

The parameters of the stochastic leaky integrate-and-fire neuronal model

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Received: 24 November 2005 / Revised: 23 March 2006 / Accepted: 28 March 2006 / Published online: 28 July 2006
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Abstract Five parameters of one of the most common neuronal models, the diffusion leaky integrate-and-fire model, also known as the Ornstein-Uhlenbeck neuronal model, were estimated on the basis of intracellular recording. These parameters can be classified into two categories. Three of them (the membrane time constant, the resting potential and the firing threshold) characterize the neuron itself. The remaining two characterize the neuronal input. The intracellular data were collected during spontaneous firing, which in this case is characterized by a Poisson process of interspike intervals. Two methods for the estimation were applied, the regression method and the maximum-likelihood method. Both methods permit to estimate the input parameters and the membrane time constant in a short time window (a single interspike interval). We found that, at least in our example, the regression method gave more consistent results than the maximum-likelihood method. The estimates of the input parameters show the asymptotical normality, which can be further used for statistical testing, under the condition that the data are collected in different experimental situations. The model neuron, as deduced from the determined parameters, works in a subthreshold regimen. This result was confirmed by both applied methods. The subthreshold regimen for this model is

characterized by the Poissonian firing. This is in a complete agreement with the observed interspike interval data.

Keywords Leaky integrate-and-fire model · Ornstein-Uhlenbeck neuronal model · Parameters estimation · Spontaneous firing

Introduction

Application of mathematical methods in neuroscience is based on construction of models aiming to mimic real objects. The models range from phenomenological mathematical models to very detailed biophysical models. From a biophysical point of view, the models of a single neuron reflect the electrical properties of its membrane via electric circuit description. Such circuit models can be written in terms of differential equations for the membrane voltage. Reducing these models, we can obtain integrate-and-fire types of model, which are reviewed in detail in most computational neuroscience monographs (Tuckwell, 1988; Koch, 1998; Dayan and Abbot, 2001; Gerstner and Kistler, 2002). These models are sometimes criticized for their too drastic simplification of reality (e.g., Segev, 1992). Simultaneously, the opposite opinion appears. For example, Kistler et al. (1997) claim that the integrate-and-fire model with a properly selected threshold, after reduction of the Hodgkin-Huxley four dimensional model, predicts 90 percent of the spikes correctly. Independently from this discussion, we observe that the number of papers devoted to the integrate-and-fire model, or at least employing it, is very high.

The simplest “realistic” neuronal model is the deterministic leaky integrate-and-fire model (Lapicque model, RC-circuit). It assumes that the membrane depolarization can

Action Editor: Nicolas Brunel

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be described by a circuit with a generator, a resistor and a capacitor in parallel. It has to be stressed that while the electrical representation is related to a small isopotential patch of neuronal membrane, the mathematical variable (the voltage) reflects an abstract representation of a complete neuron. This is another simplification based on neglecting the spatial properties of a neuron. There are attempts to overcome this situation (e.g., Pinsky and Rinzel, 1994; Rodriguez and Lansky, 2000) but still the single-point models dominate most of the applications. Due to the simplicity of the deterministic leaky integrate-and-fire model, the action potential generation is not an inherent part of the model as in more complex models and a firing threshold has to be imposed. The model neuron fires whenever the threshold is reached and then the voltage is reset to its initial value. This means that in the electrical circuit representation a switch is added to the circuit. The reset following the threshold crossing introduces a strong nonlinearity into the model. For a constant input the model neuron remains silent, never reaching the threshold (subthreshold regimen), or fires at constant intervals (suprathreshold regimen).

The experimental data recorded from very different neuronal structures and under different experimental conditions suggest a presence of stochastic variables in neuronal activity. We may assume that there is a random component, generally regarded as noise, contained in the incoming signal. The other source of noise can be the neuron itself where a random component is added to the signal. Unfortunately, there is no clear distinction between noise contained in the signal and the system noise. A phenomenological way how to introduce stochasticity into the deterministic leaky integrate-and-fire model is simply by assuming an additional noise term. If the noise is not further specified, but assumed to be Gaussian and white, then the model is well known in physical literature as an Ornstein-Uhlenbeck model (e.g., Gardiner, 1982) and this model has been widely used in neuroscience literature (Tuckwell, 1988; Koch, 1998; Dayan and Abbot, 2001; Gerstner and Kistler, 2002). An alternative way to end up with the Ornstein-Uhlenbeck model is by diffusion approximation of the model with discontinuous trajectories (Stein, 1965). An advantage of this approach is that a direct interpretation of the parameters appearing in the Ornstein-Uhlenbeck neuronal model is available (Lansky, 1997).

Models without specified parameters remain only a tool for qualitative comparison and thus finding methods for estimation is equally important as model construction. The lack of methods for parameters identification had been noticed for a long period (e.g., Tuckwell and Richter, 1978; Brillinger and Segundo, 1979). In general, the traditional approaches were more frequently focused on interspike interval (ISI) distribution. Keat et al. (2001) as well as Paninski et al. (2004) developed methods based on extracellular recordings

in vivo conditions with known input to the system. Estimation methods from in vitro voltage recordings for known input were presented by Stevens and Zador (1998), Rauch et al. (2003), Le Camera et al. (2004), Jolivet et al. (2006), Paninski et al. (2004). None of these papers treats comparison of the Ornstein-Uhlenbeck model with in vivo spontaneous activity. The likely reason is that, using the model, only interspike intervals (ISIs) were usually predicted and thus the attempts to identify the model parameters were based on observation of ISIs. Such a task is enormously complicated and leads to rather difficult numerical and mathematical problems (Inoue et al., 1995; Shinomoto et al., 1999; Ditlevsen and Lansky, 2005).

We aimed to study the estimation methods in the Ornstein-Uhlenbeck model, their stability and reproducibility. In the first Section we summarize the properties of the model. Then the methods for the estimation of its parameters are given and details of data acquisition presented. Simultaneously, the assumptions of the model are tested. Finally the parameters of the model are estimated and the obtained results are discussed. We restricted the study on a single neuron under spontaneous activity conditions. To extend the results on several neurons and different experimental conditions is possible, but beyond the scope of this article.

Model and its properties

The Ornstein-Uhlenbeck model of membrane depolarization is formally given by the stochastic differential equation,

$$dX(t) = (-\beta(X(t) - x_0) + \mu)dt + \sigma dW(t), X(0) = x_0, \quad (1)$$

where dW represents increments of a standard stochastic Wiener process (Brownian motion), and $\beta > 0$ characterizes the spontaneous decay of the membrane depolarization in the absence of input to the resting level x_0 . The drift coefficient μ reflects the local average rate of displacement due to the neuronal input and local variability is represented by the infinitesimal variance σ (the variability of the neuronal input). The spikes are not an intrinsic part of the model but are generated when the membrane depolarization $X(t)$ reaches for the first time the firing threshold S , which is an additional parameter. Then, the depolarization is reset to the resting level, x_0 , and the process of input “integration” starts anew. We should keep in mind that also the reset level, x_0 , represents an additional parameter of the model. Thus the model is fully described by Eq. (1) with its five parameters: β , μ , σ , S and x_0 . As said, the ISIs are identified in model (1) with the first-passage times of the process $X(t)$ across the boundary S ,

$$T = \inf (t > 0, X(t) \geq S > x_0) . \tag{2}$$

Due to the complete reset in defining ISI by Eq. (2) and due to the constant input μ , the ISIs form a renewal process, which means that ISIs are independent and identically distributed random variables. Formula (1) can be rewritten in a form often seen in engineering applications using the term white noise,

$$\frac{dX(t)}{dt} = -\beta(X(t) - x_0) + \mu + \sigma \xi(t), X(0) = x_0, \tag{3}$$

with the same interpretation of the parameters as above, only the white noise $\xi(t)$ is a formal derivative of the Wiener process with respect to time. For a fixed time t , $X(t)$ given by (1) or (3) is a Gaussian random variable. In absence of the threshold S and if σ tends to zero, we can solve the differential Eq. (3). The solution is identical with the mean value of the stochastic depolarization given by Eq. (1)

$$E(X(t)) = x_0 + \frac{\mu}{\beta}(1 - \exp(-\beta t)) \tag{4}$$

and the variance of $X(t)$ is

$$Var(X(t)) = \frac{\sigma^2}{2\beta}(1 - \exp(-2\beta t)). \tag{5}$$

The position of the asymptotic depolarization $E(X(\infty)) = x_0 + \mu/\beta$ determines regimes of firing of the Ornstein-Uhlenbeck model. For $\mu/\beta \gg S - x_0$, the suprathreshold regimen, the firing is almost regular and ISI histogram resembles normal distribution. The noise plays a limited role in this range of parameters. For $\mu/\beta \approx S - x_0$, the distribution of ISIs is positively skewed and resembles Gamma distribution. In the subthreshold regimen, $\mu/\beta \ll S - x_0$ the firing becomes Poissonian. Here, the noise plays a crucial role and without it the neuron would remain silent. This last regimen is important for this study, as will be seen. Of course, the signs “ \gg ” and “ \ll ” are relative to the asymptotic variance $Var(X(\infty)) = \sigma^2/2\beta$. More details on the Ornstein-Uhlenbeck neuronal model can be found, for example, in Tuckwell (1988) or in Ricciardi and Lansky (2003).

The description of the process via Eq. (3) is apparently an intuitive extension of the deterministic approach. Its advantage is in giving a method for a computer simulation of the process sample trajectories (Kloeden and Platen, 1992). The simplest discrete-time approximation of (3) is a stochastic analogue of the Euler scheme for ordinary differential equations,

$$X_{i+1} = X_i - \beta(X_i - x_0)h + \mu h + \sigma \epsilon_i, X_0 = x_0, \tag{6}$$

where h denotes the time step of simulation, X_i ($i = 1, 2, \dots$) are the simulated values of the process, and ϵ_i are independent and normally distributed random variables, $\epsilon_i \sim N(0, h)$. The increments ϵ_i in (6) can be replaced by $\pm\sqrt{h}$ selecting these values with equal probability $1/2$, which substantially decreases the simulation time (Tuckwell and Lansky, 1997). This was the procedure applied to simulate the membrane depolarization in this study. Apparently, the parameters β , σ , μ and x_0 have to be determined for the simulation procedure. If the ISIs are to be simulated, then in addition, the firing threshold S is required. As mentioned, the spikes in the model are generated when the membrane depolarization $X(t)$ reaches, for the first time, the firing threshold S . While the simulation of the trajectories X contains no systematic bias, it is not true for the simulation of the first passage times (Lansky and Lanska, 1994). It is systematically overestimated and this effect has to be minimized.

Two basic types of data can be used for the identification of the parameters appearing in Eq. (1). In the first of them only the ISIs are available, which means the realizations of the random variable defined by Eq. (2). If this is the case, then the situation is complicated and the solution can be achieved only under some additional assumptions. For example, it has to be assumed that the firing threshold and the resting level are known. In the second situation, which is investigated here, the membrane depolarization is recorded between the generation of spikes. To specify the firing threshold and reset level seems to be a simpler task than to estimate the remaining parameters of the model. We should simply record what was the reset after the end of an action potential and what was the final value of the depolarization when it started. However, we will see that the situation is not so simple and also these two parameters need to be estimated. A method of estimating the remaining parameters was proposed more than two decades ago (Lansky, 1983). Thus the novelty of this paper is mainly in application of the method to real intracellular data. For an extensive methodological review of estimation methods in stochastic diffusion processes, for which Eq. (1) is a special case, see Prakasa Rao (1999).

The aim of this article is primarily determination of the values of the parameters β , σ and μ . The question is whether these parameters are stable over a long period or whether they vary in short time ranges. Whereas σ and μ are input parameters and thus are assumed to change whenever the input to a neuron has changed, model (1) assumes that β is a property of the membrane (in the same way as S and the reset level) and these three intrinsic parameters should be stable. However, these are only assumptions which have never been confirmed. Thus, initially we estimate the parameters separately for each ISI.

Methods

(a) Estimation from a single interspike interval

The records of the depolarization within single ISI permit us to estimate β , μ and σ . Theoretically also two additional parameters S and x_0 could be determined, but as we will see, for that purpose more realizations of the ISIs are necessary.

Let us assume that in one ISI the membrane depolarization $X_i = x_i$ is sampled at $N + 1$ points ($i = 0, \dots, N$) at steps h at times $t_i = ih$ (the notation is complicated for non equal sampling step but the results are analogous). Then the formulas for the estimation of the parameters by the maximum likelihood method are

$$\hat{\beta} = \frac{1}{h} \frac{\sum_{j=0}^{N-1} x_j^2 - \sum_{j=0}^{N-1} x_{j+1} x_j + (x_N - x_0) \bar{x}}{\sum_{j=0}^{N-1} x_j^2 + \bar{x}^2 N}, \quad (7)$$

$$\hat{\mu} = \frac{x_N - x_0}{T} + \hat{\beta} \bar{x} \quad (8)$$

and

$$\hat{\sigma} = \frac{1}{T} \sum_{j=0}^{N-1} (x_{j+1} - x_j + x_j h \hat{\beta} - h \hat{\mu})^2, \quad (9)$$

where $\bar{x} = \frac{1}{N} \sum_{j=0}^N x_j$, $T = Nh$. These formulas are discrete-time variants of the formulas based on the assumption that the depolarization is continuously recorded in between the spikes.

Formula (4) suggests that the method of moments can also be used. Then, we minimize the functional

$$L(\beta, \mu) = \sum_{j=1}^N (x_j - x_0 - \frac{\mu}{\beta} (1 - \exp(-\beta j h)))^2 \quad (10)$$

with respect to the parameters β and μ by a regression method. It is obvious that efficiency of this method depends on the distance of x_0 from the asymptotic depolarization μ/β . An increase of β relatively to h also handicaps the method.

Another method for estimate of the noise amplitude is

$$\hat{\sigma}' = \frac{1}{T} \sum_{j=0}^{N-1} (x_{j+1} - x_j)^2. \quad (11)$$

This estimate follows from theoretical results established by Feigin (1976). Comparing Eqs. (9) and (11), we can see that for $h \rightarrow 0$ in (9) we end up with Eq. (11). We will compare all these estimation methods.

(b) Estimation from several interspike intervals

In this situation, if we assume that the parameters remain stable over several ISIs we can use the extension of three estimates as were formally proposed by Lansky (1983). That method takes into account the length of ISIs and in some sense shorter ISIs contribute to the estimates less than longer ones. Here we use a slightly different approach. We estimate the parameters for each ISI separately. Then, the global estimates are representative over ISI counts not the total length of the record. Further, and it is the main reason, in this way we also get some information about the dependency of the values on the lengths of ISI and their position in the record. The global record can be characterized by representative values of β_M , μ_M and σ_M , in our case we use medians (denoted by index M) of the estimated values.

If several ISIs are available, then in addition to the parameters mentioned in the previous Section, also the threshold S and the reset value x_0 can be estimated. For this purpose we simply use the medians of the values observed for each ISI.

Animal preparation for the intracellular recordings

Guinea pigs served as subjects for the intracellular recording experiments. Anaesthesia was initially induced with pentobarbital sodium (Nembutal, Abott, 35 mg/kg, ip) and maintained by supplemental doses of the same anaesthetic (about 5–10 mg/kg/hr) during the surgical preparation and recording. Throughout the recording, an electrocorticograph was monitored to assess the level of anaesthesia. The subject was mounted in a stereotaxic device following the induction of anaesthesia. A midline incision was made in the scalp and a craniotomy was performed to enable vertical access to the MGB in the right hemisphere (He, 2003; Xiong et al., 2003; Yu et al., 2004). The head was fixed with two stainless steel bolts to an extended arm from the stereotaxic frame using acrylic resin. The left ear was then freed from the ear bar, so that the subject's head remained fixed to the stereotaxic device without movement.

Cerebrospinal fluid was released at the medulla level through an opening at the back of the neck. The animal was artificially ventilated. Both sides of the animal's chest were opened, and its body was suspended to reduce vibrations of the brain caused by intra-thoracic pressure. The experimental procedures were approved by the Animal Subjects Ethics Sub-Committee of The Hong Kong Polytechnic University.

A glass-pipette as the recording electrode, filling it with 0.5M KCl (pH 7.6, 0.05M Tris HCl buffer) was used. The resistance of the electrode ranged between 40–90 M. The electrode was advanced vertically from the top of the brain by a stepping motor (Narishige, Tokyo, Japan). After the electrode was lowered to a depth of 4–5 mm, the cortical exposure was sealed using low-melting temperature paraffin.

When the electrode was near or in the target area, it was slowly advanced at 1 or 2 μm per step.

Data collection

Upon penetrating the membrane of a cell, the electrode detected the negative membrane potential. After amplification, the membrane potential as well as the auditory stimulus were stored in the computer with the aid of commercial software (AxoScope, Axon). The direct current (DC) level of the recording electrode was frequently checked and set to zero during the experiments. The DC level after each recording was used to compensate for the membrane potential of some neurons. Neurons showing a resting membrane potential lower than -50 mV and spontaneous spikes (if any) of larger than 50 mV were included in the present study. Single neuron data were selected for this article. The membrane potential was recorded (in 100 mV) with time step $h = 0.00015\text{ [s]} = 0.15\text{ [ms]}$, for period $0\text{--}501\text{ [s]}$. Accompanying the values of the membrane potential is the stimulus level. For the purpose of this study we selected only ISIs which were entirely outside the stimulation period.

Detection of spikes and determination of S and x_0

The parameter estimation method is based on the observation of the membrane depolarization between spikes. Therefore the spikes have to be removed from the data but it is not entirely obvious which part of the records can be included in the estimation procedure. At first, we detect the spikes and then we judge their beginnings and their ends. In this way ISIs are fixed. The least problematic is spike detection. The level for this purpose was experimentally chosen at the value of -35.5 [mV] (note that this is not the firing threshold S , but a value to detect spikes in continuous sampling of the voltage), see Fig. 1(a).

From visual inspection of the data it is clearly difficult to decide where exactly to start and to end the spikes, and hence to decide which data to include in the parameter estimation procedure. It follows from this inspection that for detected spikes the width of the spike as well as the voltage where ISI starts, are not always the same. This is in contrast with the assumptions of model (1). The consequences are summarized in the Discussion. Determining x_0 by the minimum voltage after detected spike failed due to the large fluctuations of these values. The final solution, which was adopted, was that all data were transformed by a moving average (over 6 values) and the minimum in “the valley” after a spike is considered to be start of an ISI. This procedure was confirmed by the following analysis (see next Section). To find this minimum, at first “the valley” has to be defined.

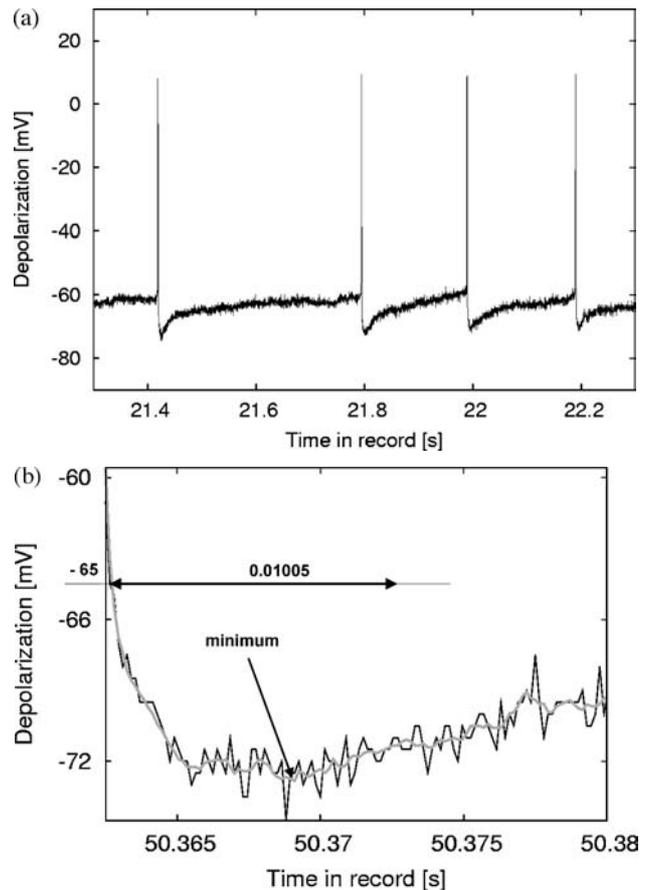


Fig. 1 Example of data used for the estimation of the parameters. (a) The spikes are not initiated at the same values and the end is not uniquely defined. (b) Schematic illustration of ISI initial point detection (for details see text). Gray line is the moving average over six observations given by black line

Its start is fixed at the moment when the depolarization reaches the value of -65 [mV] for the first time after spike generation. Its end is the time point 0.01005 [s] after its beginning. In this region the minimum depolarization is sought for (see Fig. 1(b)).

Defining the end of each ISI was not so problematic and we took the point 0.01005 [s] before detected spike, i.e., before the voltage reaches -35.5 [mV] . For threshold determination, we took the last point with decreasing depolarization before the spike detection (in other words, the depolarization only increases to the top of the spike after this point).

Model assumptions—Frequency analysis

When we tried the maximum-likelihood estimates directly from the raw data we got the results which are illustrated in Fig. 2 in a typical example.

It obvious that the simulated trajectory differs from the recorded one in several respects. The former reaches the steady-state much faster and the amplitude of the noise is

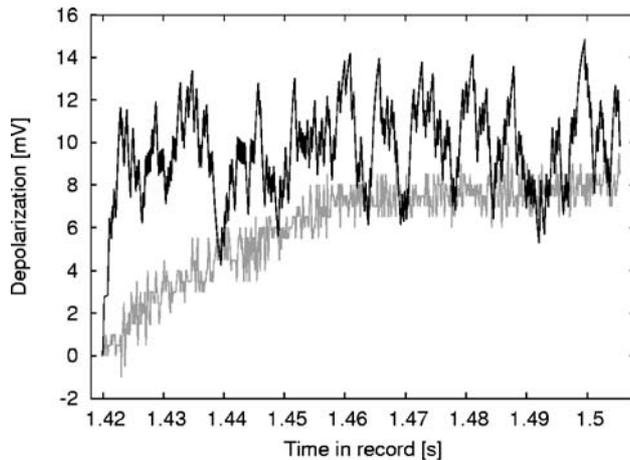


Fig. 2 Example of membrane potential trajectories, experimental (gray) and simulated (black) using the parameters estimated by the maximum likelihood method from the original data

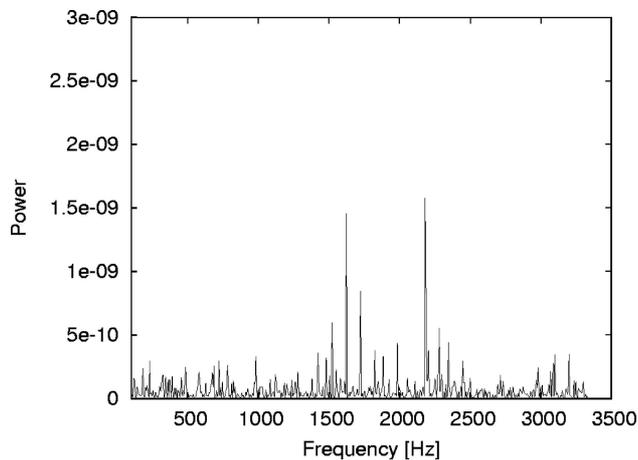


Fig. 3 Example of spectral decomposition of the data

much higher. Further, it seems that the noises is not of the same type. This suggests that the assumptions of the model should be checked. The assumptions imply that the spectra of the data should not contain a dominant frequency (white noise contains all the frequency components equally). We performed a spectral decomposition of several parts of the data and always found dominant frequency at 2180 [Hz]. An example of spectral density obtained from the data is in Fig. 3. In this example there is also high peak at 1600 [Hz].

The source of this high frequency noise is not clear and to avoid its influencing the results, all the values of the membrane depolarization were transformed by a moving average over a time window of six steps. To eliminate this high frequency noise we tried two strategies (moving averages, averages over non overlapping time windows). The second strategy appeared as inferior to the moving averaging. The success was judged from the fit of the estimates to those obtained from the regression of the data to an exponential function (4), see formula (10). In the example, on the inter-

Table 1 Example of dependence of maximum likelihood estimates on number of steps in moving average procedure

| Number of steps | Estimate σ | Estimate μ | Estimate β |
|-----------------|-------------------|----------------|------------------|
| 1 | 0.071 | 1.954 | 170.80 |
| 2 | 0.038 | 0.785 | 62.17 |
| 3 | 0.024 | 0.454 | 33.03 |
| 4 | 0.017 | 0.370 | 24.90 |
| 5 | 0.014 | 0.355 | 23.06 |
| 6 | 0.011 | 0.343 | 21.58 |
| 7 | 0.011 | 0.331 | 20.53 |
| 8 | 0.009 | 0.329 | 20.10 |
| 9 | 0.007 | 0.317 | 19.04 |
| 10 | 0.007 | 0.310 | 18.59 |

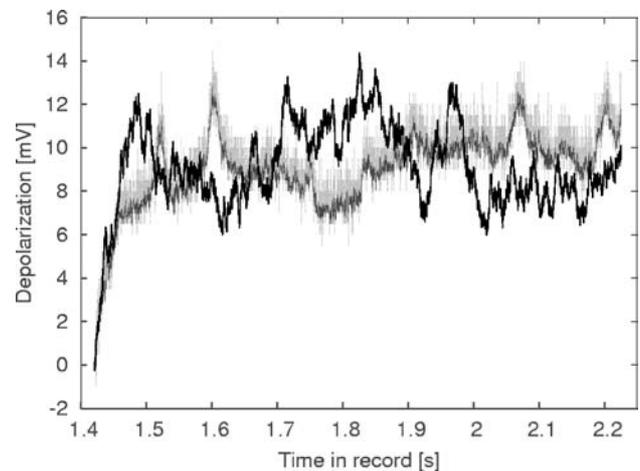


Fig. 4 Example of membrane potential trajectories, experimental (light gray), filtered (dark gray) and simulated (black) using the parameters estimated from the filtered data. Filtering decreased the amplitude of the noise and made it similar to that of the simulated signal

val (20.4201–20.54955) [s], statistical regression gives $\mu = 0.341$ [V/s] and $\beta = 21.036$ [1/s]. The results of the maximum likelihood estimate after computing moving averages are given in Table 1.

From this table we can see that, the moving average over about six steps removes the discrepancy. Subsequently we simulated the model again using the parameters estimated from the signal after the filtering (see Fig. 4. and compare with Fig. 3).

It can be seen that the high-frequency noise present in the experimental data has been removed and appears neither in the filtered nor simulated trajectory. After the signal was filtered, the estimates of the parameters for each detected ISI were calculated according to formulas (7–9). From now on, by “the data” we mean the filtered original data.

The differences in estimates of σ using formula (9) or (11) were negligible. For example, on the interval (20.4201, 20.54955); we found $\hat{\sigma}' = 0.0115$ [V/ \sqrt{s}] using (11), and $\hat{\sigma} = 0.0114$ [V/ \sqrt{s}] using (9). Therefore for the noise amplitude only estimate (9) was used.

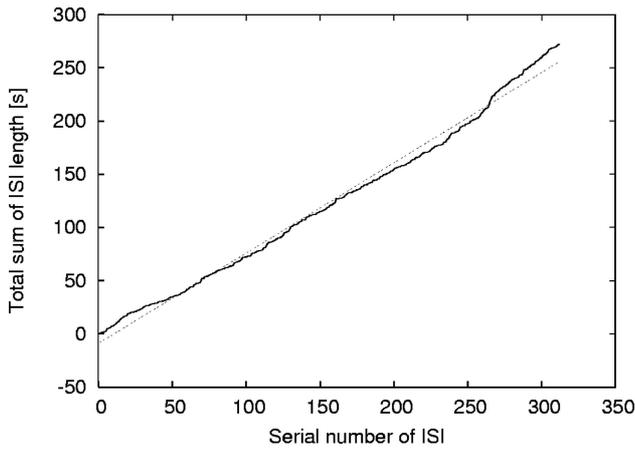


Fig. 5 Dependency of the sum of the ISIs length on the serial number of the ISI. The dotted line corresponds to the constant firing rate

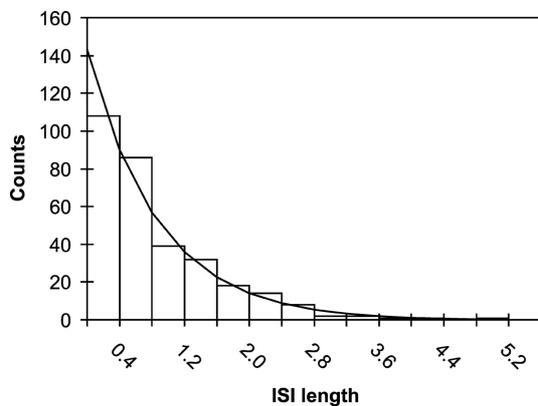


Fig. 6 Histogram of ISIs together with the corresponding density of exponential distribution normalized on the number of ISIs

Results

Parameters of the input and the membrane time constant

Using the above described procedure we identified all ISIs and estimated the parameters for each of them. In total, 312 ISIs were analyzed and before estimating the parameters of the model, we applied simple standard statistical procedures on them. The ISIs appear stable in time (see Fig. 5), which means that there is no trend in their length.

The corresponding statistical characteristics are median 0.585 [s], average 0.872 [s] and coefficient of variation 0.883. The shape of histogram of ISIs (Fig. 6) suggests that the ISIs are generated in accordance with the exponential distribution. Kolmogorov-Smirnov test does not reject the hypothesis of exponentiality, at 5% a significance level. Also the other test for normality of the estimates are at 5% significance level.

The parameters of model (1) were estimated by both methods for all the ISIs and by using the estimates in schema (6)

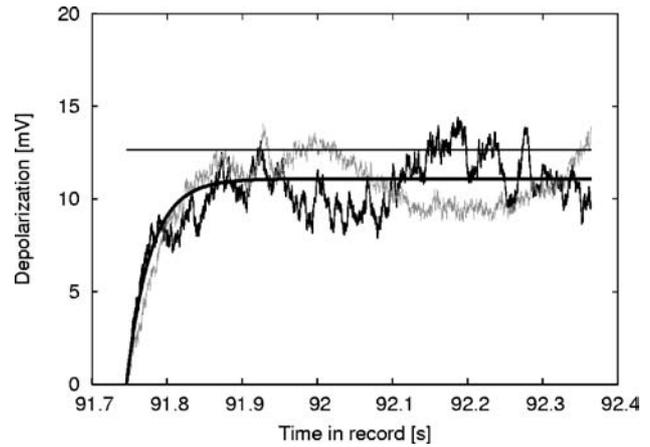


Fig. 7 Three curves: gray—data; fluctuating black—simulated model with parameters estimated by maximum likelihood method from the data; smooth black—mean value (model without noise). The horizontal line represents the estimated threshold S

the simulated depolarizations were plotted. An example is in Fig. 7.

From the simulations made with estimated parameters, it appears that the estimated asymptotical voltages, μ/β , coincide well with the data. On the other hand, in the first part of the trajectories, the real data is a bit faster in reaching the asymptote than simulated trajectory. This visual impression was confirmed by the following method which aimed to check the fit of the model to the data. For each ISI we have a vector of values of depolarization $x_i = (x_{i0}, x_{i1}, \dots, x_{in})$ a corresponding vector of depolarization, $y_i = (y_{i0}, y_{i1}, \dots, y_{in})$, obtained from simulating Eq. (1) by formula (6) using the estimated parameters. The differences $z_i = x_i - y_i$ were calculated and their averages and standard deviations evaluated. These results are illustrated in Fig. 8 for both estimation methods. The main difference between the methods is in the period just after the spike generation. This could be due to a violation of the model assumptions (for example, hyperpolarization) and possibly the method of moments could be more robust against this violation.

Apparently the regression method works better. In both cases there is a systematic hump after the origin, but for the regression method it is much smaller.

An important question is dependency of the estimated parameters on the length of ISIs. The only dependency we can expect that, if the input to neurons changes with the experiment, then μ could get smaller for longer ISI. Otherwise, μ and β should keep stable and independent on the length of ISI. The results are illustrated in Fig. 9. We can see, that the results obtained by the regression method are independent of ISI ($corr(\hat{\mu}, ISI) = 0.016$ and $corr(\hat{\beta}, ISI) = 0.136$) which is not the case of the estimates obtained by the maximum

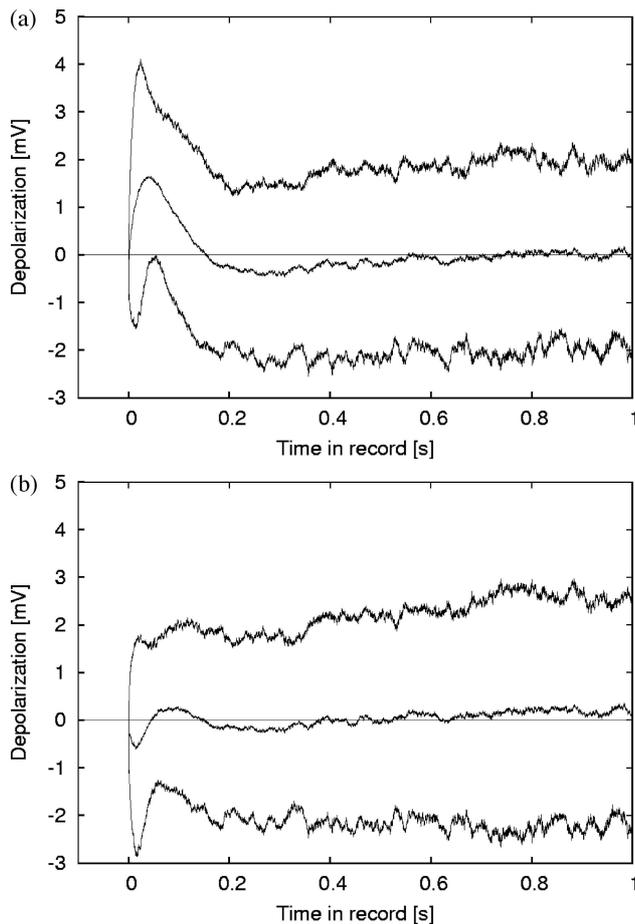


Fig. 8 Average difference between the data and simulated trajectory. (a) estimates obtained by maximum likelihood (b) estimates obtained by regression method. The region around the curves indicates $\pm 2 * \text{standard deviations}$

likelihood method ($\text{corr}(\hat{\mu}, \text{ISI}) = 0.663$ and $\text{corr}(\hat{\beta}, \text{ISI}) = 0.668$).

Similarly, we investigated the estimated value of σ and found it independent of the ISI length, ($\text{corr}(\hat{\sigma}, \text{ISI}) = -0.099$). As is apparent from the above analyses, the regression method was superior to the maximum likelihood method for estimation of μ and β (see Figs. 8 and 9), so the values from the regression are considered further on.

In Fig. 10 are presented histograms of estimated values of the input parameters μ , σ and of the inverse time constant β . We can see that the distributions are rather broad and quite symmetric resembling Gaussian density. This suggests the asymptotic normality of the estimates which can be used for future statistical inference. The Kolmogorov-Smirnov test rejected normality of $\hat{\mu}$ and $\hat{\beta}$, but not for $\hat{\sigma}$. The reason for the rejection in the case of $\hat{\mu}$ and $\hat{\beta}$ were the outliers on the right hand side of the histograms (see Fig. 10). After their removal the estimates also fit the normal distribution.

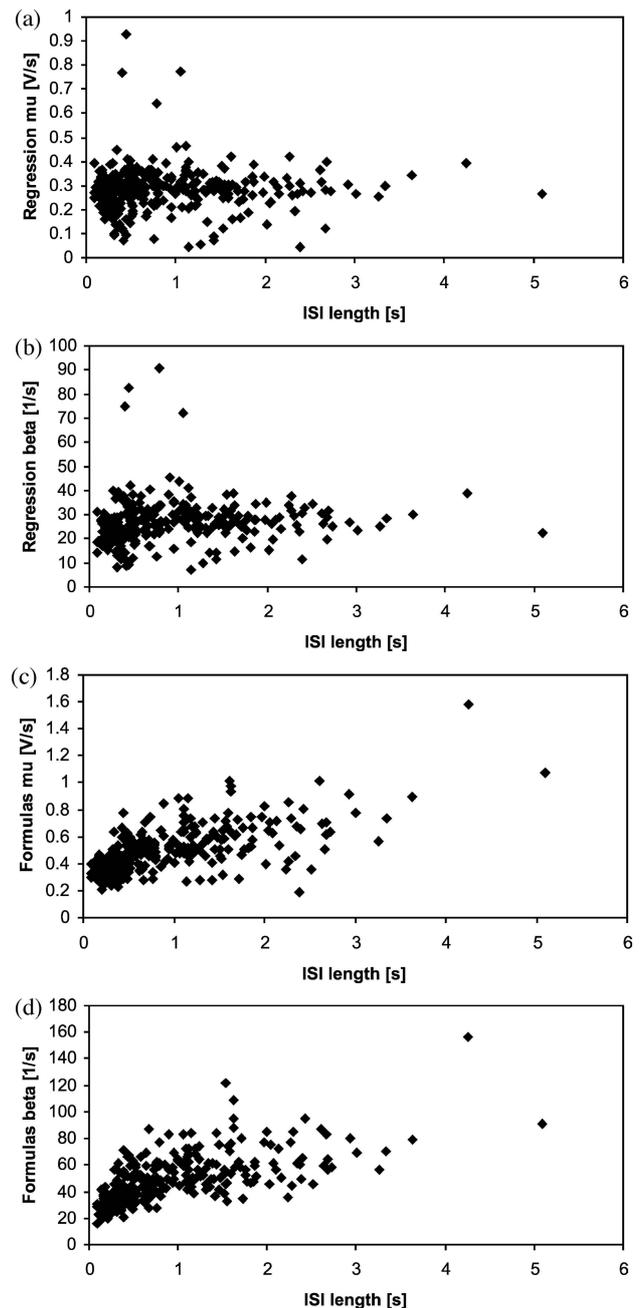


Fig. 9 Dependency of the estimated parameters (vertical axis) on the length of ISI (horizontal axis). In (Fig.9(a), and (b) are results obtained by regression method, (Fig.9(c), and (d) those obtained by the maximum likelihood method

Finally we calculated the central characteristics of the estimated parameters. Median value of the noise amplitude was $\hat{\sigma}_M = 0.013505$ [$\text{V}/\sqrt{\text{s}}$]. Median values of μ and β were by regression method, $\hat{\mu}_M = 0.2846$ [V/s], $\hat{\beta}_M = 25,8042$ [$1/\text{s}$], for the maximum likelihood method the obtained values were $\hat{\mu}_M = 0.4606$ [V/s], $\hat{\beta}_M = 43,5068$ [$1/\text{s}$]. Due to the symmetry of histograms, the averages and the medians were practically the same. We should notice that both methods give almost identical asymptotic depolarization

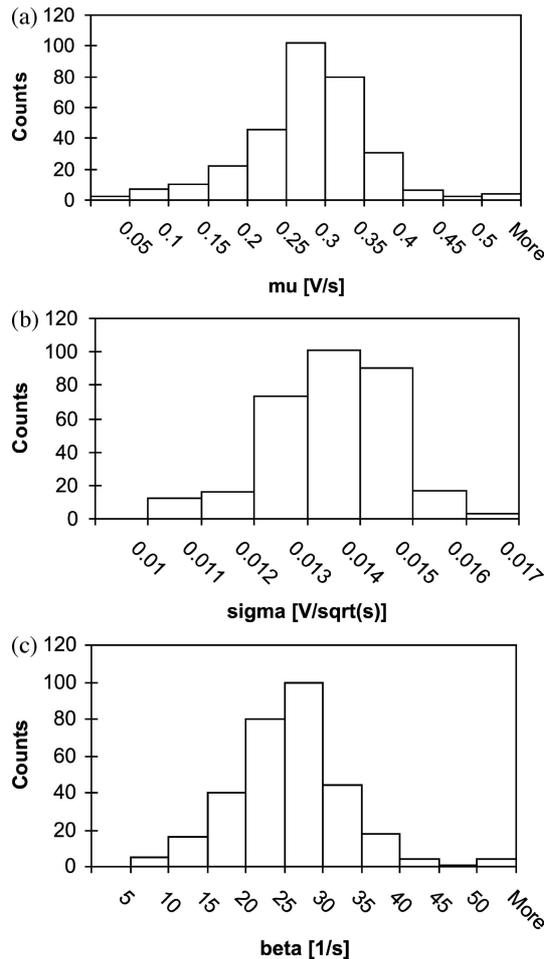


Fig. 10 Histograms of the estimated parameters. (a) the drift, (b) the noise amplitude, (c) the inverse membrane time constant

μ/β , for regression 0.0110 [V] and for maximum likelihood 0.0106 [V]. We can calculate the membrane time constant, which from the regression method yields after inverting the estimate of β , the value of 38.8 ms.

Reset, threshold and asymptotic depolarization

For each ISI we estimated the initial value of the depolarization after a spike and the firing threshold (the last value before the spike is generated), Fig. 11.

We see from comparison of Fig. 11(a) and (b) that the initial values were more variable than the thresholds S . The reason may be that the spike was not in principle generated at the time when the voltage was at its highest level during the ISI and this will be discussed later. The median value of the initial depolarization is $x_0 = -73.92$ [mV]. The median threshold value is $S = -61.0$ [mV]. It implies that, in average, the firing threshold is about 13 [mV] above the initial depolarization. It is larger than approximately 11 [mV] which is the level of asymptotic depolarization as it comes

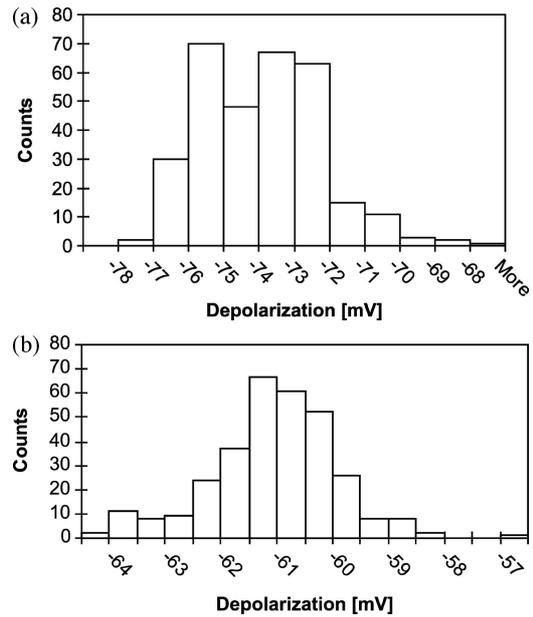


Fig. 11 Histograms of the membrane parameters. (a) initial membrane depolarization, (b) firing threshold depolarization

out from the parameters estimation. The normality of both determined parameters, x_0 and S , was rejected.

To illustrate the relationship between the firing threshold and the asymptotic depolarization we compare Fig. 12 and Fig. 11(b). Namely we can see that the estimated parameters predict subthreshold firing type, as from Fig. 12 we can see that the asymptotic depolarization is below the threshold even with respect to its variation.

Finally, to show that the neuron, as the estimation of the parameters suggests, is in the subthreshold (noise-driven) regimen, we compare directly the theoretical asymptotic depolarization and the corresponding firing threshold (Fig. 13). We can see that the difference between the threshold and the asymptotic depolarization is almost always positive (Fig. 13(a)). If we investigate some kind of two-standard-deviations envelope around the asymptotic depolarization, then we get below zero (Fig. 13(b)). The possible reasons for this result are presented in Discussion.

Discussion

This is mostly a methodological attempt to estimate the parameters of the Ornstein-Uhlenbeck neuronal model from the intracellular recordings and for an unknown input. We have to realize that only a single neuron in a single record was analyzed and thus the results are more a methodological illustration of how to deal with the problem than a statistically complete analysis.

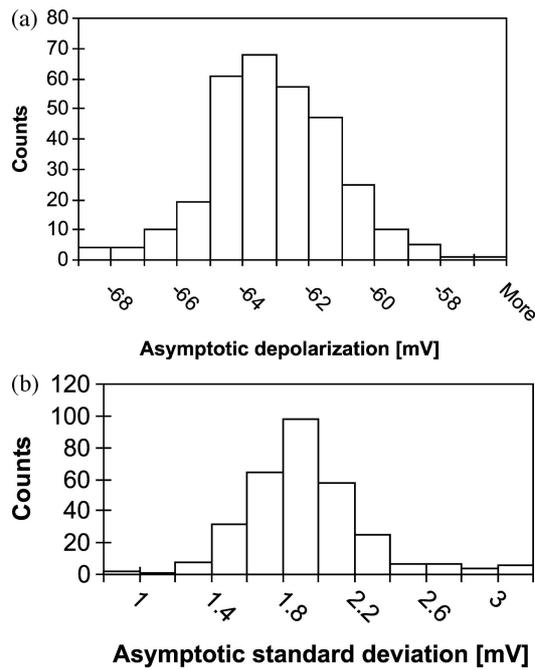


Fig. 12 Histograms of the asymptotic properties calculated from the parameter estimates. (a) asymptotic depolarization, (b) asymptotic standard deviation of the depolarization

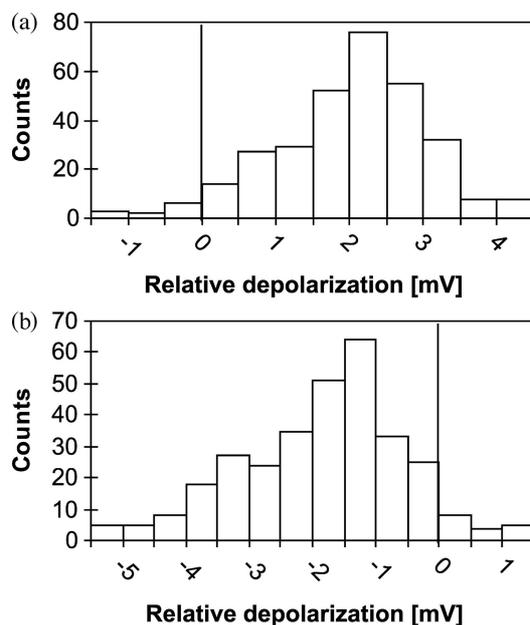


Fig. 13 Histogram of the pair wise differences between the estimated firing thresholds and the asymptotic depolarizations. (a) $\hat{S} - (\hat{x}_0 + \hat{\mu}/\hat{\beta})$, (b) $\hat{S} - (\hat{x}_0 + \hat{\mu}/\hat{\beta}) - 2\sigma/\sqrt{2\hat{\beta}}$

Spontaneous activity

We selected for statistical treatment only the unstimulated activity of the neuron. The detected ISIs are exponentially distributed which suggests that they are generated in accordance with a Poisson process. The Poisson process as a model of spontaneous activity of a neuron was experimen-

tally observed many times and on very different neuronal structures (e.g., Eggermont et al., 1993; Jones and Jones, 2000; Lin and Chen, 2000; Tateno et al., 2002). In sensory neurons, we showed in frogs (Rospars et al., 1994) and rats (Duchamp-Viret et al., 2005) that the spontaneous activity of olfactory receptor neurons can be described by a Poisson process. Theoretical arguments for the fact that the spontaneous activity is a low rate Poisson process can be found in Laughlin (2001). The spontaneous activity can be interpreted as the summation of two processes: (i) an intrinsic process which implies firing due to the noise, and (ii) an extrinsic process, which induces firing due to the uncontrolled occurrence of effects either from the environment or other neurons. Of course, Poisson process, as any other model, is an approximation which can be always questioned (Koyama and Shinomoto, 2005), in this case for example by the existence of the absolute refractory period, but such objections are marginal at this level of description.

From the point of view of the Ornstein-Uhlenbeck neuronal model, the Poisson process corresponds to the situation in which the signal is so weak that the asymptotic depolarization is far below the firing threshold, which has to be true with respect to the amplitude of noise. In other words, for model (1) and (2) this type of activity is predicted if the firing threshold S is far above the asymptotic depolarization, μ/β , given by Eq. (4) with respect the asymptotic variance (5), which is controlled by σ . We can see from Fig. 13(a), that the asymptotic depolarization is below the threshold. However, when we plot the asymptotic depolarization increased for two asymptotic standard deviations, we get above the threshold. This could break the exponentiality of ISIs distribution observed in our data. The reason why this has not happened may be that not every crossing of the voltage has induced a spike, in other words, that we had not recorded exactly the trigger zone depolarization. Namely, two-compartment version of the model would be closer to reality. Similar conclusion can be found in Jolivet et al. (2006).

Model assumptions

There are many assumptions of the model which are disputable and can be true only in idealization. First of all, it is the constancy of the input parameters μ and σ over each ISI. We selected the spontaneous activity as an experimental material, for which such a constancy can be expected. Another assumption is the Gaussian white noise on the neuronal input. This we found was not true for our data and the high-frequency noise was detected and eliminated. The source of this high frequency noise remains unclear to us. Next assumption, violated in our observations, was the first-passage time inducing the generation of a spike. Probably, we registered the membrane depolarization in other location than the spikes are generated. The traditional assumption of

the model is the fixed value of the reset depolarization (for the variants with random initial value see Lansky and Smith, 1989; Christodoulou and Bugmann, 2000). This assumption represents an oversimplification which was noticed as early as by Stevens (1964). We found that this assumption was also violated, but for the model performance the effect is negligible. Despite that any assumption of the model can be made questionable, as it is only a model, we may conclude that the data are consistent with the model. This was not the case in Stevens and Zador (1998) where model (1–2) in absence of noise was fitted to response of cortical neurons in vitro to injection of constant current. There the voltage approached the threshold as a concave curve, in contrast to Eq. (4), and our data. The authors of the paper solved the discrepancy by employing time-varying membrane resistance and time-varying membrane time “constant”. In contrast to Stevens and Zador (1998), here the investigated trajectories shown the convex shapes, but it may happen that when a neuron is stimulated, this property is met.

Intrinsic parameters

Tuckwell and Richter (1978), who pioneered the estimation of the parameters in the stochastic neuronal models, classified the model parameters into two classes—intrinsic and input. Unfortunately, their results are based on different assumptions and thus not comparable with ours. In model (1–2) are three intrinsic parameters, β , S and x_0 , and for different neurons have been reported different values of them, even without modeling concept. However, the intrinsic parameters were not in the center of our interest despite they play their important role for the model performance. Jolivet et al. (2006) analyzed spike response model which was claimed to be equivalent to the leaky integrate-and-fire model. However, their approach is not oriented on estimating the parameters μ and σ , but it is aimed on spike train prediction. The time-dependent threshold is considered in their paper, but the constant value is achieved in about 10 ms, which would not change our results as no ISI shorter of 10 ms was observed. In their Fig. 1(a) we can see, that the threshold reaches the value between -60 and -70 mV which corresponds to our results. In general, the values of intrinsic parameters obtained in this article are consistent with the values found in literature.

Input parameters

Completely different situation comes with the input parameters. The attempts to estimate them were up to now rare and based on additional assumptions. Inoue et al. (1995) analyzed spontaneous activity of the mesencephalic reticular formation neurons on the basis of ISIs. It should be noted that the term spontaneous activity has in central neurons different meaning than in the sensory systems. In the case of

neurons investigated by Inoue et al. (1995) there were either in sleeping animals or in bird watching state, but there is no apparent difference in the activity or the parameters. We should keep in mind that the firing rates were higher than in our case and none of the neurons resembled Poissonian firing. There the firing threshold and the membrane time constants were selected a priori, S was set 15 [mV] above the reset value and the time constant was taken equal to 5 [ms]. The threshold obtained in this study (approx. 13 [mV]) is not so different from the value assumed by these authors. On the other hand, the membrane time constant we estimated was about seven times larger than that used by them. This fact corresponds well to the fact that our values of the drift parameter were estimated lower than in the cited paper. The estimated μ ranges in their paper from -6 to 3 [mV/ms], whereas in this study we obtained the values in much smaller range, around 0.28 [mV/ms]. Finally, the most striking at the first sight seems to be the difference in the amplitude of noise, which usually was found much larger than in this paper. However, it is indirectly clear that the values in Inoue et al. (1995) are in different units than in this paper ([mV/ms]). After rescaling, the values the difference becomes less apparent. It is an open question if the comparison of our results with Inoue et al. (1995) can be considered as a discrepancy, or if their results are so widespread that ours can be seen included in theirs. A possible source of discrepancy between these two papers is probably difference in applied method and the overall activity of the neurons.

Another attempt to compare the Ornstein-Uhlenbeck model with ISI data was done by Shinomoto et al. (1999) with a negative result. Their method is not based on direct estimation of the model parameters but on studying mutual relationship between coefficient of variation and the skewness coefficient. They concluded that the model is not adequate to account for the spiking in cortical neurons. These authors did not estimate the membrane time constant and considered for it several optional values. This complicates the comparison of their results with ours. However, they claimed that the reason for inconsistency of their data with the Ornstein-Uhlenbeck process was mainly due to anomalous long ISIs. In our case the parameters were found in the subthreshold region and thus the long ISIs represent no problem for the fit of the data to the model. On the other hand, in the case of the stimulated activity such a situation can arise.

Both these attempts (Inoue et al., 1995; Shinomoto et al., 1999) were based on ISIs statistics. It means that for estimation of the parameters a sample of several hundreds of ISIs is necessary. Our method permits to estimate the input parameters in a short time window (in a single ISI). It appeared that the regression method was superior to the maximum likelihood. There might be several reasons for this effect. The first one can be the above mentioned violation of the model

assumptions and thus that the maximum-likelihood may be more sensitive to these discrepancies between the model and the data. The second reason is that the maximum likelihood estimates are discretized version of continuous sampling theory. The asymptotic depolarization μ/β was estimated very well by both methods, better than the parameters μ and β separately. The reason is that the membrane potential was almost permanently at the asymptotic level and in this situation the estimation of individual parameters is less precise (Lansky et al., 1988). The distinction on input and intrinsic parameters fails for more realistic leaky integrate-and-fire models (e.g., Lansky and Lanska, 1987; Richardson and Gerstner, 2005). There the membrane time constant becomes input dependent. The change is only formal at the level of description applied in this article.

Noise

The results suggest that our neuron was firing in the noise activated regimen, in other words, that in the absence of the noise it would remain silent. This corresponds very well to the fact that the driving signal is small and the neuron fires only due to the stochastic fluctuation of the membrane depolarization. Theoretical prediction of the Poissonian firing in the subthreshold regime of the Ornstein-Uhlenbeck neuronal model is well known for a long time (Nobile et al., 1985) and here the prediction and data estimation fits perfectly together. The values of the estimated noise amplitude (Fig. 10(b)) seems to be quite small, but this is only an illusion as what has to be considered comes out of Eq. (6), and it is the asymptotic standard deviation of the depolarization, $\sigma\sqrt{2\beta}$.

Conclusions

We estimated the parameters of the Ornstein-Uhlenbeck neuronal model in spontaneous neuronal activity. The achieved results are consistent with the conclusions which can be obtained from the statistical analysis of the ISIs. The neuron fires in subthreshold regimen and thus the activity is Poissonian. The advantage of the applied method is that it permits to judge quantitatively the input to the neuron within a single ISI. This property will appear more important in presence of stimulation and comparison of neuronal activity under different conditions.

Acknowledgments The authors thank to P.W.F. Poon for initiating and permanent support for this work and to P.E. Greenwood for stimulating discussions. This work was supported by Academy of Sciences of the Czech Republic Grant (Information Society, 1ET400110401), AV0Z50110509, Center for Neurosciences LC554.

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