



Effect of stimulation on the input parameters of stochastic leaky integrate-and-fire neuronal model

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ABSTRACT

The Ornstein–Uhlenbeck neuronal model is specified by two types of parameters. One type corresponds to the properties of the neuronal membrane, whereas the second type (local average rate of the membrane depolarization and its variability) corresponds to the input of the neuron. In this article, we estimate the parameters of the second type from an intracellular record during neuronal firing caused by stimulation (audio signal). We compare the obtained estimates with those from the spontaneous part of the record. As predicted from the model construction, the values of the input parameters are larger for the periods when neuron is stimulated than for the spontaneous ones. Finally, the firing regimen of the model is checked. It is confirmed that the neuron is in the suprathreshold regimen during the stimulation.

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1. Introduction

Spiking activity is the basic mode of the information transfer within the nervous system. The sequences of spikes (action potentials) are generated and sent along an axon to other neurons. These action potentials are considered to be none-or-all events with shapes irrelevant for the information they convey. Formally, they are taken in the limit as Dirac delta function and the complete sequence of them as a realization of a stochastic point process. The application of the theory of stochastic point processes in description of spike trains is very common and the phenomenological models of single neurons predicting properties of these point processes are often investigated (Tuckwell, 1988; Gerstner and Kistler, 2002; Dayan and Abbott, 2001). The models are build to generate interspike intervals (ISIs) and they are often based on the first-passage-time principle for so called integrate-and-fire models which mimic accumulation of the incoming signal and the final generation of the spike is replaced by instantaneous reset of the generator to the initial level (Brunel and van Rossum, 2007).

Attempts to compare the experimental data with the models is very common for so called biophysical models of neurons, but considering the phenomenological models, they are more frequently compared qualitatively, and the researchers are satisfied if they perform in a similar way to the real neurons. Burkitt (2006) reviewed the integrate-and-fire neuron models and mathematical

techniques to analyze them. We can see from this review that with exception of a few theoretical attempts, the comparison of the models with data has been rather neglected. Only recently the phenomenological models are confronted with experimental data, for a review see Lansky and Ditlevsen (2008).

Stochastic diffusion integrate-and-fire neuronal model (the Ornstein–Uhlenbeck process) describes the membrane potential as a continuous-time stochastic process. Along the introduction of this model there have been given many arguments why this treatment of the integrate-and-fire model is appropriate. Leakage of the neuronal membrane, it means the current which flows through the membrane due to its passive properties, was one of the first specification of the integrate-and-fire neuron model. It is a crucial property of the integrate-and-fire models and thus it is inherent for practically all the variants of the model. Generalizations were recently introduced aiming to improve flexibility of the model and its predictive power (Clopath et al., 2007; Jolivet et al., 2006).

The model investigated in this paper has parameters of two types. The first are the parameters which can be measured by indirect electrophysiological methods, deduced from the properties of other neurons or from measuring the membrane potential fluctuations. If these parameters are known, one can check how well the model predicts spiking activity under the condition of an input identical with the input to a real neuron. The second set of parameters, investigated in this paper, is identified with the signals impinging upon the neuron. Knowledge of these parameters can be used either to deduce unknown signal coming to a neuron or to check whether we are able to read correctly an artificially delivered signal.

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To estimate the input signal either the membrane depolarization or ISIs have to be at our disposal. As mentioned, the previous attempts to identify the model parameters were based on observation of ISIs. Such a task is complicated and leads to rather difficult numerical and mathematical problems (Inoue et al., 1995; Shinomoto et al., 1999; Ditlevsen and Lansky, 2005, 2006, 2007; Koyama and Kass, 2008; Muldowney and Iyengar, 2008). In the study Lansky et al. (2006) estimation of five basic parameters the Ornstein–Uhlenbeck model was studied for the membrane depolarization data. The whole estimation procedure was based on the spontaneous-firing part of the intracellular recording. The primary aim of this study is to extend the results on the stimulation part of the recorded signal.

2. Model and its properties

The deterministic leaky integrate-and-fire model (Lapicque model, RC-circuit) can be derived from the assumptions that the membrane depolarization is 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 voltage in the model reflects an abstract representation of a complete neuron; usually described as depolarization at the trigger zone. The trigger zone serves as a reference point and all the other properties of the neuron are integrated into it.

The Ornstein–Uhlenbeck model of membrane depolarization is a stochastic variant of the RC-circuit model and can be formally described by a stochastic differential equation,

$$\frac{dX(t)}{dt} = -\beta(X(t) - x_0) + \mu + \sigma\zeta(t), \quad X(0) = x_0, \quad (1)$$

where β reflects the spontaneous decay of the membrane depolarization to the resting level x_0 , μ represents the local average rate of displacement due to the neuronal input, σ reflects the variability of the membrane potential due to the neuronal input and $\zeta(t)$ stands for Gaussian white noise. The spikes are not an intrinsic part of model (1) but are generated when the membrane depolarization $X(t)$ reaches the firing threshold S for the first time. So, S is an additional parameter. After firing, the depolarization is reset to the resting level, x_0 , and the process of input “integration” starts anew. Also the reset level, x_0 , represents a parameter of the model. The model is fully described by five parameters: β , μ , σ , S and x_0 , which specify Eq. (1) together with its initial and boundary condition. More details on the Ornstein–Uhlenbeck neuronal model can be found, for example, in Tuckwell (1988) or Burkitt (2006). The parameters introduced above can be divided in two categories:

- Parameters depending on the membrane properties – β being the inverse of the membrane time constant, threshold S and resting level x_0 .
- Parameters depending on the input signal – μ representing the mean signal and σ characterizing its variability. In this study we identify these parameters. As we focus on the changes in them brought by the stimulation, we are interested in comparing the values of these two parameters in spontaneous and stimulated parts of the data.

There can be posed serious questions whether β , S and x_0 are independent of the input. Actually, from the experimental data we directly found that, at least, x_0 changes in the presence of stimulation and we further take this fact into account.

The position of the asymptotic mean depolarization $E(X(\infty)) = x_0 + \mu/\beta$, as seen from Eq. (1) determines three basic regimes of firing of the Ornstein–Uhlenbeck model:

- The subthreshold regimen ($\mu/\beta \ll S - x_0$) with Poissonian firing. As the asymptotic mean depolarization does not reach the threshold the firing depends on the noise and without it the neuron would remain silent. It was shown in our previous article Lansky et al. (2006) that the spontaneous part of the recorded data fits mostly with subthreshold regimen characterization.
- The threshold regimen ($\mu/\beta \approx S - x_0$), where the distribution of ISIs is positively skewed and resembles for example Gamma distribution.
- The suprathreshold regimen ($\mu/\beta \gg S - x_0$), where the firing is almost regular and ISI histogram resembles normal distribution. The noise plays a limited role in this range of parameters.

As already mentioned in Section 1 two basic types of data can be used for the identification of the parameters of the Ornstein–Uhlenbeck model. If only the ISIs are available, the methods applicable in this situation are reviewed in Lansky and Ditlevsen (2008). In the second situation, which is investigated here, the membrane depolarization is recorded in between the spike generation. Some methods for estimation of the parameters under this sampling were compared for this type of data in Lansky et al. (2006) and now we apply only the selected ones.

3. Methods

3.1. Data collection

3.1.1. Animal preparation and data preprocessing

Guinea pigs served as subjects for the intracellular recording experiments. Throughout the recording, an electrocorticograph was monitored to assess the level 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., 2006; Yu et al., 2004). The experimental procedures were approved by the Animal Subjects Ethics Sub-Committee of The Hong Kong Polytechnic University. 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). Single neuron data were selected for this article. The membrane potential was recorded with time step $h = 0.00015 \text{ s} = 0.15 \text{ ms}$, for period 0–501 s. For further processing we make basic noise-filtering of the membrane potential by a moving average over six values, see Lansky et al. (2006) for details. The acoustic signal used for the stimulation of neuron has duration of 0.1 s and the series of the acoustic signals divided the record into the sections of stimulated and spontaneous parts. We compare the stimulated parts of the record with the unstimulated ones.

3.1.2. Detection of spikes

We detected and selected 86 stimulated parts in the record, which were used for the analysis. An example of a data can be seen in Fig. 1.

A typical neuronal response varies between two and three spikes during the stimulation. In the spontaneous part, the spikes appear rarely. As can be seen in Fig. 2 there is a substantial change of depolarization course after the second spike within the period of stimulation.

Because of this fact we need to distinguish between the first and the following ISIs within one stimulation. For this purpose we divide the periods of stimulation according to the number of ISIs in them. We got three periods of stimulation without any complete ISI, 68 periods of stimulation containing just one ISI, 14 periods of stimulation containing two ISIs and one period of stimulation

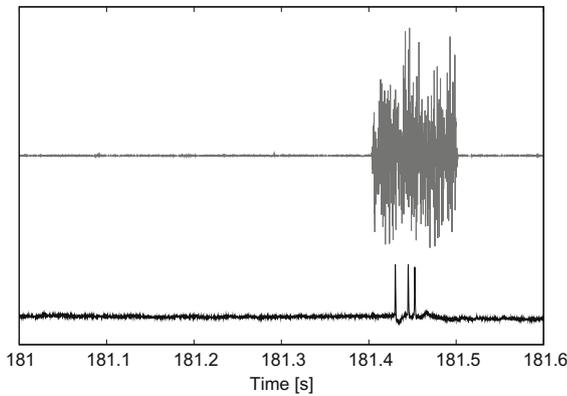


Fig. 1. Example of the acoustic signal (shaded curve) and the membrane depolarization (black curve). There are no spikes in the absence of stimulation and three spikes during the stimulation.

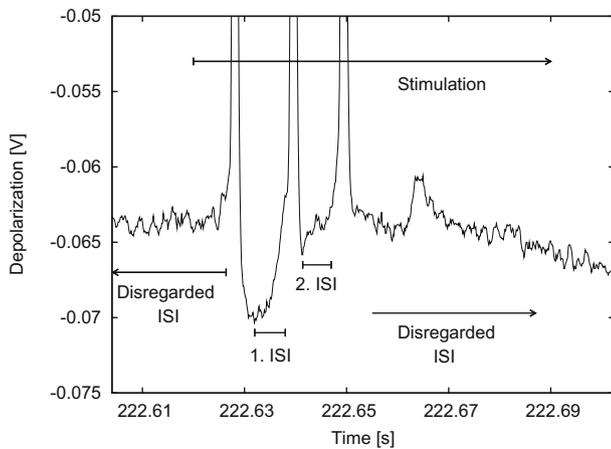


Fig. 2. An example of membrane depolarization course during the period of stimulation containing two ISIs.

containing three ISIs. It is obvious from this distribution, that for statistical evaluation only the first ISIs ($68 + 14 + 1$) can be used (the second and the third ISIs are too rare).

In the spontaneous part we got 312 complete ISIs and because the spike frequency in this part was substantially lower the shapes of membrane depolarization were similar and there was no need to distinguish serial number of ISIs in spontaneous part. Note that the comparison between stimulated and spontaneous records is based on ISIs which are completely within these specific periods and thus the ISIs which are partly in both periods are disregarded (see Fig. 2).

3.2. Precise detection of ISI

The membrane potential trajectories between spikes take a shape of valleys in the stimulated parts of the record (see Fig. 2). Firstly, we formulate a heuristic procedure how to detect these valleys in the record. As the estimation of the parameters is based on the membrane potential trajectory which is entirely outside the spikes, we have to determine carefully from what time and up to which time we consider the data. Then, these two time instances implicitly define the corresponding ISI.

For the detection of spike we fix the voltage level at -35.5 mV as in the previous study (Lansky et al., 2006). For the beginning of the valley we pose the *valley-detection* level at -50 mV. For the detection of the end of the valley we look for the maximum

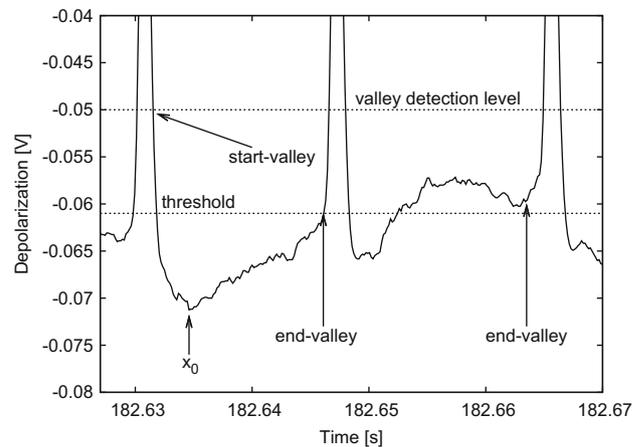


Fig. 3. ISI detection. We can see three spikes defining two ISIs within period of stimulation. The values of the membrane potential from x_0 to the end of the valley are used for the parameters estimation. See text for details.

of the last point with decreasing depolarization before the next spike or the last point when the threshold S is crossed before next spike. Both cases can be seen in Fig. 3.

Threshold S itself is not searched for in periods of stimulation, as the heuristic method used in the spontaneous part failed. Here the depolarization often goes from the valley after spike straightly (almost linearly) towards next spike without crossing any specific point, which can be clearly marked as the threshold (see Fig. 2). Model (1) considers the threshold as the membrane property and thus we take its value $S = -61$ mV as derived from the spontaneous part of the data (Lansky et al., 2006). In the same way, for the inverse of the membrane time constant we fix $\beta = 25.8$ 1/s as it was estimated from the spontaneous activity.

After detecting the valley we can detect the corresponding ISI. We identify reset potential x_0 as the minimal voltage value in the valley and it is the only intrinsic parameter determined in this paper, see Section 4.2.3. The ISI is defined as interval between the time when $X(t) = x_0$ and the end of the valley. The period from the spike to the beginning of ISI can be identified as the refractory period. For a recent review of methods for determination of refractory period from ISI data, see Hampel and Lansky (2008). Here we do not investigate this problem, but we complement the picture by giving the values derived from the depolarization but not the ISIs, see Section 4.2.4. We should note that the current procedure applied to the data is slightly different from that used in our previous paper. In this study the valley has to be defined in a more complex way as the lengths of ISIs are very short and the shapes of membrane potential are much more variable (see details in Fig. 3).

3.3. Parameters estimation

There are two parameters of model (1) driven by the incoming signal to the neuron – μ and σ . In Lansky et al. (2006), the regression method appeared to be more appropriate than the likelihood method for estimating the parameter μ . To apply the regression method we minimize the functional

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

with respect to the parameter μ , where h stands for time step and x_j are individual measured values of membrane depolarization for the total time $T = Nh$. What is minimized in Eq. (2) is the distance between observed values of the membrane potential and the mean depolarization in the absence of the threshold. There are two draw-

backs of the method. At first, it is the fact, that the predicted values are those expected in the absence of the threshold. We investigated this fact deeply in Bibbona et al. (2008) and the effect on the estimation is not substantial. At second, the observed values of the membrane depolarization are not independent realizations of random variables and it restricts the conclusions made on the basis of the regression. Nevertheless, in our experience, the method is an acceptable compromise between the tractability and efficiency.

For estimation of the noise amplitude we use the formula obtained by the maximum likelihood method

$$\widehat{\sigma}^2 = \frac{1}{T} \sum_{j=0}^{N-1} (x_{j+1} - x_j + x_j h \beta - h \hat{\mu})^2, \quad (3)$$

and also the formula established by Feigin (1976), which is independent of the other parameters estimation:

$$\widehat{\sigma}^2 = \frac{1}{T} \sum_{j=0}^{N-1} (x_{j+1} - x_j)^2. \quad (4)$$

In this way for each ISI a pair of estimated $\hat{\mu}_i, \hat{\sigma}_i$ is computed.

4. Results and discussion

We investigate the effect of stimulation in two directions. At first, we compare simulations of model (1) based on the estimated parameters with the experimental record. Secondly, we compare the stimulated ISIs and their respective μ, σ parameters to ISIs and the parameters from the spontaneous part of the record.

4.1. Model and data comparison

As already stated, we have 83 ISIs which are the first ones and completely contained in the stimulation periods. For i -th ISI ($i = 1, \dots, 83$) we have a vector of values of depolarization $\mathbf{x}_i = (x_{i0}, x_{i1}, \dots, x_{in})$, where n depends on the length of the ISI. Corresponding vector of mean depolarization, $\mathbf{y}_i = (y_{i0}, y_{i1}, \dots, y_{in})$ was obtained from simulating Eq. (1) using the estimated parameter $\hat{\mu}_i$ and $\sigma_i = 0$. The differences $\mathbf{z}_i = \mathbf{x}_i - \mathbf{y}_i$ were calculated and their average and standard deviation evaluated. The results are shown in Fig. 4. We can see that model based on the estimated parameters does not show any systematic error in the course of membrane depolarization.

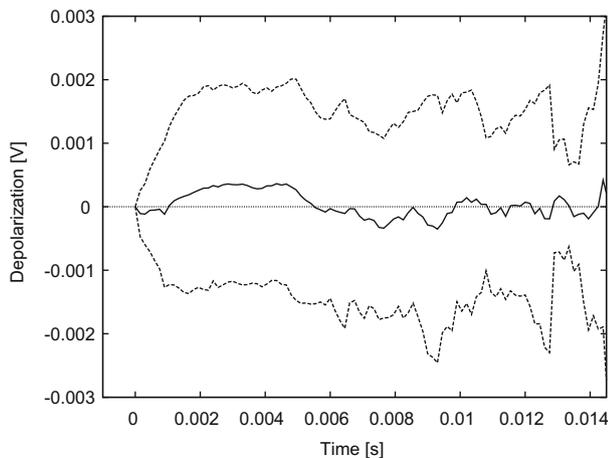


Fig. 4. Comparison of experimental data with the model. The central solid curve is an average of the differences z_i , dotted curves indicate ± 2 * standard deviations. See text for details.

4.2. Comparison of the parameters

4.2.1. Parameter μ

It can be clearly seen in Fig. 5 that the estimates of μ have much broader distribution with median around 1.1 V/s in the stimulated part than in the spontaneous part, where the distribution is located around the value of 0.3 V/s. The fact that for stimulated part all the estimated values of μ are higher than in the spontaneous one corresponds with the interpretation of μ in the Ornstein–Uhlenbeck model. The lower variability of μ in the spontaneous regime corresponds to the fact that their values are lower, see Table 1, but the relative variability, as reflected by CV, is higher for the spontaneous data.

4.2.2. Parameter σ

In Fig. 6 we can see that the situation for σ is analogous to the case of μ . The estimate of the variance σ has broader distribution with median around $0.026 \text{ V}/\sqrt{s}$ in the stimulated parts than in the spontaneous parts, where σ has more narrow range with significantly higher peak around the value of $0.013 \text{ V}/\sqrt{s}$. The results are also documented in Table 2, where we can realize that Eq. (3) gives slightly lower values of estimates than Eq. (4).

In correspondence with Lansky and Sacerdote (2001) there is higher σ for the stimulated ISIs. This is the first experimental confirmation of our results originally achieved on entirely theoretical basis. To get a better picture of the relationship between μ and σ different levels of the stimulation would be necessary.

4.2.3. Reset potential x_0

It is apparent from the data and illustrated in Fig. 2 that the reset value is influenced by the stimulation. This can be interpreted in such a way, that the accumulation of the incoming signal takes place during the reset of the membrane potential, resp., during the refractory period. Obviously, for the second ISI within one stimulation period, there are additional reasons why x_0 changes. Thus the

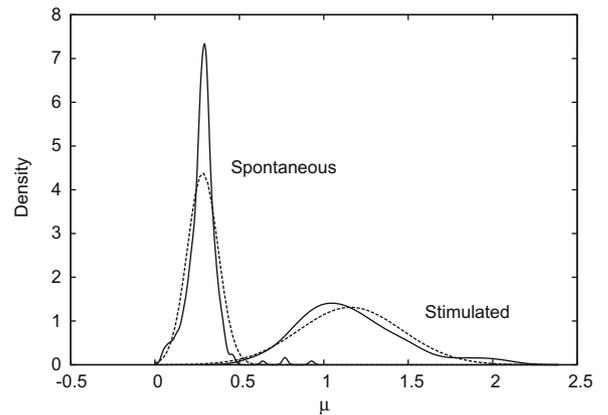


Fig. 5. Distribution of the estimates of the parameter μ : left curves – spontaneous, right curves – stimulated. Dotted lines are fitted normal distributions $f(\mu) = \frac{1}{s\sqrt{2\pi}} e^{-\frac{(\mu-m)^2}{2s^2}}$, $m_{stim} = 1.158$, $s_{stim} = 0.304$ and $m_{spont} = 0.283$, $s_{spont} = 0.091$.

Table 1
Descriptive statistics for the estimates of parameter μ .

$\hat{\mu}$ [V/s]	Stimulated	Spontaneous
Min	0.6046	0.04665
Max	2.0840	0.92737
Median	1.1061	0.28460
Mean	1.1580	0.28324
CV	0.2645	0.32156

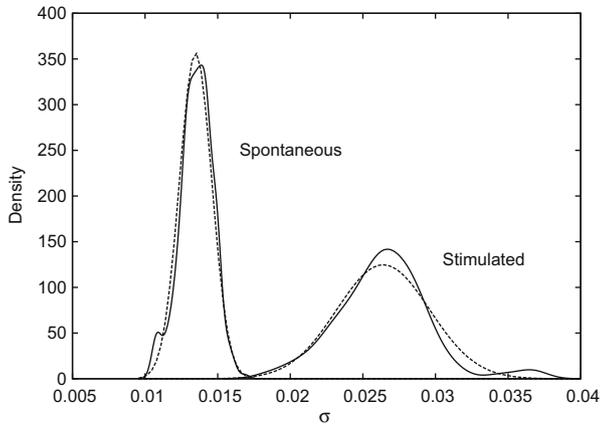


Fig. 6. Distribution of the estimates of the parameter σ : left curves – spontaneous, right curves – stimulated. Dotted lines are fitted normal distributions $f(\mu) = \frac{1}{\sigma\sqrt{2\pi}} e^{-\frac{(\mu-\mu)^2}{2\sigma^2}}$, $m_{stim} = 0.0264$, $s_{stim} = 0.0032$ and $m_{spont} = 0.0135$, $s_{spont} = 0.0012$.

Table 2
Descriptive statistics for the estimates of parameter σ .

$\hat{\sigma}$ [V/ \sqrt{s}]	Stimulated	Spontaneous	Stimulated ($\hat{\sigma}$ from Eq. (3))
Min	0.01843	0.01043	0.01576
Max	0.03686	0.01681	0.03166
Median	0.02646	0.01351	0.02262
Mean	0.02640	0.01348	0.02215
CV	0.12218	0.08310	0.12566

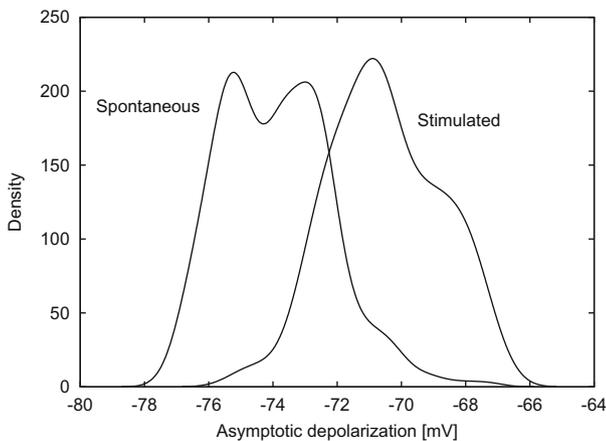


Fig. 7. Distribution of the reset potential x_0 : left curve – spontaneous, right curve – stimulated.

last parameter which we determine is x_0 . We can see in Fig. 7 that the shapes of the densities of the estimates do not differ and the range remains around 10 mV for both cases. The median value is lower in the case of spontaneous record. As mentioned, this can be explained by the fact, that the input signal contributes to the membrane potential during the refractory period. See Table 3 for the descriptive statistics of x_0 .

4.2.4. Time to reach the resting potential

We also measure how much time it takes for the membrane potential to reach the resting level after the spike. It is not a parameter of model (1), but such knowledge could help to judge how realistic the model is. In particular we take the interval which

Table 3
Descriptive statistics for parameter x_0 .

\hat{x}_0 [mV]	Stimulated	Spontaneous
Min	-74.92	-77.25
Max	-67.08	-67.33
Median	-70.58	-73.92
Mean	-70.52	-73.90
CV	-0.024	-0.023

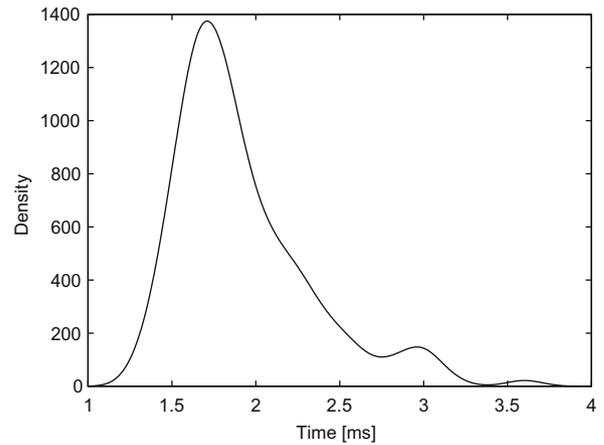


Fig. 8. Distribution of the time from the peak of the spike to the resting potential, 169 (=3 + 2 * 68 + 2 * 14 + 2 * 1 – two first spikes taken, if possible) spikes were regarded.

Table 4
Descriptive statistics for the time to reach the resting potential.

Time to reach the resting potential [ms]	
Min	1.35
Max	3.6
Median	1.8
Mean	1.9
CV	0.21

starts on the top of the spike and calculate the time till the first local minimum in the membrane depolarization after the spike. This procedure has the advantage that we can take both the first and the second spikes in stimulated region for statistical evaluation – as it follows from the previous section, it is not generally possible to define x_0 after the second spike. The density estimation of the time till x_0 is reached is in Fig. 8 and summary statistics in Table 4.

These results practically coincide with the estimation of the refractory period based on ISIs only, which was estimated around 3 ms (Hampel and Lansky, 2008), taking into account that the refractory period should be longer than the time to the minimum depolarization.

4.2.5. Firing regimen

As mentioned in Section 2, the key issue for the behavior of model (1) is the mutual position between $S - x_0$ and μ/β . To check the threshold regime we compute $S - x_0$ and μ/β , where for μ we take the vector of estimated values, S , β are medians of the estimates taken from the spontaneous part of the data and x_0 from the corresponding part (spontaneous or stimulated). In Fig. 9 we see that asymptotic mean depolarization is always higher (median is 43 mV) than threshold value in the case of stimulated data, which is in a good agreement with our expectation.

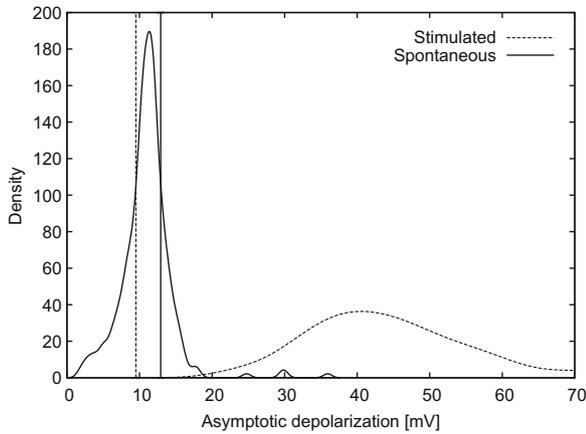


Fig. 9. Estimations of the densities of the asymptotic depolarization with regard to the threshold: left curve – spontaneous, right curve – stimulated. The values (vertical lines) of $S - x_0 = 13$ mV for the spontaneous case and 9.5 mV for stimulated case divides the supra and subthreshold regimen.

4.3. ISI distribution

Using the methods described above we got 83 first ISIs completely within the stimulated parts and 312 ISIs in the spontaneous parts. In Fig. 10 we compare their distributions. The empirical den-

Table 5
Descriptive statistics for ISIs.

ISIs [ms]	Stimulated	Spontaneous
Min	3.900	88.5
Max	24.750	5090.4
Median	8.400	584.6
Mean	9.033	871.9
CV	0.345	0.883

sity of the spontaneous ISIs suggests that they are generated in accordance with the exponential distribution (Kolmogorov–Smirnov test does not reject the hypothesis of exponentiality at 5% significance level), which may imply the Poissonian firing regime. The shape of the density for the stimulated ISIs suggests gamma distribution (Kolmogorov–Smirnov test does not reject the hypothesis of gamma distribution at 5% a significance level).

The descriptive statistics of the ISIs are in Table 5. We can see that there is a clear distinction between the spike frequency for stimulated part $f_{stim} = 110$ Hz and for spontaneous part $f_{spon} = 1.14$ Hz, for median the values are $f_{stim} = 119$ Hz, $f_{spon} = 1.71$ Hz.

4.3.1. Comparison of experimental and theoretical distribution

To compare experimental ISI distributions with the Ornstein–Uhlenbeck first-passage-time distribution, we simulated model (1) with estimated parameters. The results are in Fig. 11.

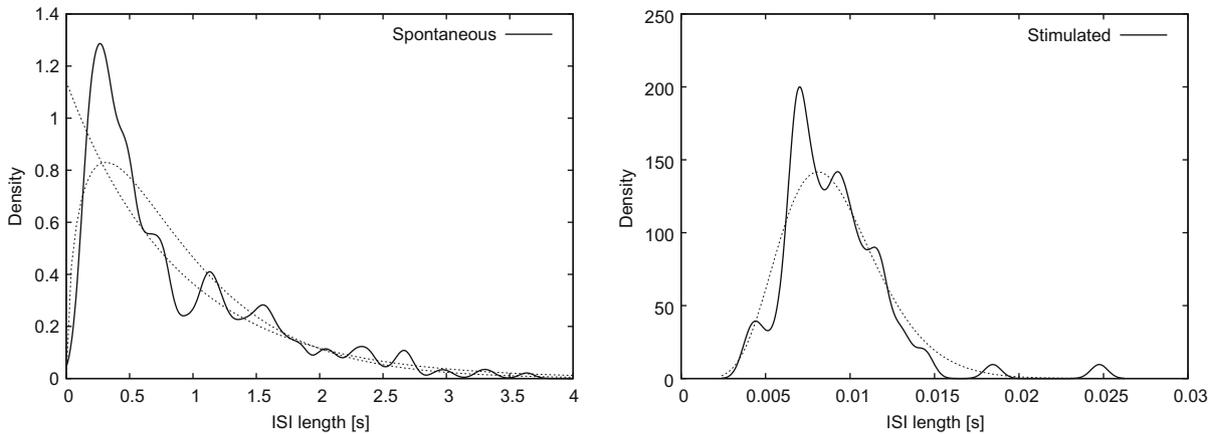


Fig. 10. Distributions of ISIs lengths: the left panel – spontaneous ISIs, the dotted line represents the fitted exponential ($f(x) = \lambda e^{-\lambda x}$, $\lambda = 1.14$) and gamma ($f(x) = x^{\alpha-1} \frac{\beta^\alpha e^{-\beta x}}{\Gamma(\alpha)}$, $\alpha = 1.56$, $\beta = 1.79$) distribution; the right panel – stimulated ISIs, the dotted line represents the fitted gamma distribution ($\alpha = 9.45$, $\beta = 1043.3$).

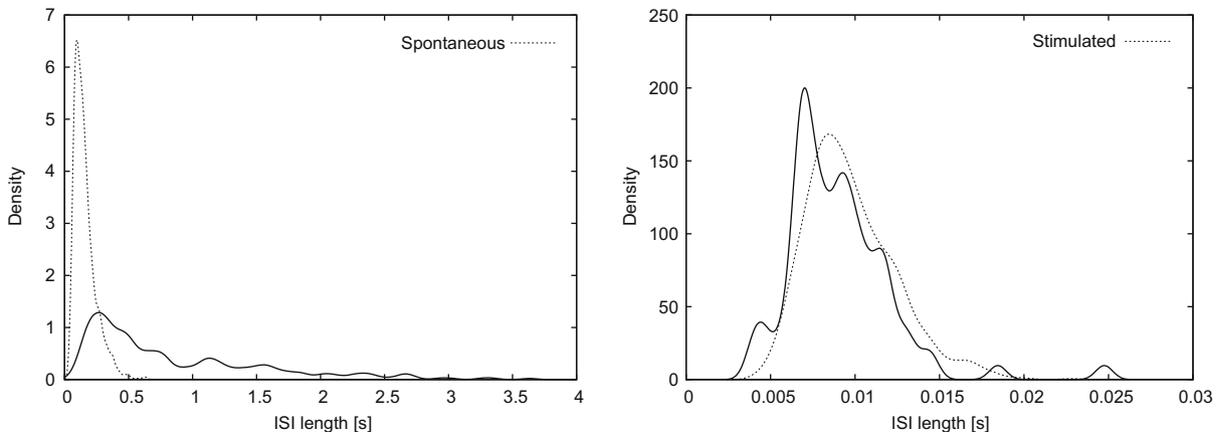


Fig. 11. Distributions of the first-passage-times obtained from Eq. (1) with parameters estimated from the trajectories: the left panel – spontaneous, the right panel – stimulated. The solid lines are estimated densities of experimentally obtained ISIs (histograms), the dotted lines are estimated densities from the simulation of first-passage-times of model (10^3 runs).

The fit of the observed ISIs to the model is perfect for the stimulated activity. It is not the case for the spontaneous activity, where from the model we obtained distribution which is more narrow and shifted in direction of short ISIs. At this moment we are not able to explain this discrepancy.

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