SEQUENTIAL ESTIMATION OF GATING VARIABLES FROM VOLTAGE TRACES IN SINGLE-NEURON MODELS BY PARTICLE FILTERING

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ABSTRACT

This paper addresses the problem of inferring voltage traces and ionic channel activity from noisy intracellular recordings in a neuron. A particle filtering method with optimal importance density is proposed to that aim, with the benefits of on-line estimation methods and Bayesian filtering theory. The method is applied to an inaccurate Morris-Lecar neuron model without loss of generality. Simulation results show the validity of the approach, where it is observed that theoretical estimation bounds are attained.

Index Terms— Neuroscience, dynamical systems, particle filtering.

1. INTRODUCTION

The membrane potential, obtained from intracellular recordings, is one of the most valuable signals of neurons' activity. Most of the neuron models have been derived from fine measurements and allow the progress of "in silico" experiments. However, other interesting quantities informing about the neuron's intrinsic activity or synaptic connections [1, 2] are either costly to obtain (channel blocking and clamping techniques [3, 4]) or impossible to measure explicitly with today's techniques. Thus, estimation methods can be very useful, mostly those that can be applied to obtain time evolution on-line; that is, avoiding the need of repetitions that could be contaminated by neuronal variability. In this paper, as a first step, we concentrate on methods to extract intrinsic activity of ionic channels, namely the probabilities of opening and closing channels. To this purpose, we consider a neuron model and, using a particle filtering (PF) algorithm with optimal importance density, we recover both the membrane potential and the activity of the potassium channel with the minimum attainable error.

The remainder of the paper is organized as follows. In Section 2 we introduce a neuron model to motivate the work, namely the model named after Morris and Lecar. The practical problem is stated in Section 3 and the resulting PF solution explained in Section 4. The main causes of model inaccuracies are enumerated in Section 5, as well as hints to account for them in the method. Section 6 discusses computer simulations, with comparison to the theoretical estimation bounds, and Section 7 concludes the paper.

2. SINGLE-NEURON MODEL WITH IONIC CHANNELS

From the myriad of existing single-neuron models, we consider the Morris-Lecar model proposed in [5]. The model can be related (see [6]) to the $I_{\mathrm{Na,p}} + I_{\mathrm{K}}$-model (pronounced persistent sodium plus potassium model). The dynamics of the neuron is modeled by a continuous-time dynamical system composed of the current-balance equation for the membrane potential, $v = v(t)$, and the K$^+$ gating variable $0 \leq n = n(t) \leq 1$, which represents the probability of the K$^+$ ionic channel to be active. Then, the system of differential equations is

$$\begin{aligned} C_m \dot{v} &= -I_{\mathrm{L}} - I_{\mathrm{Ca}} - I_{\mathrm{K}} + I_{app} \qquad (1) \\ \dot{n} &= \phi \frac{n_\infty(v) - n}{\tau_n(v)} \,, \qquad (2) \end{aligned}$$

where C_m is the membrane capacitance and ϕ a non-dimensional constant. I_{app} represents the (externally) applied current. The leakage, calcium, and potassium currents are of the form $I_{\mathrm{L}} = g_{\mathrm{L}}(v - E_{\mathrm{L}})$, $I_{\mathrm{Ca}} = g_{\mathrm{Ca}} m_\infty(v)(v - E_{\mathrm{Ca}})$, and

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$I_{\rm K} = g_{\rm K} n(v - E_{\rm K})$, respectively. $g_{\rm L}$, $g_{\rm Ca}$, and $g_{\rm K}$ are the maximal conductances of each current. $E_{\rm L}$, $E_{\rm Ca}$, and $E_{\rm K}$ denote the Nernst equilibrium potentials, for which the corresponding current is zero, a.k.a. reverse potentials.

The dynamics of the activation variable m is considered at the steady state, and thus we write $m = m_\infty(v)$. On the other hand, the time constant $\tau_n(v)$ for the gating variable n cannot be considered that fast and the corresponding differential equation needs to be considered. The formulae for these functions is $m_\infty(v) = \frac{1}{2} \cdot (1 + \tanh[\frac{v-V_1}{V_2}])$, $n_\infty(v) = \frac{1}{2} \cdot (1+\tanh[\frac{v-V_3}{V_4}])$, and $\tau_n(v) = 1/(\cosh[\frac{v-V_3}{2V_4}])$, which parameters V_1, V_2, V_3, and V_4 can be measured experimentally [6].

The knowledgeable reader would have noticed that the Morris-Lecar model is a Hodgin-Huxley type-model with the usual considerations, where the following two extra assumptions were made: the depolarizing current is generated by Ca^{2+} ionic channels (or Na^{+} depending on the type of neuron modeled), whereas hyperpolarization is carried by K^{+} ions; and that $m = m_\infty(v)$. The Morris-Lecar model is very popular in computational neuroscience as it models a large variety of neural dynamics while its phase-plane analysis is more manageable as it involves only two states [7].

3. PROBLEM STATEMENT

The problem investigated in this paper considers recordings of noisy voltage traces to infer the hidden gating variables of the neuron model, as well as filtered voltage estimates. Data is recorded at discrete time-instants at a sampling frequency $f_s = 1/T_s$. The problem can thus be posed in the form of a discrete-time, state-space model. The observations are

$$y_t \sim \mathcal{N}(v_t, \sigma^2_{y,t}) \ , \tag{3}$$

with $\sigma^2_{y,t}$ modeling the noise variance due to the sensor or the instrumentation inaccuracies when performing the experiment. To provide comparable results, we define the signal-to-noise ratio (SNR) as $\mathrm{SNR} = P_s/P_n$, with P_s being the average signal power and $P_n = \sigma^2_{y,t}$ the noise power.

On the other hand, we have models for the evolution of the voltage-traces and the hidden variables of a neuron. For instance, the Morris-Lecar model presented in Section 2. The unknown state vector in this case is $\mathbf{x}_t = (v_t, n_t)^T$. Notice that the presented neuron model is defined by a set of continuous-time, ordinary differential equations (ODE). However, we are interested in expressing the model in the general, sequential form $\mathbf{x}_t = f_t(\mathbf{x}_{t-1}) + \nu_t$, where $\nu_t \sim \mathcal{N}(\mathbf{0}, \mathbf{\Sigma}_{x,t})$ is the process noise which includes the model inaccuracies. The covariance matrix $\mathbf{\Sigma}_{x,t}$ is used to quantify our confidence in the model $f_t : \{v_{t-1}, n_{t-1}\} \mapsto \{v_t, n_t\}$. If we focus on the Morris-Lecar model, the resulting discrete version of the ODE system in (1)-(2) is:

$$\begin{aligned} v_t &= v_{t-1} - \frac{T_s}{C_m}\left(g_{\rm L}(v_{t-1} - E_{\rm L})\right. \\ &+ g_{\rm Ca} m_\infty(v_{t-1})(v_{t-1} - E_{\rm Ca}) \\ &+ \left. g_{\rm K} n_{t-1}(v_{t-1} - E_{\rm K}) - I_{app}\right) \quad (4) \\ n_t &= n_{t-1} + \phi \frac{n_\infty(v_{t-1}) - n_{t-1}}{\tau_n(v_{t-1})} \ , \quad (5) \end{aligned}$$

4. SEQUENTIAL ESTIMATION OF GATING VARIABLES BY PARTICLE FILTERING

Bayesian filtering involves the recursive estimation of states $\mathbf{x}_t \in \mathbb{R}^{n_x}$ given measurements $y_t \in \mathbb{R}^{n_y}$ at time t based on all available measurements, $y_{1:t} = \{y_1, \dots, y_t\}$. To that aim, we are interested in the filtering distribution $p(\mathbf{x}_t|y_{1:t})$, which can be recursively expressed as

$$p(\mathbf{x}_t|y_{1:t}) = \frac{p(y_t|\mathbf{x}_t)p(\mathbf{x}_t|\mathbf{x}_{t-1})}{p(y_t|y_{1:t-1})} p(\mathbf{x}_{t-1}|y_{1:t-1}) \ , \tag{6}$$

with $p(y_t|\mathbf{x}_t)$ and $p(\mathbf{x}_t|\mathbf{x}_{t-1})$ referred to as the likelihood and the prior distributions, respectively. Unfortunately, (6) can only be obtained in closed-form in some special cases and in more general setups we should resort to more sophisticated methods. In this paper we consider PF to overcome the nonlinearity of the model [8].

PFs approximate the filtering distribution by a set of N weighted random samples, forming the random measure $\left\{\mathbf{x}_t^{(i)}, w_t^{(i)}\right\}_{i=1}^N$. These random samples are drawn from the importance density distribution, $\pi(\cdot)$,

$$\mathbf{x}_t^{(i)} \sim \pi(\mathbf{x}_t|\mathbf{x}_{0:t-1}^{(i)}, y_{1:t}) \tag{7}$$

and weighted according to the general formulation

$$w_t^{(i)} \propto w_{t-1}^{(i)} \frac{p(y_t|\mathbf{x}_{0:t}^{(i)}, y_{1:t-1}) p(\mathbf{x}_t^{(i)}|\mathbf{x}_{t-1}^{(i)})}{\pi(\mathbf{x}_t^{(i)}|\mathbf{x}_{0:t-1}^{(i)}, y_{1:t})} \ . \tag{8}$$

The importance density from which particles are drawn is a key issue in designing efficient PFs. It is well-known that the optimal importance density is $\pi(\mathbf{x}_t|\mathbf{x}_{0:t-1}^{(i)}, y_{1:t}) = p(\mathbf{x}_t|\mathbf{x}_{t-1}^{(i)}, y_t)$, in the sense that it minimizes the variance of importance weights. Weights are computed using (8) as $w_t^{(i)} \propto w_{t-1}^{(i)} p(y_t|\mathbf{x}_{t-1}^{(i)})$. This choice requires the ability to draw from $p(\mathbf{x}_t|\mathbf{x}_{t-1}^{(i)}, y_t)$ and to evaluate $p(y_t|\mathbf{x}_{t-1}^{(i)})$. In general, the two requirements cannot be met and one needs to resort to suboptimal choices. However, we are able to use the optimal importance density since the state-space model assumed here is Gaussian, with nonlinear process equations but related linearly to observations [9]. The equations are:

$$p(\mathbf{x}_t|\mathbf{x}_{t-1}^{(i)}, y_t) = \mathcal{N}(\boldsymbol{\mu}_{\pi,t}^{(i)}, \mathbf{\Sigma}_{\pi,t}) \tag{9}$$

with

$$\boldsymbol{\mu}_{\pi,t}^{(i)} = \boldsymbol{\Sigma}_{\pi,t}\left(\boldsymbol{\Sigma}_{x,t}^{-1} f_t(\mathbf{x}_{t-1}^{(i)}) + \frac{y_t}{\sigma_{y,t}^2}\right) \quad (10)$$

$$\boldsymbol{\Sigma}_{\pi,t} = \left(\boldsymbol{\Sigma}_{x,t}^{-1} + \sigma_{y,t}^{-2}\mathbf{I}\right)^{-1} , \quad (11)$$

and the importance weights can be updated using

$$p(y_t|\mathbf{x}_{t-1}^{(i)}) = \mathcal{N}(\mathbf{h} f_t(\mathbf{x}_{t-1}^{(i)}), \mathbf{h}\boldsymbol{\Sigma}_{x,t}\mathbf{h}^T + \sigma_{y,t}^2) , \quad (12)$$

with $\mathbf{h} = (1, 0)$. The PF provides a discrete approximation of the filtering distribution of the form $p(\mathbf{x}_t|y_{1:t}) \approx \sum_{i=1}^N w_t^{(i)} \delta(\mathbf{x}_t - \mathbf{x}_t^{(i)})$, which gather all information from $\mathbf{x}_t$ that the measurements up to time t provide. For instance, the minimum mean square error estimator can be obtained as

$$\hat{\mathbf{x}}_t = \sum_{i=1}^N w_t^{(i)} \mathbf{x}_t^{(i)} , \quad (13)$$

where $\hat{\mathbf{x}}_t = (\hat{v}_t, \hat{n}_t)^T$. Recall that the method discussed in this section could be easily adapted to other neuron models simply substituting by the corresponding transition function f_t and constructing the state vector $\mathbf{x}_t$ conveniently.

As a final step, PFs incorporate a resampling strategy to avoid collapse of particles into a single state point. Resampling consists in eliminating particles with low importance weights and replicating those in high-probability regions [10].

5. MODEL INACCURACIES

The proposed estimation method highly relies on the fact that the neuron model is known. This is true to some extend, but most of the parameters in the model discussed in Section 2 are to be estimated beforehand. Therefore, the robustness of the method to possible inaccuracies should be assessed. In this section, we point out possible causes of missmodeling. In next section, computer simulations are used to characterize the performance of the method under these impairments.

In the single-neuron model considered, it can be identified three major sources of inaccuracies:

1. The applied current I_{app} can be itself noisy, with a variance depending on the quality of the instrumentation used and the experiment itself. We model the actual applied current as the random variable

   $$I_{app} = I_o + \nu_I \ , \ \nu_I \sim \mathcal{N}(0, \sigma_I^2) , \quad (14)$$

   where I_o is the nominal current applied and σ_I^2 the variance around this value. Plugging (14) into (4) we obtain that the contribution of I_{app} to the noise term is $\frac{T_s}{C_m}\nu_I \sim \mathcal{N}(0, (T_s/C_m)^2\sigma_I^2)$.

2. The conductance of the leakage term has to be estimated beforehand. In general, this term is considered constant although it gathers relatively distinct phenomena that can potentially be time-varying. The maximal conductance of the leakage term is therefore inaccurate and modeled as

   $$g_L = \bar{g}_L + \nu_g \ , \ \nu_g \sim \mathcal{N}(0, \sigma_g^2) , \quad (15)$$

   where $\bar{g}_L$ is the nominal, estimated conductance and σ_g^2 the variance of this estimate. Similarly, inserting (15) into (4) we see that the contribution of g_L to the noise term is $\frac{T_s}{C_m}\nu_g \sim \mathcal{N}(0, (T_s/C_m)^2(v_{t-1} - E_L)\sigma_g^2)$.

3. The parameters in $m_\infty(v_t)$, $n_\infty(v_t)$, and $\tau_n(v_t)$ are to be estimated. In general, these parameters are properly obtained by standard methods [6]. However, as they are estimates, a residual error typically remains. To account for these inaccuracies, we consider that the equation governing the evolution of gating variables is corrupted by a zero-mean additive white Gaussian process with variance σ_n^2.

At the end of the day, we came up with a way of constructing the model covariance matrix, as the contribution of the aforementioned inaccuracies. In a practical setup, in order to compute the noise variance due to leakage, we need to use the approximation $\hat{v}_{t-1} \approx v_{t-1}$, where $\hat{v}_{t-1}$ is computed by the filter in (13). We construct the covariance matrix of the model as

$$\boldsymbol{\Sigma}_{x,t} = \mathrm{diag}(\sigma_v^2, \sigma_n^2) , \quad (16)$$

where we used that the overall noise in the voltage model is $\frac{T_s}{C_m}(\nu_I - \nu_g) \sim \mathcal{N}(0, \sigma_v^2)$ and

$$\sigma_v^2 = \left(\frac{T_s}{C_m}\right)^2 \left(\sigma_I^2 + (\hat{v}_{t-1} - E_L)^2\sigma_g^2\right) . \quad (17)$$

6. RESULTS

We simulated data of a neuron of the type described in Section 2, i.e. following a Morris-Lecar model. Particularly, we generated 500 ms of data, sampled at $f_s = 4$ kHz. The model parameters were set to $C_m = 20$ μF/cm^2, $\phi = 0.04$, $V_1 = -1.2$ mV, $V_2 = 18$ mV, $V_3 = 2$ mV, and $V_4 = 30$ mV; the reverse potentials were $E_{\mathrm{L}} = -60$ mV, $E_{\mathrm{Ca}} = 120$ mV, and $E_{\mathrm{K}} = -84$ mV; and the maximal conductances were $g_{\mathrm{Ca}} = 4.4$ mS/cm^2 and $g_{\mathrm{K}} = 8.0$ mS/cm^2. We considered a measurement noise with a standard deviation of 1 mV.

In the simulations we considered the aforementioned model inaccuracies. To excite the neuron into spiking activity a nominal applied current was injected with $I_o = 110$ μA/cm^2 and two values for σ_I where considered, namely 1% and 10% of I_o. The nominal conductance used in the model was $\bar{g}_{\mathrm{L}} = 2$ mS/cm^2, whereas the underlying neuron had a zero-mean Gaussian error with standard deviation $\sigma_{g_{\mathrm{L}}}$. Two variance values where considered as well, 1% and 10% of

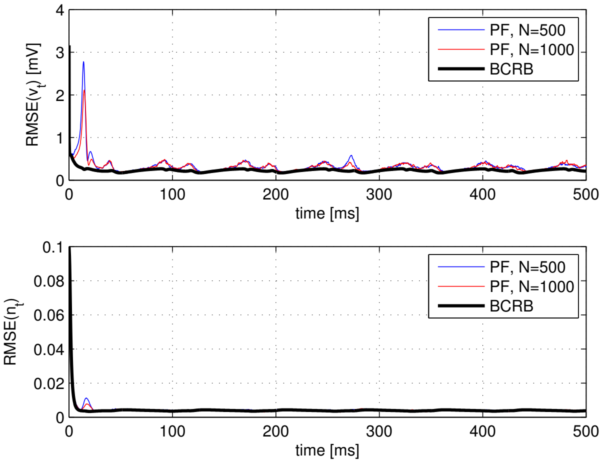

Fig. 1. Evolution of the RMSE and the BCRB over time. Model inaccuracies where $\sigma_I = 0.01 \cdot I_o$ and $\sigma_{g_{\mathrm{L}}} = 0.01 \cdot \bar{g}_{\mathrm{L}}$.

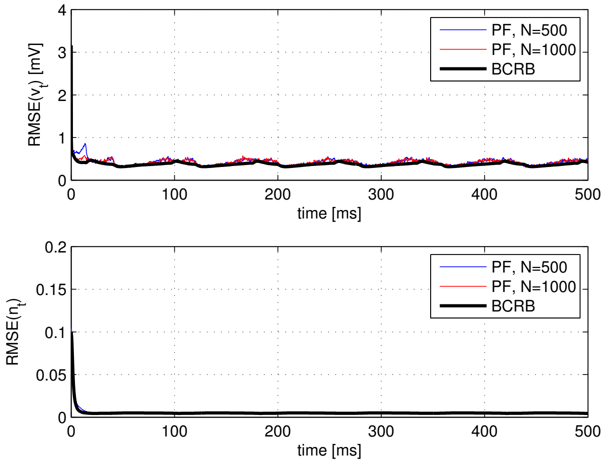

Fig. 2. Evolution of the RMSE and the BCRB over time. Model inaccuracies where $\sigma_I = 0.1 \cdot I_o$ and $\sigma_{g_{\mathrm{L}}} = 0.1 \cdot \bar{g}_{\mathrm{L}}$.

$\bar{g}_{\mathrm{L}}$. Finally, we considered $\sigma_n = 10^{-3}$ in the dynamics of the gating variable.

In order to evaluate the efficiency of the proposed estimation method, we computed the Bayesian Cramér-Rao Bound (BCRB) according to the recursive formulation given in [11], which we plot as a benchmark for the Root Mean Square Error (RMSE) curves obtained by computer simulations after 200 independent Monte Carlo trials. Figures 1 and 2 show the time course of the RMSE using $N = \{500, 1000\}$ particles and the BCRB. We see that in both scenarios, our method attains the BCRB and thus is efficient. We measure the efficiency ($\eta \geq 1$) of the method as the quotient between the RMSE and the BCRB, averaged over the entire simulation time. The worse efficiency on estimating v_t was 1.43 corresponding to 500 particles and 10% of inaccuracies, the best was 1.11 for 1000 particles and 1% of errors. In estimating n_t the discrepancy was even lower, 1.06 and 1.03 for maximum and minimum η. To sum up, the PF approaches the BCRB with the number of particles and the performance (both theoretical and empirical) can be improved if model inaccuracies are reduced, i.e., if the model parameters are better estimated at a previous stage.

7. CONCLUSIONS

In this paper we proposed a particle filtering method with optimal importance density that is able to sequentially infer the time-course of the membrane potential and the intrinsic activity of ionic channels from noisy observations of voltage traces. The results show the validity of the approach. The procedure can be applied to any neuron model. Forthcoming applications would be: i) validating the method using real data recordings; ii) combining the presented algorithm with fittings of voltage traces to neuron models; iii) adding synaptic terms to the neuron model and use our method to infer the synaptic conductances. The latter problem is a challenging hot topic in the neuroscience literature, which is recently focusing on methods to extract the conductances from single-trace measurements, [2], [12]. We think that our PF method would give useful and interesting results to physiologists that aim at inferring brain's activation rules from neurons' activities.

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