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Published in:
Neural Computation

DOI:
10.1162/neco.2008.11-07-653

2008

Link to publication

Citation for published version (APA):
Picchini, U., Ditlevsen, S., De Gaetano, A., & Lansky, P. (2008). Parameters of the diffusion leaky integrate-and-fire neuronal model for a slowly fluctuating signal. *Neural Computation*, *20*(11), 2696-2714. https://doi.org/10.1162/neco.2008.11-07-653

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4

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Parameters of the diffusion leaky integrate-and-fire neuronal model for a slowly fluctuating signal

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The final version of this article has been published in *Neural Computation* 20(11) 2696-2714, 2008, published by The MIT Press, `http://mitpress.mit.edu/NECO`.

Abstract

The stochastic leaky integrate-and-fire (LIF) neuronal models are common theoretical tools for studying properties of real neuronal systems. Experimental data of frequently sampled membrane potential measurements between spikes show that the assumption of constant parameter values is not realistic, and that some (random) fluctuations are occurring. In this paper we extend the stochastic LIF model allowing for a noise source determining slow fluctuations in the signal. This is achieved by adding a random variable to one of the parameters characterizing the neuronal input, considering each ISI as an independent experimental unit with a different realization of this random variable. In this way, the variation of the neuronal input is split into fast (within-interval) and slow (between intervals) components. A parameter estimation method is proposed, allowing the parameters to be estimated simultaneously over the entire data set. This increases the statistical power and the average estimate over all ISIs will be improved in the sense of decreased variance of the estimator compared to previous approaches, where the estimation has been conducted separately on each individual ISI. The results obtained on real data show a good agreement with classical regression methods.

Keywords: stochastic differential equations, mixed-effects, random parameters, maximum likelihood estimation, interspike interval, spontaneous firing.

1 Introduction

The stochastic leaky integrate-and-fire (LIF) neuronal models are common theoretical tools for studying properties of real neuronal systems. They represent a compromise between similarity to real neurons and mathematical tractability (see e.g. Ricciardi (1977); Tuckwell (1988); Dayan and Abbott (2001); Gerstner and Kistler (2002); Burkitt (2006)). In these models, a neuron is characterized by a single stochastic differential equation describing the evolution of neuronal membrane potential over time. Firing is not an intrinsic property of the LIF models, and a firing threshold has to be imposed. An action potential (spike) is produced when the membrane voltage reaches the voltage threshold and corresponds to the first-passage time for the associated stochastic process describing the voltage. In the moment of spike generation, the voltage is instantaneously reset to the resting membrane potential.

Studies devoted to the comparison of the stochastic leaky integrate-and-fire neuronal models with experimental data are rare. The data are typically either intracellular measurements of the membrane potential, or extracellular measurements of the spike times. Obviously there is more information contained in the intracellular recordings of the otherwise hidden membrane potential. One line of research attempts to estimate intrinsic parameters characterizing the neuron assuming the neuronal input known. This is useful for predicting spiking activity with different kinds of input, as well as to do comparisons of prediction and real output, when the same input is applied to a model neuron and a real neuron. Some references in this line using frequently sampled membrane potential measurements between spikes are Rauch et al. (2003); Jolivet et al. (2004, 2006); La Camera et al. (2004); Paninski et al. (2005); Huys et al. (2006); Clopath et al. (2007) and references using first-passage time data are Paninski et al. (2004, 2005). Another line of research attempts to identify the signal impinging upon the neuron, assuming the intrinsic neuronal parameters known. This is equally an important task, where the goal is to reconstruct the signal to the neuron from the neuronal output. Some references using frequently sampled membrane potential measurements between spikes are Lansky (1983); Lanska and Lansky (1998); Lansky et al. (2006); Höpfner (2007) and references using first-passage time data are Inoue et al. (1995); Shinomoto et al. (1999); Ditlevsen and Lansky (2005, 2006, 2007); Ditlevsen and Ditlevsen (2007). In these last studies, two parameters of the model characterizing the neuronal input were estimated or methods for this purpose were proposed. All parameters were assumed fixed for the whole period of an experiment, without any internal fluctuations.

From the point of view of potential applications, it is of interest to be able to characterize

the signalling environment to which the recorded neuron is exposed. The main feature of this environment is the intensity of stimulation, which may well be variable over the course of the experiment. Indeed, the degree of this background signal variability could be the main piece of information to be extracted from available data. In fact, experimental data of frequently sampled membrane potential measurements between spikes show that the assumption of constant parameter values is not realistic (Lansky et al. (2006)), and that some (possibly random) fluctuations are occurring. It is difficult to evaluate the time scale of such fluctuations, and in this paper we have made a somehow arbitrary choice of the time scale of the ISIs as a start to explore this variability. This choice is supported by the study in Lansky et al. (2006) where it is apparent that there is variation from one interspike interval to the next. An argument for this choice could be that the spike itself has some feedback on the neuron under study.

One way to approach between-interval variability has been to estimate parameters individually on each interspike interval and then interpret the results through some summary statistics, e.g. the median and the range of estimates. In this paper, we will take a different approach and extend the stochastic LIF model allowing for a second noise source determining slow fluctuations in the signal. In this way, the variation of the neuronal input is split into fast (within-interval) and slow (between intervals) components. This is achieved by adding a zero mean random variable to one of the parameters characterizing the neuronal input, considering each interspike interval (ISI) as an independent experimental unit with a different realization of this random variable. This is also termed a *random effect* and allows part of the neuronal input to be characterized by a distribution of two parameters (instead of one parameter for each single ISI), which are estimated simultaneously over the entire data set. This increases the statistical power and the average estimate over all ISIs will be improved in the sense of decreased variance of the estimator compared to previous approaches, where the estimation has been conducted separately on each individual ISI (see e.g. Diggle et al. (2002); McCulloch and Searle (2001); Pinheiro and Bates (2000)).

2 Model and parameter estimation

2.1 The Model

The changes in the membrane potential between two consecutive neuronal firings are represented by a stochastic process X_t indexed by the time t. The reference level for the membrane potential is taken to be the resting potential. The initial voltage (the reset value following a spike) is assumed to be equal to the resting potential. An action potential is produced when the membrane voltage X_t exceeds a voltage threshold S for the first time. It follows from the model assumptions that for time-homogeneous input containing either a Poissonian or white noise only, the membrane potentials during different interspike intervals are independent and

the initial time following a spike can always be identified with zero.

A scalar diffusion process $X = \{X_t;\, t \geq 0\}$ can be described by the stochastic differential equation

$$\mathrm{d}X_t \;=\; \mu(X_t, t)\,\mathrm{d}t + \sigma(X_t, t)\,\mathrm{d}W_t, \qquad X_0 = x_0 \tag{1}$$

where $W = \{W_t;\, t \geq 0\}$ is a standard Wiener process and $\mu(\cdot)$ and $\sigma(\cdot)$ are real-valued functions of their arguments. The function $\mu(\cdot)$ is usually called the "infinitesimal mean" and $\sigma^2(\cdot)$ the "infinitesimal variance". Traditionally, for the LIF model, the diffusion process given in equation 1 is specified by the infinitesimal mean

$$\mu(X_t, t) = -\frac{X_t}{\tau} + \mu, \tag{2}$$

where the constant μ [V/s] characterizes the neuronal input and $\tau > 0$ [s] reflects spontaneous voltage decay (the membrane time constant) in the absence of input. Moreover, the constant square root of the infinitesimal variance,

$$\sigma(X_t, t) = \sigma > 0 \tag{3}$$

also characterizes the neuronal input, see also Ditlevsen and Lansky (2005). The diffusion process in equation 1 with the infinitesimal moments given by equation 2 and 3 defines the Ornstein-Uhlenbeck (OU) diffusion process:

$$\mathrm{d}X_t \;=\; \left(-\frac{X_t}{\tau} + \mu\right)\mathrm{d}t + \sigma\,\mathrm{d}W_t \;\;;\;\; X_0 = x_0. \tag{4}$$

The parameters appearing in model 4, together with the threshold S, can be divided into two groups: parameters characterizing the input, μ and σ, and intrinsic parameters, τ, x_0 and S, which describe the neuron irrespectively of the incoming signal (Tuckwell and Richter (1978)).

Solving the Fokker-Planck equation for model 4 yields the transition density function

$$p_X(x, t|x_s, s) = (2\pi V)^{-\frac{1}{2}} \exp\left\{-\frac{(x-M)^2}{2V}\right\} \tag{5}$$

where

$$M \;=\; x_s\, e^{-(t-s)/\tau} + \mu\tau(1 - e^{-(t-s)/\tau}), \tag{6}$$

$$V \;=\; \frac{\sigma^2\tau}{2}(1 - e^{-2(t-s)/\tau}) \tag{7}$$

for $t > s$. Hence, at each time t the transition probability density function is normal with mean M and variance V (Ricciardi (1977)).

Since the intrinsic parameters describe inherent physiological characteristics of the neuron, they are usually expected to be constant in time, whereas the input parameters fluctuate, depending on incoming signals. However, experimental studies suggest that the effective membrane constant τ changes in dependence of the time elicited since the last spike (Powers and Binder (1996); Jolivet et al. (2004)). This refinement is ignored and the approximation of a constant τ is used throughout the paper. As we shall see later, this creates fitting problems in the maximum likelihood estimation, and a correction is proposed.

If it is reasonable to assume the neuron is operating in a stationary state during some time interval of interest, then the input parameters would be assumed constant during this period. We may however generalize, by assuming that additionally to the input characterized by the parameter μ there is a random component changing from one ISI to the next, which could be caused by the naturally occurring variations of environment signalling, by experimental irregularities or by other sources of noise, not included in the model. The main interest rests in the overall μ, whereas the specific values during each ISI are not of interest but for their distribution. Thus, neuronal input is assumed to consist of a constant component μ, representing average global input, and an ISI-specific random component B^i with realization b^i representing time-local input oscillations.

This extends model 4 to the following model of the membrane potential during the ith ISI,

$$dX_t^i = \left(-\frac{X_t^i}{\tau} + \mu + B^i\right) \mathrm{d}t + \sigma \, \mathrm{d}W_t^i, \qquad X_0^i = x_0^i, \tag{8}$$

$$B^i \sim \mathcal{N}(0, \sigma_\mu^2), \qquad i = 1, ..., M \tag{9}$$

where M is the total number of ISIs, $\mathcal{N}(0, \sigma_\mu^2)$ is the normal distribution with mean zero and variance σ_μ^2 and the W_t^i are standard Brownian motions. The distribution of B^i in this paper is assumed normal for simplicity, but other distributions could be considered. Note the different nature of the two noise intensity parameters, which also follows from different units of σ [V/$\sqrt{\text{s}}$] and σ_μ [V/s]. The W_t^i and B^j are assumed mutually independent for all $1 \leq i, j \leq M$. Thus, the neuronal input in the drift during the ith ISI ($\mu + B^i$) is a draw from the normal distribution with mean μ and variance σ_μ^2. Model 8–9 assumes that in each of the M ISIs the evolution of X follows a common functional form, and differences between ISIs are due to different realizations of the Brownian motion paths $\{W_t^i\}_{t \geq 0}$ and of the random parameters B^i.

The model is still a renewal process and ignores afterspike effects, like the $I_{hist}(t)$ in Paninski et al. (2004). The addition of a spike aftereffect describing the afterhyperpolarization and/or inclusion of a time-dependent time constant in equation (8) could surely make the model more realistic. However, such modifications would substantially complicate the statistical inference. As always, it is necessary to find a compromise between model tractability

and realism. In this paper a simpler model is used permitting a more transparent treatment. Our model corresponds to the stimulus current for which $I_{stim}(t) = \mu + B^i$ if t belongs to the ith ISI, see Paninski et al. (2004).

Suppose that the membrane potential is sampled during the ith ISI at $n_i + 1$ equidistant time points. Let x_j^i denote the observed membrane potential during the ith ISI at time $j\Delta$, $1 \leq i \leq M$, $0 \leq j \leq n_i$, where Δ is the constant time-interval between observations. Notice that while there is no conceptual difference in considering non-equidistant time points, this would make notation more cumbersome, and it is not relevant for our application. Using simultaneously all data $\{x_j^i\}_{j=0,\ldots,n_i}^{i=1,\ldots,M}$ the goal is to estimate $\theta = (\mu, \tau, \sigma, \sigma_\mu^2)$ by maximum likelihood, as explained in the following, see also Ditlevsen and De Gaetano (2005); Picchini et al. (2006).

2.2 Parameter Estimation

It follows from equations 6 and 7 that the conditional mean and variance of X_t^i are

$$\begin{aligned} \mathbb{E}(X_t^i | B^i = b^i) &= x_0^i e^{-t/\tau} + (\mu + b^i)\tau(1 - e^{-t/\tau}) \\ \mathrm{Var}(X_t^i | B^i = b^i) &= \frac{\sigma^2 \tau}{2}(1 - e^{-2t/\tau}) \end{aligned}$$

and from equation 5 it follows that the transition density is normal and given by

$$\begin{aligned} p_X(x_j^i, \Delta | x_{j-1}^i, b^i) &= \left(\pi\sigma^2\tau\big(1 - e^{(-2\Delta/\tau)}\big)\right)^{-1/2} \\ &\times \exp\left(-\frac{\big(x_j^i - x_{j-1}^i e^{-\Delta/\tau} - (\mu + b^i)\tau(1 - e^{-\Delta/\tau})\big)^2}{\sigma^2\tau(1 - e^{-2\Delta/\tau})}\right). \end{aligned}$$

Integrating this conditional density with respect to the marginal density of the random effects yields the likelihood function of $\theta = (\mu, \tau, \sigma, \sigma_\mu^2)$

$$L(\theta) = \prod_{i=1}^{M} \int_{-\infty}^{+\infty} \left(\prod_{j=1}^{n_i} p_X(x_j^i, \Delta | x_{j-1}^i, b^i)\right) \varphi(b^i)\, db^i \tag{10}$$

where φ is the probability density function of B^i, here assumed to be Gaussian for every i. In equation 10 we have used that X_t^i given B^i is Markov, and that W_t^i and B^i are assumed

independent. Since $B^i \sim \mathcal{N}(0, \sigma_\mu^2)$, the likelihood function in equation 10 can be written as

$$\begin{aligned} L(\theta) &= (2\pi\sigma_\mu^2)^{-M/2}\Big(\pi\sigma^2\tau(1-e^{-2\Delta/\tau})\Big)^{-\sum_{i=1}^M n_i/2} \\ &\times \prod_{i=1}^M \int_{-\infty}^{+\infty} \exp\Big\{-\sum_{j=1}^{n_i}\Big[\frac{\big(x_j^i - x_{j-1}^i e^{-\Delta/\tau} - (\mu+b^i)\tau(1-e^{-\Delta/\tau})\big)^2}{\sigma^2\tau(1-e^{-2\Delta/\tau})}\Big] - \frac{(b^i)^2}{2\sigma_\mu^2}\Big\} db^i. \quad (11) \end{aligned}$$

The estimator is obtained by maximizing the likelihood over the parameters, or equivalently, minimizing $-\log L(\theta)$. The asymptotic variance of the estimator is provided by solving numerically the Hessian of the log-likelihood at the optimum and inverting it. If it is of interest to estimate the random parameters b^i separately for each ISI this can be done in the standard way from *mixed-effects* theory by

$$\hat{b}^i = \arg\min_{b^i}\Big\{-\sum_{j=1}^{n_i}\log p_X(x_j^i, \Delta | x_{j-1}^i, b^i)\Big\}, \qquad i = 1, ..., M \quad (12)$$

where the estimates of μ, τ and σ have been plugged in.

2.3 Numerical procedure for the estimation

We have no closed-form solution to the integral in equation 11. However, when an integral over the real line with respect to a variable x contains an $\exp(-x^2)$ multiplicative term, it can be approximated by the Gauss-Hermite quadrature (e.g. Fröberg (1985), Krommer and Ueberhuber (1998)). Here, a grid of R evaluation points was applied, i.e.

$$L(\theta) \simeq \tilde{L}(\theta) = \prod_{i=1}^M \Big(\sum_{r=1}^R \frac{\prod_{j=1}^{n_i} p_X(x_j^i, \Delta | x_{j-1}^i, \sqrt{2}\sigma_\mu z_r)}{\sqrt{\pi}} w_r\Big) \quad (13)$$

where z_r is the rth zero of the Hermite polynomial of degree R and w_r is a corresponding weight factor (the z_r's and the w_r's values are tabulated e.g. in Salzer et al. (1952) or Table 25.10 in Abramowitz and Stegun (1964), where values up to order $R = 20$ are provided). A set of $R = 40$ points has been applied in the Gauss-Hermite quadrature (also $R = 100$ was applied but the results were not appreciably different; notice that some authors consider $R = 20$ sufficient for a good degree of approximation (McCulloch and Searle, 2001, p. 272)). The resulting approximate maximum likelihood estimator of θ is given by $\tilde{\theta} = \arg\min_\theta(-\log\tilde{L}(\theta))$. Notice that, due to the large number of observations in each ISI (from few hundreds to tens of thousands), the product $\prod_{j=1}^{n_i} p_X$ in equation 13 might be difficult to evaluate numerically. This can be solved e.g. by normalizing the densities by a common constant or optimizing only a kernel of the likelihood, or by applying an arbitrary/variable precision package, e.g. we used the package by Barrowes (2007) for MATLAB.

3 Application

The experimental ISI data were measured intracellularly from the auditory system of a guinea pig (for details on data acquisition and processing see Yu et al. (2004)). These data were analyzed in Lansky et al. (2006) where model 4 was fitted individually to each ISI data series, applying methods already proposed in Lansky (1983).

The data consists of $M = 312$ ISIs, with membrane potential recorded every 0.15 ms, see Figure 1 for a histogram of the ISI lengths and Figures 4–5 for sample trajectories. The parameter estimates and 95% confidence intervals obtained using model 8-9 and the estimation method described in sections 2.2-2.3 are given in Table 1 where it is evident that the parameters are well identified. In other words, the statistical uncertainty on the estimated parameters is in all cases smaller than 5% of the estimated value. These conclusions are of course conditioned on the model. To evaluate if the random effect on μ is statistically significant, the hypothesis $H_0 : \sigma_\mu = 0$ was tested against $H_1 : \sigma_\mu > 0$ in a likelihood ratio test (see Appendix). H_0 was rejected with $p < 0.001$, and thus we conclude that model 8–9 describes the data better than model 4. This can also be seen from Figure 2, where the variability in the estimated random effects does not support a conclusion of all b^i's being zero. The random effects b^i were estimated using equation 12 and the sample mean and standard deviation of the 312 obtained estimates are given by -0.001 V/s and 0.0762 V/s, respectively, the former being close to zero and the latter close to the σ_μ estimate, as they should be, see Table 1. The histogram of the $\hat{b}^i$'s is given in Figure 2.

By inspecting Figure 2, ten outliers were identified, namely those $\hat{b}^i$'s smaller than -0.15 V/s. Each outlier corresponds to one of the black trajectories in Figure 3, the latter reporting all the observations from the 312 ISIs, grouped in the same time-frame. Notice how the ten black trajectories form a cluster with a lower asymptotic depolarization, as expected since they were chosen exactly to have low values of μ. The outliers were also located chronologically to see if they clustered in time, maybe indicating a temporary different state of the neuron. This was not the case, these ISIs were randomly appearing from time to time, and we have no biological explanation to this. In order to check the sensitivity of the results to those ten trajectories, we estimated the parameters again on the set of $M = 312 - 10 = 302$ ISIs. The parameter estimates are reported in Table 1. The sample mean and standard deviation of the $\hat{b}^i$'s are -0.0041 V/s and 0.0649 V/s, respectively. The estimates of τ and σ are not affected by the extreme trajectories, and the estimate of μ is slightly larger and that of σ_μ slightly smaller than the estimates from the full data set, as they should be when the lower tail is removed. Thus, the estimation seems robust to those outliers and in the following we refer to the case $M = 312$ only.

For ease of comparison between the observations and the theoretical model, Figure 4 reports only five observed trajectories from the 312 ISIs with lengths less than 0.16 s (the

median of the empirical distribution of the ISI lengths is 0.58 s), grouped in the same time-frame, the empirical mean of 2000 trajectories simulated from model 8–9 according to the Euler-Maruyama scheme (Kloeden and Platen (1992)) using the estimated parameters, the empirical 95% confidence bands of the 2000 trajectories and five simulated trajectories. For each simulated trajectory a different realization of B^i has been produced by drawing from the normal distribution with mean zero and standard deviation $\sigma_\mu = 0.0723$ V/s. In Figure 5 more observed trajectories (with lengths less than 0.4 s) over a longer time interval are compared with the simulated model using the same settings above.

The results are in agreement with the maximum likelihood estimates obtained in Lansky et al. (2006), where $1/\tau$ was estimated at 43.5068 s^{-1}, corresponding to $\tau = 0.023$ s, and the medians of the estimates were 0.4606 V/s for μ and 0.0135 V/$\sqrt{s}$ for σ (compare with our Table 1). Note that in Lansky et al. (2006) different sets of estimates for the input parameters were obtained for each ISI, whereas the introduction of the random effect and the extra noise parameter σ_μ in our approach provides only one set of estimates of input parameters based on the full data.

From Figures 4-5 it would seem that immediately after a spike the model prediction increases faster than the observed trajectories. This is probably due to model misspecification caused by not considering possible changes in τ depending on the time elicited since last spike. The maximum likelihood method is in fact a parametric method sensitive to this kind of model misspecifications, whereas e.g. the method of moments might be more robust. Since it is not obvious exactly how to correct the model, in order to fix the misspecification problem we proceed in two steps. We first obtain an estimate of τ with a regression method (first step), which depends mostly on the first moment, and is thus effective in identifying the initial rise, where there is a clear drift. In this way we have a better estimate of τ, and may then continue (second step) with our maximum likelihood procedure to obtain estimates for the remaining parameters. In practice, we simply repeated the maximum likelihood estimation after having fixed the value of τ to $0.039 = 1/25.8042$ s, as obtained in Lansky et al. (2006) by their regression method based on the first moment, equation 6. The final estimates of μ, σ, and σ_μ are reported in Table 1. These last results are in agreement with the regression estimates obtained in Lansky et al. (2006), where the median of the estimates were 0.2846 V/s for μ and 0.0135 V/$\sqrt{s}$ for σ. Figures 6-7 report the same observed trajectories considered in Figures 4-5, this time compared with the model simulated using the estimates obtained by fixing τ to 0.039 s. The model fit appears more convincing here, though there might still be some misspecification towards the end of the trajectories. The truth probably lies somewhere in between with τ varying between the two values found. The histogram of the corresponding random effects estimates is given in Figure 8 with sample mean and standard deviation of the $\hat{b}^i$ estimates given by 0.0036 V/s and 0.0467 V/s, respectively. In this case the empirical

distribution of the $\hat{b}^i$'s seems to be closer to a normal distribution than in the previous case represented in Figure 2.

4 Discussion

In this paper, a new model for the evolution of the neuronal membrane potential between spikes has been proposed and compared to a limited amount of experimental data. This comparison should be considered an illustration of the model and its verification methods more than a basis for biological conclusions. Thus, despite we found that the model gave a better description of the available data, an extensive confrontation with large data sets recorded under different experimental conditions are necessary.

The model is an extension of the stochastic LIF model and introduces a new parameter to describe a slowly fluctuating signal received by the neuron. Whereas the classical stochastic LIF with Gaussian noise encompass fast fluctuations of the membrane potential, it assumes that the mean signal is constant over the observed period. Here, the mean signal is variable at the scale of the ISIs. The statistical methods used for the estimation of the parameters of the model show that it is in fact possible to clearly distinguish between the two fluctuation sources that are working on different time scales. The model is therefore appealing because it coherently describes the behavior of a neuron over a large time span, more than the classical stochastic LIF. Moreover, only a single analysis on the full data set is required instead of splitting the data in smaller individually analyzed subsets, with a substantial gain in statistical estimation power. This holds, of course, only under the assumption of stationarity in the ISI generation.

The choice of a random effect on μ is natural since it is a parameter describing the intensity of neuronal input, and thus, the random effect describes the slow fluctuations in the total signal that the neuron receives from its environment between spikes. Also a random effect on σ could be considered, since it has been claimed that signal and noise are not independent quantities in the neuronal context in general (Cecchi et al. (2000)) and in the stochastic LIF specifically (Lansky and Sacerdote (2001)). It would correspond to variations in the synchronization or coherence of the source neurons in the environment. However, from Figure 10 in Lansky et al. (2006) it is clear that the estimates of σ do not vary much from ISI to ISI (most estimates differ less than 10% from the median value) and could be explained by statistical uncertainties in the estimation from finite samples. On the other hand, the variation in the estimates of μ is more substantial from ISI to ISI, and is more likely to represent a true biological effect.

We realize that there are more sophisticated variants of the LIF model (Burkitt (2006); Brunel and van Rossum (2008)) and new methods for signal estimation would be useful for their evaluation. The problem is that a minimal knowledge is required to develope these

methods, like knowledge of the transition density. However, there are still open questions concerning inference for the diffusion LIF, e.g. identification of the input parameters under periodic stimulation. Periodical stimulation has a long-lasting tradition in experimental studies as well as theoretical ones, and establishing a method for estimation of the signal would contribute to the verification of the model. This was also noted by Habib and Thavaneswaran (1990).

The approach used in this paper is common in biomedical research, where studies in which repeated measurements are taken on a series of individuals or experimental units play an important role. In these models it is assumed that all responses follow a similar functional form, but with parameters that vary among units. The increasing popularity of such mixed-effects models ("mixed-effects" means that the model contains both fixed and random effects, sometimes also called multi-level or hierarchical models) lies in the flexible modeling of correlation structures, where the total variation is specifically split in within-units and between-units variation. The theory for mixed-effects models is well developed for deterministic models (without system error), both linear and non-linear (Davidian and Giltinan (1995); McCulloch and Searle (2001); Diggle et al. (2002)), and standard software for model fitting is available, see e.g. Pinheiro and Bates (2000), Pinheiro et al. (2007) and Lavielle et al. (2007). Recently stochastic differential equation models with random effects have been considered (Ditlevsen and De Gaetano (2005); Tornøe et al. (2005); Overgaard et al. (2005); Picchini et al. (2006); Mortensen et al. (2007); Donnet and Samson (2008)), with different authors following different statistical approaches.

In conclusion, we have presented an extension of the stochastic LIF model which gives a significantly better description of experimental data, and simultaneously a statistical method to estimate parameters of the new model from experimental data.

Acknowledgments

The authors thank J.F. He for making the experimental data available. Supported by grants from the Danish Medical Research Council and the Lundbeck Foundation to S. Ditlevsen, and the Center for Neurosciences LC554, AV0Z50110509 and Academy of Sciences of the Czech Republic (Information Society, 1ET400110401) to P. Lansky.

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Appendix

Hypothesis testing

Testing whether a variance component is zero leads to a boundary problem, and a little extra care is required when evaluating the likelihood ratio statistic (see e.g. (McCulloch and Searle, 2001, section 8.7a)). The hypothesis $H_0 : \sigma_\mu = 0$ is tested against $H_1 : \sigma_\mu > 0$. Given $\theta = (\mu, \tau, \sigma, \sigma_\mu^2)$ denote with $\hat{\theta}$ the estimate of θ and let $\hat{\theta}_0$ be the estimate of (μ, τ, σ) under the restriction that $\sigma_\mu = 0$. The likelihood ratio statistic Λ is

$$\Lambda = \frac{L(\hat{\theta}_0, \sigma_\mu = 0)}{L(\hat{\theta})}$$

where L is given by (13). The large-sample distribution of $-2\log\Lambda$ is a 50/50 mixture of the constant 0 and a χ_1^2 distribution. The critical values are thus given by $\chi^2_{1,1-2\alpha}$ for a test at the specified critical level α (compare to $\chi^2_{1,1-\alpha}$ for an ordinary likelihood ratio test for nested models). Here $\chi^2_{1,\beta}$ is the β-percentile of the χ^2 distribution with one degree of freedom.

	μ [V/s]	τ [s]	σ [V/$\sqrt{\text{s}}$]	σ_μ [V/s]
$M = 312$	0.4944 [0.4829, 0.5058]	0.0210 [0.0206, 0.0215]	0.0135 [0.0135, 0.0135]	0.0723 [0.0692, 0.0753]
$M = 302$	0.5019 [0.4872, 0.5166]	0.0212 [0.0208, 0.0216]	0.0135 [0.0135, 0.0135]	0.0627 [0.0552, 0.0694]
$M = 312$	0.2779 [0.2733, 0.2824]	Fixed at 0.039	0.0135 [0.0135, 0.0135]	0.0414 [0.0379, 0.0447]

Table 1: Parameter estimates and 95% confidence limits.

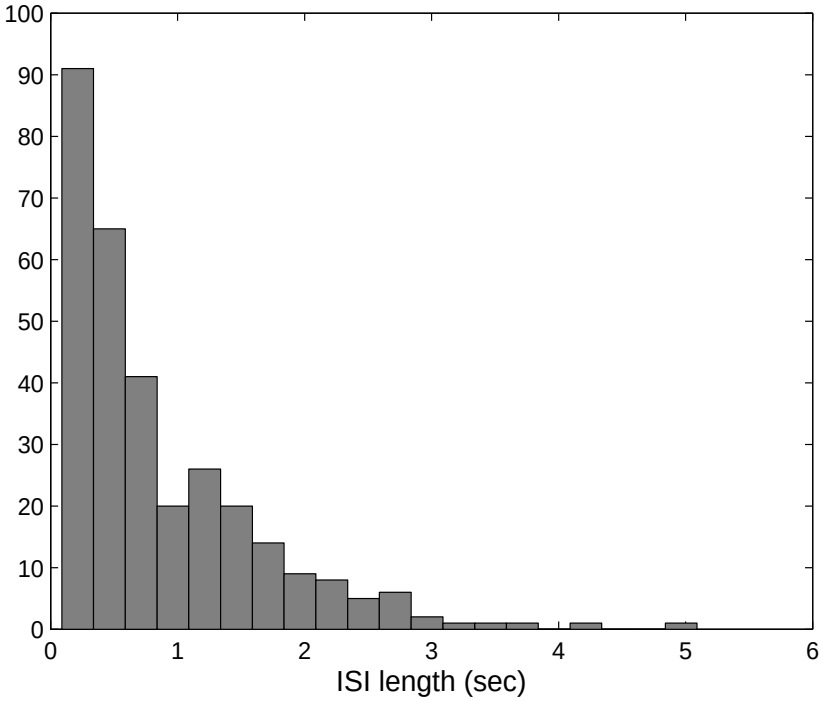

Figure 1: Histogram of the 312 ISI lengths.

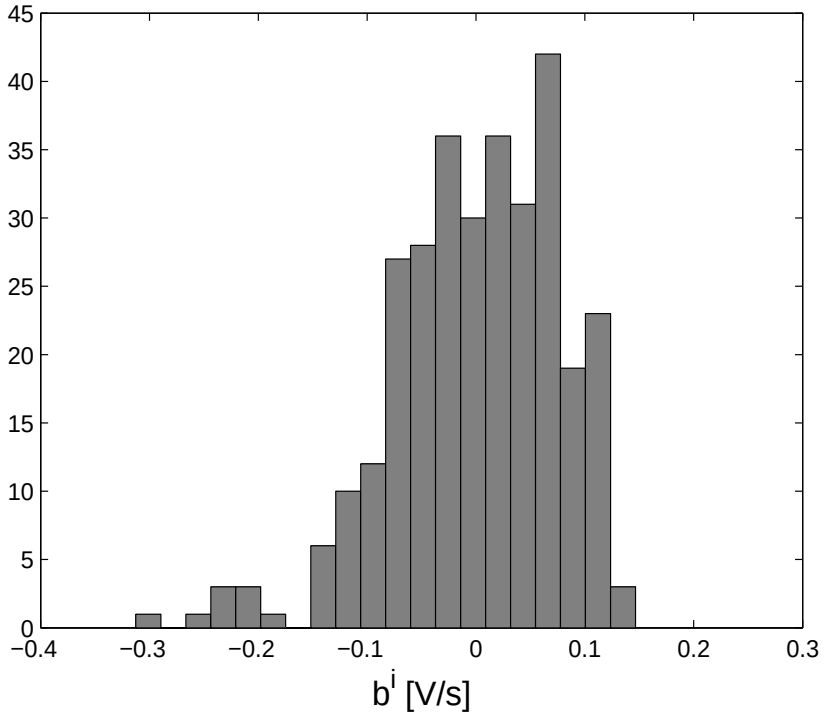

Figure 2: Histogram of the random effects $\hat{b}^i$ estimated from the 312 ISIs.

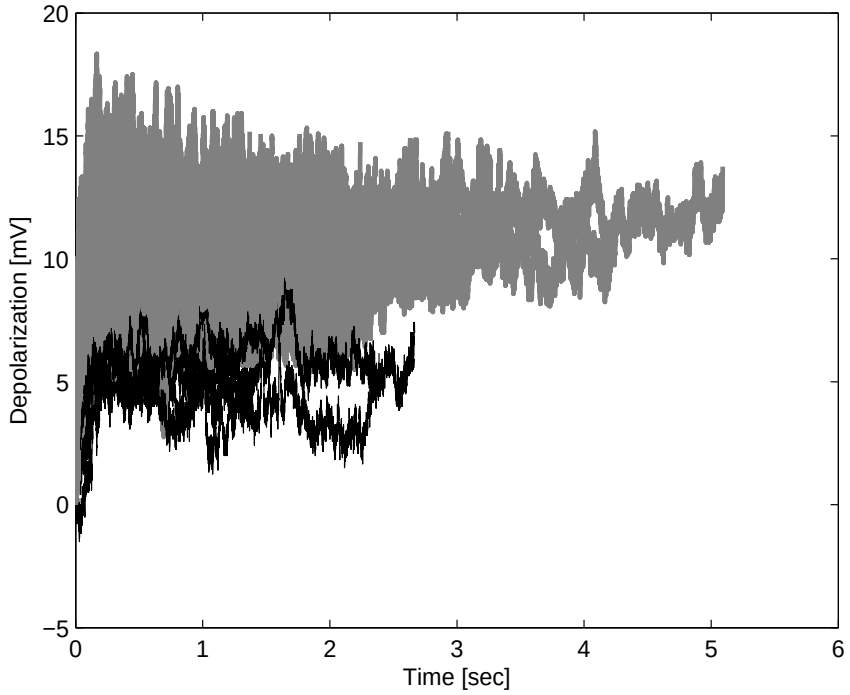

Figure 3: Observations from 312 ISIs: in black are the ISIs observations corresponding to $\hat{b}^i < -0.15$ [V/s].

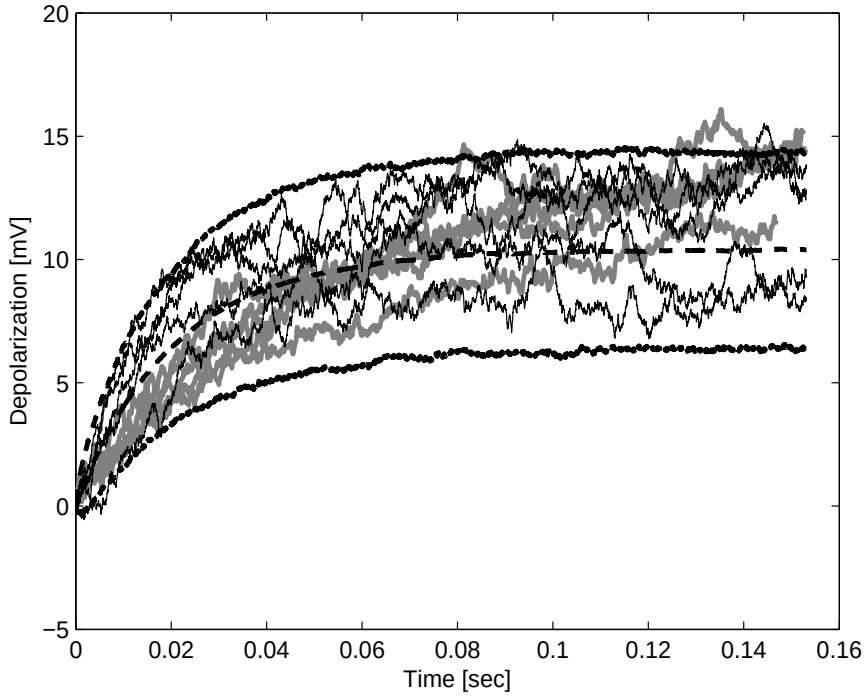

Figure 4: Observations from five of the 312 ISIs (grey) with lengths less than 0.16 s, empirical mean curve of 2000 trajectories of the stochastic process defined by model 8-9 with their 95% confidence bands (bold black lines) and five simulated trajectories.

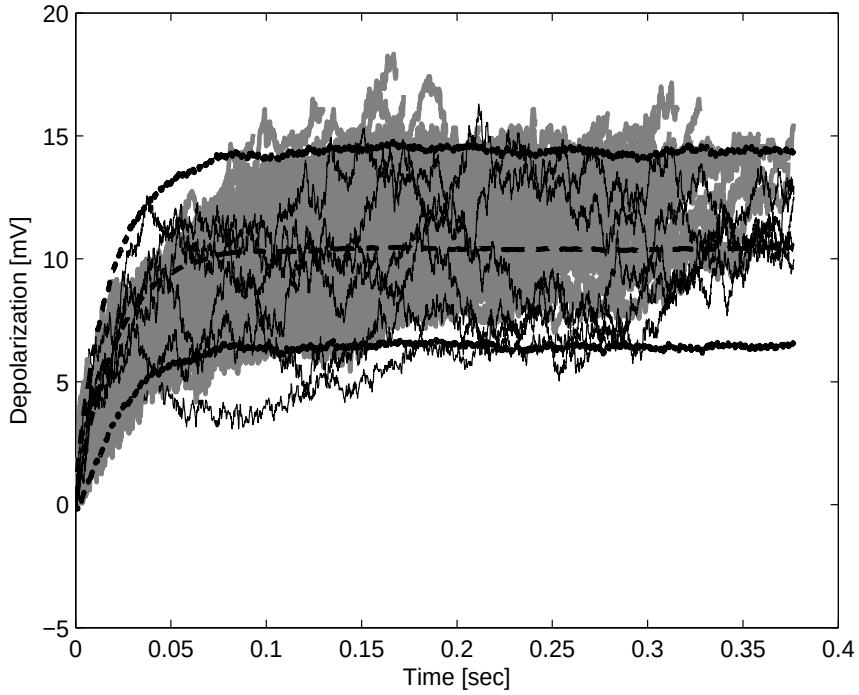

Figure 5: Observations from one hundred of the 312 ISIs (grey) with lengths less than 0.4 s, empirical mean curve of 2000 trajectories of the stochastic process defined by model 8-9 with their 95% confidence bands (bold black lines) and five simulated trajectories.

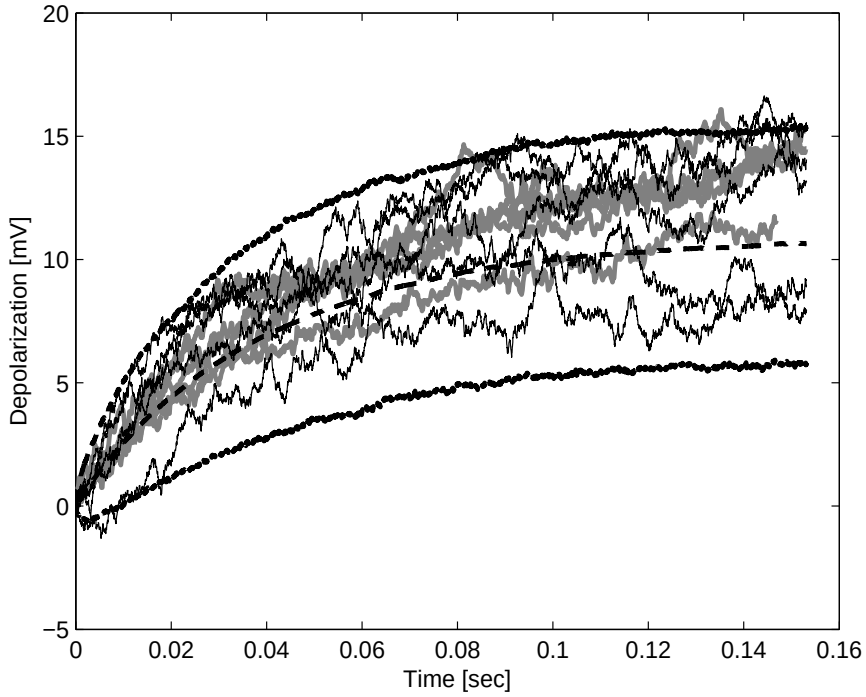

Figure 6: The same as in Figure 4 but using the estimates when τ is fixed to 0.039 s.

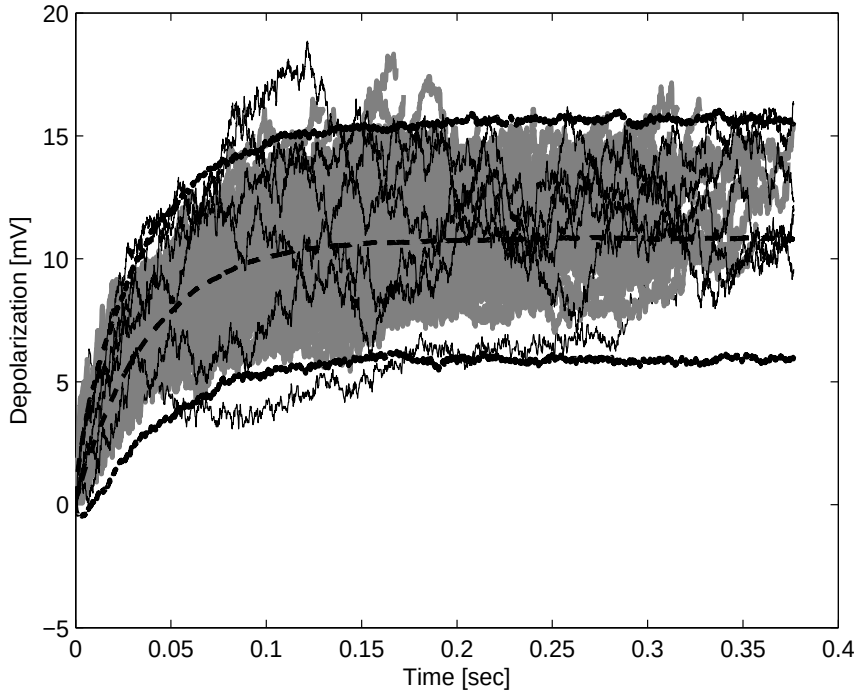

Figure 7: The same as in Figure 5 but using the estimates when τ is fixed to 0.039 s.

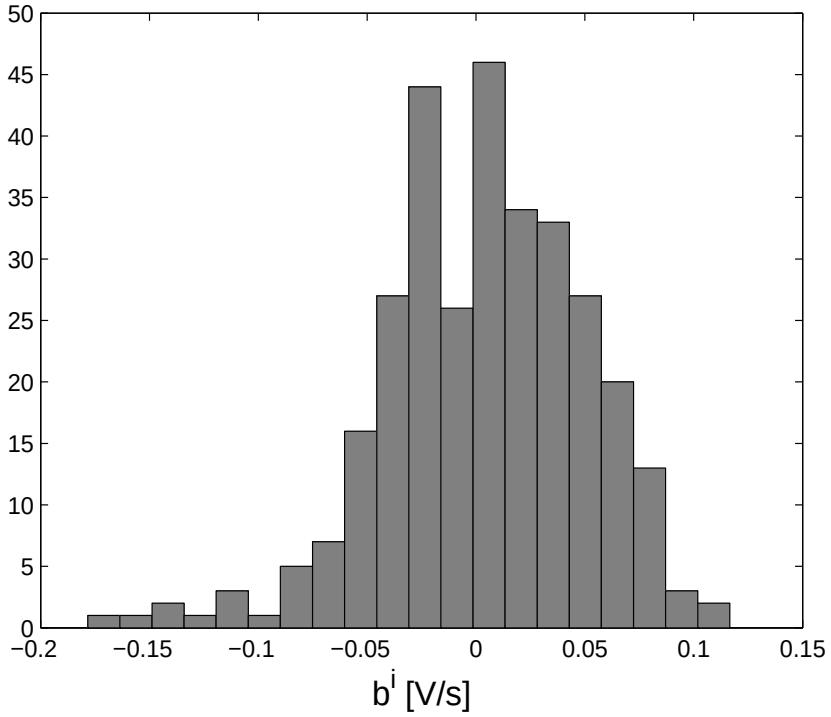

Figure 8: Histogram of the random effects $\hat{b}^i$ when τ is fixed to 0.039 s.