as a special case of MC, (Lánská, 1979). For our example the contrast function $f(x, \alpha, \beta)$ has been chosen of the form

$$f(x,\alpha,\beta) = -\frac{\alpha x^2 - 2\beta x + \beta}{2x(1-x)} + \frac{(-\alpha x + \beta)^2}{2x(1-x)} \tag{3.10}$$

For $\alpha > 1$, $\beta > \frac{1}{2}$ and the function given by (Eq. (3.10)) the above introduced condition (Eq. (3.9)) is fulfilled. Applying the observed data, the function that has to be minimized is

$$f_N(\alpha, \beta) = \sum_{i=1}^{N} \int_{\tau_{i-1}}^{\tau_i} f(X(s), \alpha, \beta)\mathrm{d}s. \tag{3.11}$$

The usual procedure of solving the following system of equations

$$\frac{\partial}{\partial\alpha} f_N(\alpha, \beta) = 0, \ \frac{\partial}{\partial\beta} f_N(\alpha, \beta) = 0$$

gives us the MC estimators $\tilde{\alpha}_N$ and $\tilde{\beta}_N$. Therefore

$$\tilde{\alpha}_N = \frac{\sum C_i \sum E_i + \sum D_i \sum E_i - 2\left(\sum C_i\right)^2}{2\left[\sum D_i \sum E_i - \left(\sum C_i\right)^2\right]},$$

$$\tilde{\beta}_N = \frac{\sum D_i \sum E_i - \sum C_i \sum D_i}{\sum D_i \sum E_i - \left(\sum Ci\right)^2}. \tag{3.12}$$

Second order partial derivatives are computed directly:

$$\frac{\partial^2}{\partial\alpha^2} f_N(\alpha, \beta) = \sum D_i, \quad \frac{\partial^2}{\partial\beta^2} f_N(\alpha, \beta) = \sum E_i,$$

$$\frac{\partial^2}{\partial\alpha\partial\beta} f_N(\alpha, \beta) = \frac{\partial^2}{\partial\beta\partial\alpha} f_N(\alpha, \beta) = -\sum C_i.$$

Since the matrix of second order partial derivatives is positive definite, $f_N(\alpha, \beta)$ is convex. Therefore, the minimum of $f_N(\alpha, \beta)$ is the global one. Under the condition (Eq. (3.6)) the estimates given by (Eq. (3.12)) are strongly consistent and asymptotically normal (Lánská, 1979) and thus, similar hypotheses on (α,β) as for ML case can be verified. It means that $\tilde{\alpha}_N \to \alpha_0$ and $\tilde{\beta}_N \to \beta_0$ almost surely as $N \to \infty$, where (α_0,β_0) are true values of unknown parameters and it holds that $\sqrt{N}[(\tilde{\alpha}_N, \tilde{\beta}_N)' - (\alpha_0, \beta_0)']$ has asymptotically two dimensional normal distribution with mean $(0,0)'$ and the covariance matrix $V, V = \Sigma^{-1} D \Sigma^{-1}$, where Σ is given by (Eq. (3.7)) and

$$D = \begin{bmatrix} d_{\alpha\alpha} & d_{\alpha b} \\ d_{\alpha b} & d_{\beta\beta} \end{bmatrix}$$

where

$$\mathrm{d}_{ab} = \frac{2\int_0^1 \frac{\partial}{\partial a} f(x,\alpha_0,\beta_0) \int_x^{1/2} \int_0^y \frac{\partial}{\partial b} f(z,\alpha_0,\beta_0)\mathrm{d}m_0(z)\mathrm{d}p_0(y)\mathrm{d}m_0(x)}{m_0(1) - m_0(0)},$$

and a, b is replaced by α or β, and $\mathrm{d}p_0(y) = \exp(-B(y))\mathrm{d}y, B(y) = \int^y \mu(x)\sigma^{-2}(x)\mathrm{d}x$. The formulas introduced above follow from Mandl (1968). An advantage of the minimum contrast estimates is no need to calculate integrals with respect to the process X, which appears important for a discrete sampling. On the other hand, the ML estimates are characterized by a lower variance that the minimum contrast ones.

A more detailed comparison of the proposed methods will be possible to make only after extensive simulations and comparing the estimates with known results.

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