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

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Abstract

Dynamics of the membrane potential in a single neuron can be studied 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. More 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.

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, 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 in-

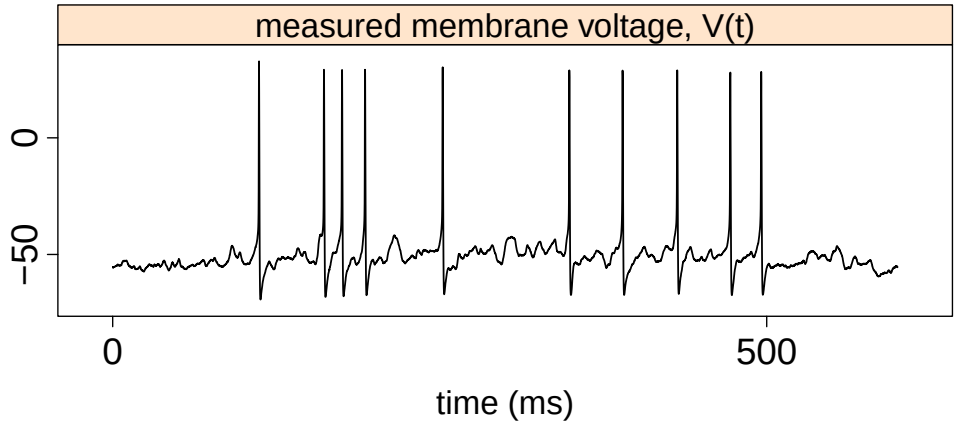

Figure 1: Observations of the membrane potential in a spinal motoneuron of an adult red-eared turtle during 600 ms measured every 0.1 ms. Data from Berg Laboratory, see Berg *et al.* (2007).

hibitory or excitatory synaptic input. If $d = 1$ then $X_t = V_t$. Here, $b(x)$ is the drift function taking values in $\mathbb{R}^d$, $\Sigma(x)$ 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).

2 Models

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

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

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

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

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, whereas in the real system, a spike takes a couple of miliseconds. If measuring around every 0.1 ms, as is costumary, 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. In Lansky *et al.* (2006) they 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 $\mu > 0$ such 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 exist always. 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; $b(v,t;\theta) = -\beta(t)v + \mu(t)$.

In Picchini *et al.* (2008) the model is extended 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.

In Paninski *et al.* (2005) a more involved model is proposed, 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 $v_0 \geq V_I$. In Bibbona *et al.* (2010) estimation methods for the Feller process are reviewed and compared 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 $\hat{\rho} = -\log\Delta/\hat{\tau}$.

In Hoepfner (2007) a kernel estimator is applied 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.

In Lanska and Lansky (1998) a model of type (1) is derived 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,

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

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

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

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

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 on 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 on all components has not been treated much in the literature.
In the next two subsections, we focus on model (3) with noise only on the hidden components ($\sigma = 0$), which has been considered by Rudolph and Destexhe (2003); Destexhe *et al.* (2004); Rudolph *et al.* (2004a,b); 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 on 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.*, 2004a,b; 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:

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

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 it. However, it is emphasized by Rudolph *et al.* (2004a) that since $\rho(v,t)$ is highly non-linear in θ, the maximization procedure may not converge. They instead propose to approximate $\rho(v,t)$ with a Gaussian distribution, which corresponds to a second-order Taylor expansion of (4):

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

where $\bar{V}$ and σ_V^2 are functions of θ (see Rudolph *et al.*, 2004a, 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.* (2004a) 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 can be studied.
Following Rudolph *et al.* (2004a), 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 can be 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 $p_k = p(g_e(t_{k+1}), g_i(t_{k+1})|g_e(t_k), g_i(t_k))$,

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

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 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 synaptic conductance equations written as

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

where $I_e(t)$ and $I_i(t)$ are (random) presynaptic inputs 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 **[[ADELINE: And also lacks to multiply by the length of the discretization interval?] [SUSANNE: If I understood well their paper, it is not multiply by the length of the interval. But I agree with you]]**

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

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 $\text{diag}(V_s - V_{0:n})K_s$) 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

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

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

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

where λ is a tuning parameter and pen is a penalty function. Paninski *et al.* (2010) suggest $\text{pen}(\mathbf{a}) = \sum_i \log(a_i)$ (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 claim that this optimization reduces to the joint optimization of

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

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.

Presynaptic conductance and parameter estimation In Berg and Ditlevsen (2013) 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

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

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 Morris-Lecar K^+ channel, 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, 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 problem of simultaneous estimation of the diffusion coefficient and of the hidden path, noticed by Roberts and Stramer (2001). Then, 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.

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. Their method is based on an EM algorithm coupled to a particle filter. Standard 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). Ditlevsen and Samson (2014) extend 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.

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