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Parameter estimation in neuronal stochastic differential equation models from intracellular recordings of membrane potentials in single neurons: a Review

Titre: Revue des méthodes d'estimation paramétrique pour des modèles neuronaux sous forme d'équations différentielles stochastiques à partir de données neuronales intra-cellulaires

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Abstract: Dynamics of the membrane potential in a single neuron can be studied by estimating biophysical parameters from intracellular recordings. Diffusion processes, given as continuous solutions to stochastic differential equations, are widely applied as models for the neuronal membrane potential evolution. One-dimensional models are the stochastic integrate-and-fire neuronal diffusion models. Biophysical neuronal models take into account the dynamics of ion channels or synaptic activity, leading to multidimensional diffusion models. Since only the membrane potential can be measured, this complicates the statistical inference and parameter estimation from these partially observed detailed models. This paper reviews parameter estimation techniques from intracellular recordings in these diffusion models.

Résumé : On peut étudier la dynamique du potentiel de la membrane d'un neurone en estimant des paramètres biophysiques à partir d'enregistrement intracellulaire. Les processus de diffusion, définis comme solution Ã temps continu d'équations différentielles stochastiques ont été très utilisés pour modéliser l'évolution du potentiel membranaire. Parmi les processus de dimension un, les plus connus sont les modèles de diffusion intègre-et-tire. D'autres modèles neuronaux sont plus biophysiques et prennent en compte la dynamique des canaux ioniques ou de l'activité synaptique. Ce sont des processus de diffusion multidimensionnels. L'estimation des paramètres de ces modèles est difficile car seulement le potentiel membranaire peut être mesuré. Ce papier résume les techniques d'estimation qui ont été proposées pour ces modèles de diffusion de données intracellulaires.

Mots-clés : modèles de diffusion intègre-et-tire, modèles de conductances, modèles à espace d'Ã©tats, estimation synaptique, maximum de vraisemblance, filtre particulaire, fonctions estimantes, MCMC, observations partielles
Keywords: integrate-and-fire models, conductance based models, state space models, synaptic input estimation, maximum likelihood estimation, particle filter, estimating functions, MCMC methods, partial observations
AMS 2000 subject classifications: 62Mxx, 62F10, 62F15

1. Introduction

Neurons communicate by short and precisely shaped electrical impulses, the so-called spikes or action potentials. It is therefore of major interest to understand the principles of the underlying spike generating mechanisms, starting by understanding the dynamics of the membrane potential in a single neuron. Intracellular recordings provide high frequency observations of good precision,

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typically measured around every 0.1 ms. There is thus a growing demand for robust methods to estimate biophysical relevant parameters from such data.

Diffusion processes, given as continuous solutions to stochastic differential equations, are widely applied as models for the neuronal membrane potential evolution. The stochastic integrate-and-fire neuronal diffusion models are one-dimensional, though they have also been extended to include a recovery variable to model memory in the system. They are probably some of the most common mathematical representations of single neuron electrical activity, and result from more or less dramatic simplifications of more involved neuronal models. The simplification implies that the shape of the action potential is neglected and represented by a point event, typically represented by the first hitting time to a firing threshold, an upper bound of the membrane potential. More biophysical neuronal models take into account the dynamics of ion channels or synaptic activity, leading to multidimensional diffusion models. Electrical activity in neurons consists of ionic currents through the cell membranes. Conductance-based models are simple biophysical representations of excitable cells like neurons, and are based on an electrical circuit model of a cell membrane. In these models current flows across the membrane due to charging of the capacitance and movement of ions across ion channels in the membrane. These models are based on the seminal work by Hodgkin and Huxley (1952), which formulated a mathematical model including dynamics of gating variables in dependence of the membrane potential, and in turn influencing the evolution of the membrane potential, creating a feedback system capable of producing oscillatory behavior and spikes. Since only the membrane potential can be measured, this complicates the statistical inference and parameter estimation from these partially observed detailed models.

This paper reviews parameter estimation techniques from intracellular recordings in models of the type

$$dX_t = b(X_t;\theta)dt + \Sigma(X_t;\theta)dW_t$$

where $X_t = (V_t, Y_t)$ is a d-dimensional process with first coordinate V_t representing the membrane potential, and Y_t being unobserved coordinates representing for example gating variables, proportion of open ion channels of a specific ion or inhibitory or excitatory synaptic input. If $d = 1$ then $X_t = V_t$. Here, $b(x;\theta)$ is the drift function taking values in $\mathbb{R}^d$, $\Sigma(x;\theta)$ is the diffusion matrix taking values in $\mathbb{R}^{d\times m}$ and W_t is an m-dimensional standard Wiener process. The goal is to estimate the parameter vector $\theta \in \Theta \subset \mathbb{R}^p$. Data are discrete measurements of V_t. Denote $t_0 < t_1 < \cdots < t_n$ the observation times, which we assume equidistant, and denote the sampling step by $\Delta = t_i - t_{i-1}$. We denote $V_i = V_{t_i}$ the observation at time t_i, and $V_{0:n} = (V_0, V_1, \ldots, V_n)$ the vector of all observed data. An example of a sample trace of the membrane potential in a spinal motoneuron of an adult red-eared turtle during 600 ms (6000 data points) is shown in Figure 1.

The models and different parameter estimation approaches will be discussed next. To read more about the derivation of the models and biophysical justifications, we refer to Tuckwell (1988); Gerstner and Kistler (2002); Izhikevich (2007); Laing and Lord (2010); Bachar et al. (2013); Gerstner et al. (2014).

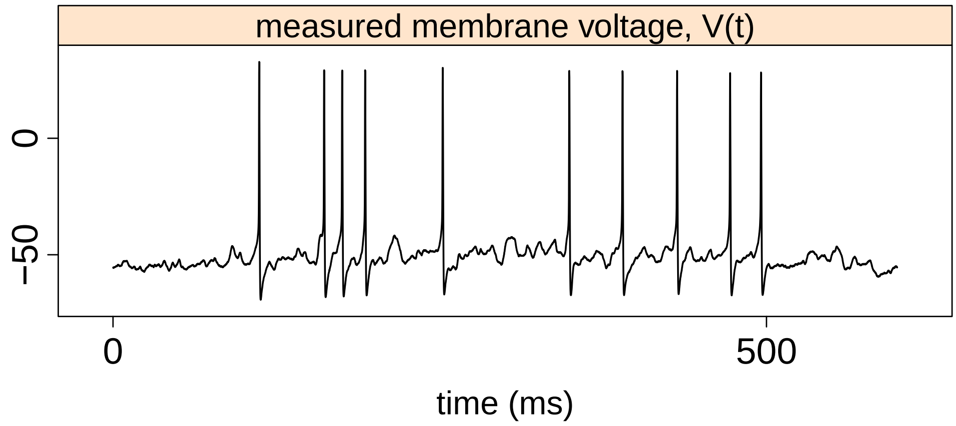

FIGURE 1. *Observations of the membrane potential in a spinal motoneuron of an adult red-eared turtle during 600 ms measured every 0.1 ms. Data from Berg Laboratory, see Berg et al. (2007).*

2. Models

The model for the membrane potential is given by an equation of the form

$$C\frac{dV}{dt} = \text{sum of currents + noise}$$

where C is the cell membrane capacitance, and V is the membrane potential evolution. Sometimes the constant C is not specifically stated and absorbed into other parameters. The currents are ions, such as sodium, potassium, calcium and chloride, flowing in and out of the cell through ion channels in the cell membrane, as well as input currents received from other neurons in the surrounding network, or injected current controlled by the experimentalist. The noise models the inherent stochasticity of neural activity. These models fall into two classes, posing different statistical challenges, namely one-dimensional models (integrate-and-fire models), where there are no hidden components, and multi-dimensional models with unobserved coordinates, complicating the statistical analysis considerably.

2.1. Integrate-and-fire models

The integrate-and-fire neuronal models are reviewed in Burkitt (2006), see also references therein. We will only treat the subclass of diffusion integrate-and-fire models given as solutions to the Itô-type stochastic differential equation

$$dV_t = b(V_t;\theta)\,dt + \sigma(V_t;\theta)dW_t\,, \quad V_0 = v_0. \tag{1}$$

For the theory of diffusion processes, see e.g. Kloeden and Platen (1992); Øksendal (2010). Due to the simplicity of the model, spike generation is not an inherent part of process (1) as in more complex models, and a firing threshold has to be imposed. An action potential is produced when the membrane voltage V exceeds a voltage threshold, V_{th}, for the first time, and such that $V_{th} > v_0$. Formally, the spike time is identified with the first-passage time T of the threshold,

$$T = \inf\{t > 0 : V_t \geq V_{th}\}, \tag{2}$$

and V_t is then reset to v_0. When estimating θ from equation (1), only recordings of the subthreshold fluctuations between spikes are used, and the parameter estimation problem reduces to estimation in one-dimensional diffusions from discrete observations. In this model, the spike is reduced to a point event, triggered by a fixed value of V_t, whereas in the real system, a spike takes a couple of miliseconds, and the threshold seems random, see e.g. Fig. 6 in Jahn et al. (2011). This makes the estimation of the threshold a non-trivial task. If measuring is done around every 0.1 ms, as is customary, many observations during each spike has to be discarded. Furthermore, it is not clear when the diffusive behavior ends and the more deterministic behavior of the spike begins, see Figure 1. Different ad-hoc methods have been proposed, and in most studies it is not even specified how it was done. It is straightforward to localize the peak of all spikes, and the problem is to decide how large an interval to cut out around this peak. Lansky et al. (2006) defined the beginning of the spike as the last point with decreasing depolarization before the spike in an interval from 10.05 ms before the voltage reaches -35.5 mV. Then the data was transformed by a moving average over 6 values and they then defined the end of a spike as the minimum in the first valley after the peak. The valley is defined to start when the membrane potential reaches the value of -65.5 mV for the first time after the spike, and ends 10.05 ms later. The same approach was adopted in Picchini et al. (2008). In Jahn et al. (2011) all spikes were aligned according to the peak, and then the empirical variance was estimated cross-sectionally at each time point backwards in time from the peak. The spike initiation was then defined to be where the variance started decreasing, determined to be 4 ms before the peak.

Maximum likelihood estimation can be used in some few cases where the transition density is available, but in general other approaches are necessary. The methodology of parameter estimation in one-dimensional diffusions, equation (1), from discrete observations is well studied, see for example Prakasa Rao (1999); Sørensen (2004); Forman and Sørensen (2008); Iacus (2008); Sørensen (2012), and references therein. There is a bias issue with the drift parameters, though, caused by the sampling conditioned on being below the threshold, see Bibbona et al. (2010); Bibbona and Ditlevsen (2013). This is more pronounced when the neuron is frequently firing. The problem is commonly ignored when analysing data, which we will also do in the sequel. Here we review estimators from maximum likelihood or martingale estimating functions for a few common integrate-and-fire models.

The simplest integrate-and-fire model is just the Wiener process with constant drift, the diffusion approximation of the random walk model for the membrane dynamics, first introduced in Gerstein and Mandelbrot (1964). Here, $b(v;\theta) = \mu$ and $\sigma(v;\theta) = \sigma$ are just constants so that $\theta = (\mu, \sigma^2)$. It is assumed that $\mu > 0$ so that the waiting time for a spike is finite. The process is Gaussian, and the maximum likelihood estimators are

$$\hat{\mu} = \frac{V_n - V_0}{n\Delta} \quad ; \quad \hat{\sigma}^2 = \frac{1}{n\Delta} \sum_{i=1}^{n} (V_i - V_{i-1} - \Delta\hat{\mu})^2$$

with asymptotic variances $\mathrm{Var}(\hat{\mu}) = \sigma^2/n\Delta$ and $\mathrm{Var}(\hat{\sigma}^2) = \sigma^4/n$. This is one of the few models where the first passage time distribution is known, which is an inverse Gaussian distribution, and justifies why this model has been popular.

The Wiener model does not take into account the leakage of the neuronal membrane, namely that current flows through the membrane due to its passive properties. The most popular leaky integrate-and-fire model is the Ornstein-Uhlenbeck process, where $b(v;\theta) = -v/\tau + \mu$ and $\sigma(v;\theta) = \sigma$. Here, μ characterizes neuronal input and $\tau > 0$ is the membrane time constant and reflects spontaneous voltage decay in absence of input. For an input $\mu > V_{th}/\tau$, the neuron fires regularly, whereas for $\mu \leq V_{th}/\tau$, the model only fires due to noise. This defines the sub– and suprathreshold regimes. Parameters V_{th}, v_0 and τ characterize the neuronal membrane, μ characterizes the input signal, and σ scales the noise.

The maximum likelihood estimators are given as solutions to the equations

$$
\begin{aligned}
\hat{\alpha} &= \frac{\sum_{i=1}^{n}(V_i - V_{i-1}\hat{\rho})}{n(1-\hat{\rho})} \\
\hat{\rho} &= \frac{\sum_{i=1}^{n}(V_i - \hat{\alpha})(V_{i-1} - \hat{\alpha})}{\sum_{i=1}^{n}(V_{i-1} - \hat{\alpha})^2} \\
\hat{\sigma}^2 &= \frac{2\sum_{i=1}^{n}(V_i - \hat{\alpha} - (V_{i-1} - \hat{\alpha})\hat{\rho})^2}{n(1-\hat{\rho}^2)\hat{\tau}}
\end{aligned}
$$

where $\hat{\alpha} = \hat{\mu}\hat{\tau}$ estimates the asymptotic variance, and $\hat{\rho} = -\log\Delta/\hat{\tau}$ estimates the autocorrelation, see Ditlevsen and Samson (2013). The maximum likelihood estimator exists only if $\sum_{i=1}^{n}(V_i - \hat{\alpha})(V_{i-1} - \hat{\alpha}) > 0$. Note that if τ is known, the likelihood equations become particularly simple, the estimators are explicit and always exist. The asymptotic variances obtained by inverting the Fisher information are $\mathrm{Var}(\hat{\tau}) = 2\tau^3/n\Delta$, $\mathrm{Var}(\hat{\alpha}) = \sigma^2\tau/n\Delta$ and $\mathrm{Var}(\hat{\sigma}^2) = 2\sigma^4/n$. Using that intracellular recordings are high-frequency, i.e., $\Delta \ll \tau$, the above likelihood equations can be simplified using the approximation $\rho = e^{-\Delta/\tau} \approx 1 - \Delta/\tau$, in which case the estimators become explicit, see Lansky (1983). The same estimator is derived in Habib and Thavaneswaran (1990) and extended to allow time varying parameters such that the drift function is also a function of time; $b(v,t;\theta) = -\beta(t)v + \mu(t)$.

Picchini et al. (2008) extended the model to accomodate a slowly fluctuating signal, by permitting μ to change stochastically between spikes, assuming a normal distribution. This is a random effects model. The likelihood is no longer tractable, but is approximated by Gauss-Hermite quadrature.

Paninski et al. (2005) proposed a more involved model, based on the basic integrate-and-fire model, generalizing the spike-response model in Gerstner and Kistler (2002). The model accomodates memory effects, and thus is a generalization of the renewal model, now allowing for burstiness, refractoriness or adaptation. The maximum likelihood estimator is derived for all model parameters, including the threshold. The threshold value V_{th} is biased, though, probably caused by assuming a fixed threshold, when it is more likely not so sharp, see also discussion above. They propose to solve this by first detecting the spiking times (via automatic thresholdings), then fit the parameters except V_{th} by linear least squares, and finally estimate V_{th} using the likelihood depending on V_{th} only.

The Ornstein-Uhlenbeck leaky integrate-and-fire model is unbounded and does not take into account non-linearities, for example caused by the inhibitory reversal potential, V_I, a lower limit for the membrane potential. The Feller model (also called the square-root model, or the Cox-Ingersoll-Ross model in mathematical finance) has the same drift term as the Ornstein-Uhlenbeck, and diffusion term $\sigma(v;\theta) = \sigma\sqrt{v - V_I}$. When $2\mu + 2V_I/\tau \geq \sigma^2$, the process stays above V_I if $v_0 \geq V_I$. Bibbona et al. (2010) reviewed and compared estimation methods for the Feller process in simulations, assuming τ known, thus estimating $\theta = (\mu, \sigma^2)$. They use least squares, conditional least squares, martingale estimating functions, a Gauss-Markov method, optimal estimating functions, and maximum likelihood estimation. They discuss the bias issue in the estimation of μ arising from the conditional sampling under the threshold, and suggest a bias correction. They recommend to use martingale estimating functions, or the Gauss-Markov method if only μ is estimated, with the bias correction. If all parameters should be estimated, we refer to Forman and Sørensen (2008) for martingale estimating functions, which only treats the case of unconditional sampling. Their estimators are

$$\begin{aligned}
\hat{\alpha} &= \frac{1}{n}\sum_{j=1}^{n} V_j + \frac{\hat{\rho}}{n(1-\hat{\rho})}(V_n - V_0) \\
\hat{\rho} &= \frac{n\sum_{j=1}^{n}\frac{V_j}{V_{j-1}} - \left(\sum_{j=1}^{n} V_j\right)\left(\sum_{j=1}^{n}\frac{1}{V_{j-1}}\right)}{n^2 - \left(\sum_{j=1}^{n} V_{j-1}\right)\left(\sum_{j=1}^{n}\frac{1}{V_{j-1}}\right)} \\
\hat{\sigma}^2 &= \frac{\sum_{j=1}^{n}\frac{1}{V_{j-1}}\left(V_j - V_{j-1}\hat{\rho} - \hat{\alpha}(1-\hat{\rho})\right)^2 \hat{\beta}}{\sum_{j=1}^{n}\frac{1}{V_{j-1}}\left((\frac{\hat{\alpha}}{2} - V_{j-1})\hat{\rho}^2 - (\hat{\alpha} - V_{j-1})\hat{\rho} + \frac{\hat{\alpha}}{2}\right)}
\end{aligned}$$

where, as before, $\hat{\alpha} = \hat{\mu}\hat{\tau}$ and $\hat{\rho} = -\log\Delta/\hat{\tau}$.

Hoepfner (2007) applied a kernel estimator to non-parametrically estimate the drift and the diffusion functions in (1) to data from a pyramidal neuron from a cortical slice preparation exposed to different levels of potassium. He finds both Ornstein-Uhlenbeck and Feller behavior in different trials. The same approach is employed in Jahn et al. (2011) on data from a spinal motoneuron from a red-eared turtle, where the most suitable model is first determined non-parametrically, and then fitted parametrically. Here it is found that the neural activity is well described by a Feller process when the neuron is stimulated, and by an Ornstein-Uhlenbeck under spontaneous activity with no stimulation.

Lanska and Lansky (1998) derived a model of type (1) taking into account both inhibitory and excitatory reversal potentials. The drift is linear with a leaky term as in the Ornstein-Uhlenbeck process, with diffusion term $\sigma(v;\theta) = \sigma\sqrt{(1-v)v}$. This is a Jacobi diffusion, called this way because the eigenfunctions of its generator are the Jacobi polynomials, see Forman and Sørensen (2008). It lives on a bounded interval, in this formulation on the interval $(0,1)$, after a suitable affine transformation of the observations. The exact likelihood is not available for this model. Three estimation methods are proposed in Lanska and Lansky (1998); maximum likelihood based on a discretization of the continuous time likelihood, a Bayesian approach assuming Gaussian priors on the parameters in the drift, and a minimum contrast method. Estimators, based on martingale estimating functions, are given as solutions to the equations,

$$
\begin{aligned}
\hat{\alpha} &= \frac{\sum_{j=1}^{n} \frac{V_j - V_{j-1}\hat{\rho}}{V_{j-1}(1-V_{j-1})}}{(1-\hat{\rho})\sum_{j=1}^{n} \frac{1}{V_{j-1}(1-V_{j-1})}} \\
\hat{\rho} &= \frac{\sum_{j=1}^{n} \frac{(V_j - \hat{\alpha})(V_{j-1} - \hat{\alpha})}{V_{j-1}(1-V_{j-1})}}{\sum_{j=1}^{n} \frac{(V_{j-1} - \hat{\alpha})^2}{V_{j-1}(1-V_{j-1})}} \\
\hat{\sigma}^2 &= \frac{1}{n\Delta}\sum_{j=1}^{n} \frac{(V_j - V_{j-1}\hat{\rho} - \hat{\alpha}(1-\hat{\rho}))^2}{V_{j-1}(1-V_{j-1})}
\end{aligned}
$$

where, as before, $\hat{\alpha} = \hat{\mu}\hat{\tau}$ and $\hat{\rho} = -\log\Delta/\hat{\tau}$.

When the estimators are based on a (approximate) maximum likelihood or estimating equations, asymptotic variances can be derived.

3. Synaptic conductance based model

The neuronal membrane potential is as in the previous Section only modeled during sub-threshold fluctuations (i.e. between spikes), but now the membrane equation is driven by two independent sources of synaptic conductance noise, namely excitatory and inhibitory currents. These models are called point-conductance models by Destexhe et al. (2001). For notational reasons we now write $V(t) = V_t$, to distinguish between a subindex and the time variable. The system is given by

$$
\begin{aligned}
CdV(t) &= (-g_L(V(t)-V_L) - g_e(t)(V(t)-V_e) - g_i(t)(V(t)-V_i) + I)dt + \sigma dW(t) \\
dg_e(t) &= -\frac{1}{\tau_e}(g_e(t) - g_{e0})dt + \sigma_e dW_e(t) \\
dg_i(t) &= -\frac{1}{\tau_i}(g_i(t) - g_{i0})dt + \sigma_i dW_i(t) \qquad (3)
\end{aligned}
$$

where g_L, $g_e(t)$, $g_i(t)$ are the conductances of leak, excitatory and inhibitory currents, V_L, V_e and V_i are their respective reversal potentials, C is the capacitance, I is a constant current, $W(t)$, $W_e(t)$ and $W_i(t)$ are independent Brownian motions, and σ, σ_e and σ_i are the diffusion coefficients. We set $C = 1$, since it only enters as a proportionality constant, and is thus unidentifiable. Unknown parameters are $\theta = (g_L, g_{e0}, g_{i0}, \tau_e, \tau_i, V_e, V_i, V_L, I, \sigma^2, \sigma_e^2, \sigma_i^2)$.

Note that the two hidden components $g_e(t)$ and $g_i(t)$ are autonomous: they do not depend on the membrane potential $V(t)$. This simplifies the statistical analysis. Moreover, they are Ornstein-Uhlenbeck processes.

Estimation in these synaptic conductance models using discrete observations of $V(t)$ has been widely studied, and depends on the noise and whether some of the diffusion coefficients are set to

0. When noise appears in all three equations, then system (3) can be viewed as a hidden Markov model (HMM). We refer to Cappé et al. (2005) for a well documented review of estimation methods. Nevertheless, the synaptic conductance based model with noise in all components has not been treated much in the literature.

In the next two subsections, we focus on model (3) with noise only in the hidden components ($\sigma = 0$), which has been considered by Rudolph and Destexhe (2003); Destexhe et al. (2004); Rudolph et al. (2004b,a); Pospischil et al. (2007, 2009a,b), and then on model (3) with noise only on the first equation ($\sigma_e = \sigma_i = 0$), which has been considered by Huys et al. (2006); Paninski et al. (2010).

3.1. *Noise on the synaptic conductance equations*

Two main estimation methods have been proposed for model (3) with noise only in the hidden components ($\sigma = 0$), a method based on the probability distribution of the membrane potential $V(t)$, and a method based on the extraction of the synaptic conductances. We start with the distribution of $V(t)$.

V probability distribution method The seminal paper is Rudolph and Destexhe (2003) which computes the probability distribution of the membrane potential $V(t)$ at steady-state. Following this idea, several papers have derived estimators of some parameters (Destexhe et al., 2004; Rudolph et al., 2004b,a; Pospischil et al., 2009a). The probability distribution of the membrane potential $V(t)$ at time t is denoted $\rho(v,t)$. Using intensive Itô calculus on the two Ornstein-Uhlenbeck processes $g_e(t)$ and $g_i(t)$, the dynamics of $\rho(v,t)$ can be described by a Fokker-Planck equation. Then under the steady-state assumption ($t \to \infty$), an analytic expression of $\rho(v,t)$ is available:

$$\begin{aligned}\rho(v,t) \quad &= \quad N \exp\Big(A_1 \log\big(\sigma_e^2 \tau_e (v-V_e)^2 + \sigma_i^2 \tau_i (v-V_i)^2\big) \\ &\quad + A_2 \arctan\left(\frac{\sigma_e^2 \tau_e (v-V_e) + \sigma_i^2 \tau_i (v-V_i)}{(V_e - V_i)\sqrt{\sigma_e^2 \sigma_i^2 \tau_e \tau_i}}\right)\Big)\end{aligned} \tag{4}$$

where A_1 and A_2 are two constants which depend on all the parameters θ, and N is a normalizing constant.

Given the expression of $\rho(v,t)$, Destexhe et al. (2004) claim that it is possible to estimate θ directly by maximizing $\prod_{i=1}^{n} \rho(V(t_i),t_i)$. However, it is emphasized by Rudolph et al. (2004b) that since $\rho(v,t)$ is highly non-linear in θ, standard maximization procedure may not converge. While some maximization procedure such that simulated annealing could converge, they instead propose to approximate $\rho(v,t)$ with a Gaussian distribution, which corresponds to a second-order Taylor expansion of (4):

$$\rho(v,t) \approx \exp\Big(-\frac{(v-\bar{V})^2}{2\sigma_V^2}\Big)$$

where $\bar{V}$ and σ_V^2 are functions of θ (see Rudolph et al., 2004b, for analytic expressions). They focus on the estimation of the conductance parameters, namely $(g_{e0}, g_{i0}, \sigma_e^2, \sigma_i^2)$. There are thus four parameters, but only two quantities can be identified using the Gaussian approximation (namely the expectation $\bar{V}$ and the variance σ_V^2). Rudolph et al. (2004b) propose to use two sets of experimental data traces $V_{0:n}$, corresponding to two sets of experimental conditions, to identify and estimate the four parameters $(g_{e0}, g_{i0}, \sigma_e^2, \sigma_i^2)$ (the others assumed fixed and known). No theoretical properties of these estimators have been studied and it might be difficult to derive the asymptotic variance of these estimators.

Following Rudolph et al. (2004b), Pospischil et al. (2009a) suggest the use of the power spectral density of $V(t)$ to estimate two parameters more, τ_e and τ_i. An approximation of the power spectral density is given by

$$S_V(u) = C\frac{1}{1+u^2\tau_m^2}\left(\frac{\sigma_e^2\tau_e(V_e-\bar{V})^2}{1+u^2\tau_e^2} + \frac{\sigma_i^2\tau_i(V_i-\bar{V})^2}{1+u^2\tau_i^2}\right)$$

where $\tau_m = 1/g_T$ is the effective time constant, $g_T = g_L + g_{e0} + g_{i0}$ is the total conductance, and $\bar{V} = (g_L V_L + g_{e0}V_e + g_{i0}V_i)/g_T$ is the mean membrane potential. Maximizing S_V yields estimators of τ_e and τ_i. No theoretical properties of these estimators have been studied.

Extraction of synaptic conductance method Pospischil et al. (2007, 2009a,b) focus on the estimation of the synaptic currents $g_e(t), g_i(t)$, which are non-observed random processes. They propose to discretize the first equation of model (3) using an Euler scheme with a time step Δ, and to derive an approximation of g_i at discrete times t_k. We call this approximation $\bar{g}_i(t_k)$, which is a function of $V(t_k)$ and $g_e(t_k)$, $V(t_k)$ being observed but not $g_e(t_k)$. Then, discretizing the two last equations of (3) using an Euler-Maruyama scheme with a time step Δ, and plugging $\bar{g}_i(t_k)$ into these discretized equations, one can obtain an approximation of the transition density $p_k = p(g_e(t_{k+1}), g_i(t_{k+1})|g_e(t_k), g_i(t_k))$,

$$\begin{aligned} p_k \;\approx\; & \exp\left(-\frac{1}{2\Delta}\left(\frac{1}{\sigma_e^2}(g_e(t_{k+1}) - g_e(t_k) - \frac{\Delta}{\tau_e}(-g_e(t_k) - g_{e0}))^2 \right.\right. \\ & \left.\left. + \frac{1}{\sigma_i^2}(\bar{g}_i(t_{k+1}) - \bar{g}_i(t_k) - \frac{\Delta}{\tau_i}(-\bar{g}_i(t_k) - \bar{g}_{i0}))^2\right)\right) \end{aligned}$$

Maximizing $\prod_{k=1}^n p_k$ with respect to $(g_e(t_k))$ provides an estimator $(\hat{g}_e(t_k))$ of the excitatory synaptic conductance which is then used in the expression of $\bar{g}_i(t_k)$ to estimate also the inhibitory synaptic conductance, $(\hat{g}_i(t_k))$. Extensions of this method are considered by Pospischil et al. (2007) who suggest an averaging of this procedure in space, and by Pospischil et al. (2009a) treating the case of correlated Brownian motions $(W_e(t))$ and $(W_i(t))$.

Note that this approach assumes that the parameters θ are known. Therefore, Pospischil et al. (2009b) propose a criteria to estimate also θ. This criteria, called a likelihood in their paper, even if it is not a likelihood in the statistical sense, is the following

$$f(V_{0:n}, \theta) = \frac{\int \prod_{k=1}^n p(g_e(t_{k+1}), \bar{g}_i(t_{k+1}, g_e(t_{k+1}), V_{k+1}))|g_e(t_k), \bar{g}_i(t_k, g_e(t_k), V_k))dg_e(t_k)}{\int \prod_{k=1}^n p(g_e(t_{k+1}), g_i(t_{k+1}))|g_e(t_k), g_i(t_k))dg_e(t_k)dg_i(t_k)}$$

Pospischil et al. (2009b) then maximize $f(V_{0:n}, \theta)$ to estimate θ.

Note that it is not explained how these multidimensional integrals can be computed efficiently in practice, especially the one appearing in the denominator, nor is it explained how the optimization is performed. Moreover, no theoretical properties such as the asymptotic variance have been stated for this procedure. The approximated $\bar{g}_i(t_k)$ is in the same spirit as the approximation of the hidden state proposed by Samson and Thieullen (2012) for a two-dimensional hypoelliptic system (no noise on the first equation). Samson and Thieullen (2012) prove that a direct plug-in of $\bar{g}_i(t_k)$ in an Euler discretization of the transition density of $(g_e(t), g_i(t))$ induces a bias when maximizing the corresponding criteria.

3.2. Noise on the membrane voltage equation

Consider model (3) with $\sigma_e = \sigma_i = 0$ and the mean values g_{e0}, g_{i0} replaced by presynaptic inputs:

$$\begin{aligned} \frac{dg_e(t)}{dt} &= -\frac{1}{\tau_e} g_e(t) - I_e(t) \\ \frac{dg_i(t)}{dt} &= -\frac{1}{\tau_i} g_i(t) - I_i(t) \end{aligned} \tag{5}$$

where $I_e(t)$ and $I_i(t)$ are (random) functions that should be estimated.

Presynaptic input estimation A first approach focuses on the estimation of these presynaptic inputs, assuming parameters θ to be known.

Huys et al. (2006) show that the two synaptic conductances $g_e(t)$ and $g_i(t)$ can be written as convolutions of the presynaptic inputs, $g_s(t) = \int^t I_s(u) e^{-(t-u)/\tau_s} du$, for $s = e$ or i being the two synaptic conductances. Then, by discretizing the signals, the convolution can be approximated by

$$g_s(t_k) \approx \sum_{j \le k} e^{-(t_k - t_j)/\tau_s} I_s(t_j) = K_s I_s, \tag{6}$$

where K_s is a convolution matrix. The first equation of model (3) is also discretized using an Euler-Maruyama scheme with step size Δ, and written in vectorial form as

$$\begin{aligned} \Delta V_{0:n} &= \Delta(-g_L(V_L - V_{0:n}) - \mathrm{diag}(V_e - V_{0:n}) K_e I_{e0:n} + \mathrm{diag}(V_i - V_{0:n}) K_i I_{i0:n} - I) \\ &\quad + \sigma \varepsilon_{0:n} \end{aligned}$$

where $\mathrm{diag}(V_s - V_{0:n})$ is a diagonal matrix with the kth diagonal term being $V_s - V(t_k)$, and K_s is a convolution matrix operating as described in (6). Then the problem of estimating $I_{e0:n}$ and $I_{i0:n}$ reduces to a linear estimation problem with Gaussian noise, under the constraints that $I_{e0:n}$ and $I_{i0:n}$ are non-negative. Concatenating all the shape matrices ($(V_L - V_{0:n})$ or $\mathrm{diag}(V_s - V_{0:n}) K_s$) in $\mathbf{J}$ and the parameter vectors in $\mathbf{a} = (g_L, I_{e0:n}, I_{i0:n}, I)$, the model can be written

$$\Delta V_{0:n} = \mathbf{J}\mathbf{a} + \sigma \varepsilon_{0:n}$$

A solution to this linear equation can be written as a constrained optimization

$$\widehat{\mathbf{a}} = \arg \min_{\mathbf{a}, a_i \ge 0} ||\Delta V_{0:n} - \mathbf{J}\mathbf{a}||^2.$$

As emphasized by Paninski et al. (2010), this is equivalent to solving a penalized criteria

$$\widehat{\mathbf{a}} = \arg\min_{\mathbf{a}} ||\Delta V_{0:n} - \mathbf{J}\mathbf{a}||^2 + \lambda \ \mathrm{pen}(\mathbf{a}),$$

where λ is a tuning parameter and pen is a penalty function. Paninski et al. (2010) suggest $\mathrm{pen}(\mathbf{a}) = \sum_i \log(a_i)$ (they call this approach the log-barrier method).

As an alternative to this linear optimization, Paninski et al. (2012) use a particle filter to infer the hidden synaptic inputs $I_e(t)$ and $I_i(t)$. Particle filters have been widely developed in the HMM context, which is the case here because the hidden presynaptic inputs $I_e(t)$ and $I_i(t)$ are autonomous and do not depend on $V(t)$. We refer the reader to Cappé et al. (2005) for a general presentation.

Parameter estimation Paninski et al. (2010) also consider the estimation of θ, but they now assume that the input signals $I_e(t)$ and $I_i(t)$ are known. They assume noisy measurements $y_{0:n}$ of $V_{0:n}$. This simplifies the statistical problem in the sense that it enters the well-known framework of HMMs. The likelihood is

$$p(y_{0:n};\theta) = \int p(y_{0:n}|V_{0:n};\theta)p(V_{0:n};\theta)dV_{0:n}.$$

One would like to optimize the log-likelihood, namely computing

$$\arg\max_{\theta} \log p(y_{0:n};\theta).$$

They replace this optimization by the related problem of the joint optimization of

$$\arg\max_{\theta}\max_{V} (\log p(y_{0:n}|V;\theta) + \log p(V;\theta))$$

As this function is jointly quadratic in (V,θ), they use a single step of Newton's method.

As an alternative, Paninski et al. (2012) couple an EM algorithm to a particle filter. The particle filter is used to infer the hidden synaptic inputs $I_e(t)$ and $I_i(t)$ (see above). Using inferred (or simulated) synaptic inputs, the M step of the EM algorithm consists in maximizing the log likelihood of the complete trajectories $(V(t), g_e(t), g_i(t))$. This is performed using a Newton-Raphson or a conjugate gradient ascent method. No asymptotic variance of these estimators have been described. It should be possible to compute the Fisher Information Matrix based on the EM algorithm and the Louis's principle (Louis, 1982) .

Presynaptic conductance and parameter estimation To the best of our knowledge, there is no known method to jointly estimate the parameters and the presynaptic conductance in model (3). Note that identifiability issue arises and at least the parameters of the first equation in (3) should be considered as known. The only reference we found is Berg and Ditlevsen (2013) where only the first equation for the membrane potential in (3) is considered, with the conductances $g_e(t)$ and $g_i(t)$ time-varying functions, which should be estimated. They propose to make a moving window, within which the process is assumed approximately stationary. Inside this window the process is approximated by an Ornstein-Uhlenbeck process, and the time constant and the asymptotic mean are estimated, either by fitting the empirical autocorrelation function to a mono-exponential decay, or by maximum likelihood with subsampling to correct for the short time scales, where the model is not suitable. The estimates can be used to identify the two conductances, assumed constant within the window. By sweeping through the data trace, time-varying synaptic input conductances are estimated.

4. Voltage conductance based model

In the previous models, only subthreshold fluctuations are modeled, and spikes are either ignored or imposed by a point event triggered by high membrane potential values. In the following models, the membrane voltage dynamics, also during spiking activity, is modeled by a membrane equation driven by voltage conductances. The model is given by

$$CdV(t) = \Big(-g_L(V(t)-V_L) - \sum_c \bar{g}_c f_c(t)(V(t)-V_c) - I\Big)dt + \sigma dW(t) \qquad (7)$$

where $W(t)$ is a Brownian motion, σ is the diffusion coefficient, g_L is the leak conductance, $\bar{g}_c$ are maximal membrane conductances for several conductance types c (like K, Na or Ca), functions f_c represent the time-varying open fraction of the c-ion channel, and is typically given by complex, highly nonlinear functions of time and voltage. For example, for the K^+ channel in the model introduced by Morris and Lecar (1981), the kinetics are given by $f_K(t) = U(t)$ with

$$dU(t) = (\alpha_U(V(t))(1-U(t)) - \beta_U(V(t))U(t))dt + \sigma_U(V(t),U(t))dW_U(t) \qquad (8)$$

where $W_U(t)$ is a Brownian motion, $\sigma_U(\cdot)$ is the diffusion coefficient function (the simplest case is $\sigma_U(v,u) = \sqrt{u(1-u)}$), and $\alpha_U(v)$ and $\beta_U(v)$ are non-linear functions of v, depending on some parameters ϕ. We set $C = 1$ for parameter identifiability. Unknown parameters are $\theta = (g_L, \bar{g}_c, V_L, V_c, I, \phi, \sigma^2, \sigma_c^2)$.

Estimation of θ has been considered assuming both noisy and exact observations of $V_{0:n}$. Counter-intuitively, noisy observations provide simpler estimation approaches. The two situations are now detailed.

Noisy observations of the membrane potential With noisy observations $y_{0:n}$ of the voltage $V_{0:n}$, the model enters the HMM framework. This has been considered by Kostuk et al. (2012) and Huys and Paninski (2009). Both papers approximate the transition density of the SDE with a Gaussian Euler-Maruyama scheme.

Kostuk et al. (2012) estimate the parameters with an MCMC algorithm. The authors notice a bias in the parameter estimates. It could be due to the Euler-Maruyama scheme, which induces a bias when the data are low frequency. Then, as noticed by Roberts and Stramer (2001), a data augmentation scheme should be used. This has been underlined again by Jensen et al. (2012) in the case of a 2-dimensional neural FitzHugh Nagumo-model, assuming no observation noise and both components observed (which is not plausible working with real data). We refer to Roberts and Stramer (2001); Papaspiliopoulos et al. (2013) for more details on data augmentation.

Huys and Paninski (2009) focus on parameters in the membrane potential equation, assuming known all the parameters entering the voltage conductance equations (called ϕ in the description above). Then they propose an EM algorithm coupled to a standard particle filter. As already said, particle filters have been widely developed in the HMM context. As Huys and Paninski (2009) focus on parameters of the first observed component, the conditional expectation (E step) is Gaussian and the maximization step of the EM algorithm reduces to a linear optimization. No asymptotic variance of these estimators have been described. This should be possible based on the EM algorithm.

Direct observations of the membrane potential Huys and Paninski (2009) consider this case assuming deterministic kinetics of the voltage conductances ($\sigma_U = 0$ in (8)). They also assume all the parameters involved in these kinetics known, thus the voltage conductances can be computed with an Euler discretization scheme given the observations of $V_{0:n}$. The estimation problem of the parameter $\mathbf{a} = (g_L, \bar{g}_c, V_L, V_c, I)$ then reduces to a linear problem, similarly to the synaptic conductance model. It can be written

$$\Delta V_{0:n} = \mathbf{J}\mathbf{a} + \sigma \varepsilon_{0:n}$$

where $\mathbf{J}$ is the regressor matrix. The optimization in $\mathbf{a}$ is performed under constraints on $\mathbf{a}$, since the conductances are non-negative. Thus, it is a constraint optimization problem

$$\widehat{\mathbf{a}} = \arg \min_{\mathbf{a}, a_i \geq 0} ||\Delta V_{0:n} - \mathbf{J}\mathbf{a}||^2.$$

Ditlevsen and Samson (2014) consider the conductance based model when voltage conductance kinetics are assumed to be deterministic. They focus on the two-dimensional Morris-Lecar model, which has only one hidden conductance channel (8). Unlike in Huys and Paninski (2009), this model does not enter the class of HMMs, because the hidden component is not autonomous. Ditlevsen and Samson (2014) propose an estimation method which also includes the estimation of an unknown parameter in the conductance kinetics and with stochastic kinetics and provide standard errors of the estimators. Their method is based on an EM algorithm coupled to a particle filter. Particle filters, which have been developed in the HMM context, can not be used in this case, as it could in Huys and Paninski (2009), because the transition density entering in the computation of the weights does not depend only of the hidden components, but also on the observations. Ditlevsen and Samson (2014) propose a particle filter to this non-autonomous hidden state. Then the maximization step is also linear, like Huys and Paninski (2009), because only linear parameters entering both the $V(t)$ and the $U(t)$ equations are estimated. Ditlevsen and Samson (2014) prove the convergence of their algorithm, which requires the number of particles to increase at a logarithmic rate with the iterations of the EM algorithm.

5. Conclusion

The estimation problem in stochastic diffusion neuronal models from intracellular recordings of the membrane potential evolution becomes more difficult the more realistic the model is. For one-dimensional models the problem is relatively straightforward, since only the observed component enters the model. The complications here arise because of lack of fit, for example the time course of the action potential does not enter the model and has to be cut out of the data. Also the different time scales present in the data (but not in the model) can cause problems, and it is important to be aware on what time scales the one-dimensional models are appropriate. Notwithstanding these problems, the one-dimensional models can still be useful approximations and reproduce many of the statistical characteristics of the neuronal dynamics. For example they can serve as building blocks for network models where more biophysical models would be entirely intractable.

For multi-dimensional models, where unobserved components such as channel dynamics or synaptic input enter the equations, the estimation problem is more complex, and not all parameters can be estimated from only partial observations, either because of identifiability issues of the model itself, or because there is not enough information in the data inducing a large variance of the estimates. It is then important to remember that conclusions and results depend on the assumptions of the model, and which parameters are assumed known, as well as their presumed specific values. The multi-dimensional and non-linear models are also difficult to handle because the likelihood is not tractable, and the statistical machinery is complex. Often approximations assuming Gaussian distributions are employed, which facilitates the estimation procedure a lot, but comes at a price of loosing precision and tail behaviors. Moreover, in Gaussian and linear models often fewer parameters are identifiable. In the future, numerical sampling such as Particle MCMC (Andrieu et al., 2010) could be an alternative to estimate parameters of these models. Research interest is now on how estimating parameters from complex hypoelliptic system, that might have multi-dimensional hidden states.

Several models have been proposed but very few papers deal with model validation or model choice. When the likelihood is computable, models could be compared with standard criteria such as AIC or BIC, even if it is not commonly done in this field. Recently, tests have been developed for extra-cellular data (Albert et al., 2015). For model validation with intra-cellular data, tools from stochastic process theory such as uniform residuals (Pedersen, 1994) could be employed, but it is not yet commonly done in this field.

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