

## State Estimation Problem for the Action Potential Modeling in Purkinje Fibers

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### Abstract

In this work we use the Particle Filter Method to solve a state estimation problem resulting from the application of Hodgkin-Huxley's model to Purkinje fibers, by applying Liu and West's Auxiliary Sampling Importance Resampling (ASIR) algorithm. This algorithm allows the simultaneous estimation of state variables and parameters. The estimation of the action potential in Purkinje fibers can be related to the identification of heart anomalies. The use of Bayesian particle filters is of great interest for such specific application, since they take into account uncertainties in the mathematical models for the evolution of the state variables and the measurements. Simulated measurements are used in this work to examine the accuracy of the Particle Filter Method under analysis.

**Keywords:** Particle Filters, Bayesian estimate, Hodgkin-Huxley's model, Purkinje fibers.

### Introduction

Hodgkin and Huxley (1952) proposed a model for the action potential in an axon, in terms of an electric circuit with capacitance and ionic currents. Sodium and potassium ions are the most important in the action potential and are distinguished in terms of their own proper currents, in comparison to the other ions. The model involves a non-linear system of four ordinary differential equations, whose coefficients are given in terms of functions of the applied potential. Although Hodgkin-Huxley's model has been originally proposed for the experimental data involving an axon, it has also been used to model the action potential in heart cells, like Purkinje fibers (Noble, 1962).

State estimation problems are dynamically solved within the Bayesian framework (Kaipio and Somersalo, 2004; Arulampalam et al., 2001). In this framework, an attempt is made to utilize all available information in order to reduce the amount of uncertainty present in inferential or decision-making problems. As new information is obtained, it is combined with previous information to form the basis for statistical procedures. The formal mechanism that combines the new information with the previously available information is known Bayes' theorem (Kaipio and Somersalo, 2004). Monte Carlo methods have been developed in order to represent the posterior density in terms of random samples and associated weights and can be applied to non-linear models with non-Gaussian errors (Kaipio and Somersalo, 2004; Arulampalam et al., 2001; Ristic et al., 2004; Doucet et al., 2001; Orlande et al., 2012), such as the one under analysis in this work.

In this paper we extend our previous work (Estumano et al., 2013) in order to compare the results obtained with the Sampling Importance Resampling (SIR) algorithm and the Auxiliary Sampling Importance Resampling (ASIR) algorithm (Kaipio and Somersalo, 2004; Arulampalam et al., 2001; Ristic et al., 2004; Doucet et al., 2001), to results obtained with the algorithm proposed by Liu and West (2001). This paper is focused on the use of Hodgkin-Huxley's models for the action potential in Purkinje Fibers (Noble, 1962). The three algorithms are compared in terms of their computational times and RMS errors. We note, beforehand, that Liu and West's algorithm is the most general of the three algorithms listed above, since uncertainties in the model parameters are taken into account through Gaussian kernel smoothing (Liu and West, 2001). Other recent applications of inverse

problems to Hodgkin-Huxley's model include the works of Dokos and Lovell (2004) and Meng et al. (2011).

### Hodgkin-Huxley's Model

Hodgkin and Huxley, in their classical paper of 1952, examined the behavior of an axon under the effects of an imposed electric current across the cell membrane. The cell electric potential was assumed to be independent of the position within the cell, that is, the intracellular electric resistance was neglected. In their experiments, Hodgkin and Huxley (1952) observed that the conductance of some ions across the cell membrane, like sodium and potassium, varied with changes in the axon's potential. The imposed electric current across the cell membrane was then modeled in terms of capacitive and ionic currents. Being the sodium and potassium ions recognized as the most important ones in this process, their currents were treated separately from those corresponding to the other ions, which were quantified in a global manner and referred to as leakage current. For the model, an inflow of ions was assumed as positive.

A basic difference between axons and Purkinje fibers results from the fact that in the last ones the potassium flow is governed by both a fast and a slow channel dynamics. In addition, the flow of ions other than sodium and potassium through the cell membrane can be neglected, so that the analogous electric circuit for the problem is presented in Figure 1. The imposed electric current is null for the case involving Purkinje fibers because these cells are auto-excitable (Noble, 1962). Therefore, the equation for the action potential in Purkinje fibers is given by (Noble, 1962):

$$C_m \frac{dV_m}{dt} + G_{Na} (V_m - V_{Na}) + G_K (V_m - V_K) = 0 \quad (1)$$

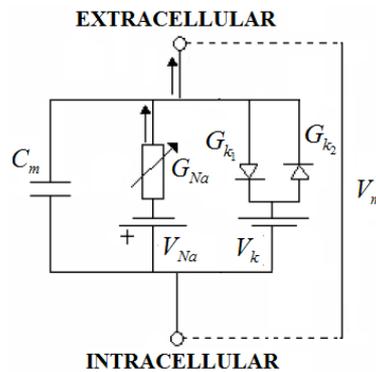


Figure 1. – Electric circuit for a Purkinje fibers (Noble, 1962)

The equations given by Noble (1962) for sodium and potassium conductances of a Purkinje fiber are given, respectively, by:

$$G_{Na} = G_{Na}^{max} m^3 h + G_{Na,l} \quad (2)$$

$$G_K = 1.2 \exp\left(-\frac{V_m + 90}{50}\right) + 0.015 \exp\left(\frac{V_m + 90}{60}\right) + 1.2n^4 \quad (3)$$

where  $m$  and  $n$  represent the open fraction, or probability of the channels being open, for sodium and potassium, respectively, while  $h$  is the probability of the channel being closed for the sodium ions. The variables  $m$  and  $n$  are also referred to as the *activations* of the ion transfer through the

cell membrane, while  $h$  is referred to as the *inactivation* for the sodium ion transfer. In equation (2),  $G_{Na}^{max}$  refers to the maximum sodium conductance.

Hodgkin and Huxley (1952) proposed the following ordinary differential equations to describe the ion channels opening/closing dynamics:

$$\frac{dm}{dt} = \alpha_m(1-m) + \beta_m m \quad \frac{dh}{dt} = \alpha_h(1-h) + \beta_h h \quad \frac{dn}{dt} = \alpha_n(1-n) + \beta_n n \quad (4-6)$$

The parameters for the computation of the activations  $m$  and  $n$  and inactivation  $h$  in Eq. (4)-(6) are given as (Noble, 1962):

$$\alpha_m = -0.1 \frac{V_m + 48}{\exp\left[-\frac{V_m + 48}{15}\right] - 1} \quad \beta_m = \frac{0.12(V_m + 8)}{\exp\left[\frac{V_m + 8}{5}\right] - 1} \quad \alpha_h = 0.17 \exp\left[-\frac{V_m + 90}{20}\right] \quad (7-9)$$

$$\beta_h = \left[ \exp\left(-\frac{V_m + 42}{10}\right) + 1 \right]^{-1} \quad \alpha_n = -\frac{10^{-4}(V_m + 50)}{\exp\left(-\frac{V_m + 50}{10}\right) - 1} \quad \beta_n = 0.002 \exp\left[-\frac{V_m + 90}{80}\right] \quad (10-12)$$

Other parameters for the application of Hodgkin-Huxley's model for a Purkinje fiber are presented in Table 1 (Estumano et al., 2013).

**Table 1. Parameters for Hodgkin-Huxley's model for Purkinje fiber**

Parameter	Values	Parameter	Values	Parameter	Values
$C_m (\mu F cm^{-2})$	12	$V_{Na} (mV)$	40	$G_{Na,l} (mS)$	0.14
$G_{Na}^{max} (mS)$	400	$V_k (mV)$	-100		

### State Estimation Problem

In order to define the state estimation problem, consider a model for the evolution of the vector  $\mathbf{x}$  in the form (Kaipio and Somersalo, 2004; Arulampalam et al., 2001; Ristic et al., 2004; Doucet et al., 2001; Orlande et al., 2012):

$$\mathbf{x}_k = \mathbf{f}_k(\mathbf{x}_{k-1}, \mathbf{v}_{k-1}) \quad (13)$$

where the subscript  $k = 1, 2, \dots$ , denotes a time instant  $t_k$  in a dynamic problem. The vector  $\mathbf{x} \in R^{n_x}$  is called the *state vector* and contains the variables to be dynamically estimated. This vector advances in accordance with the *state evolution model* given by Eq. (13), as a non-linear function of the state variables  $\mathbf{x}$  and of the *state noise* vector  $\mathbf{v} \in R^{n_v}$ . Consider also that measurements  $\mathbf{z}_k \in R^{n_z}$  are available at  $t_k$ ,  $k = 1, 2, \dots$ . The measurements are related to the state variables  $\mathbf{x}$  through the general function  $\mathbf{h}$  in the form

$$\mathbf{z}_k = \mathbf{h}_k(\mathbf{x}_k, \mathbf{n}_k) \quad (14)$$

where  $\mathbf{n} \in R^n$  is the *measurement noise*. Equation (14) is referred to as the *observation (measurement) model*.

The state estimation problem aims at obtaining information about  $\mathbf{x}_k$  based on the state evolution model (13) and on the measurements  $\mathbf{z}_{1:k} = \{\mathbf{z}_i, i = 1, K, k\}$  given by the observation model (14). The state estimation problem addressed in this work deals with Hodgkin-Huxley's model applied to Purkinje fibers. Therefore, the state variables are given by

$$\mathbf{x}^T = [V_m, m, h, n] \quad (15)$$

with state evolution models given by Eqs. (1) to (12). Measurements of the cell potential,  $V_m$ , are supposed available for the estimation of the state variables.

Due to its nonlinear character, the Particle Filter Method was used for the solution of the present state estimation problem (Kaipio and Somersalo, 2004; Arulampalam et al., 2001; Ristic et al., 2004; Doucet et al., 2001; Orlande et al., 2012). In this method, the required posterior density function is represented by a set of random samples (particles) with associated weights, which are then used for the sequential computation of its associated statistics. The particle filter algorithms generally make use of an *importance density*, which is proposed to represent another density that cannot be exactly computed, that is, the sought posterior density in the present case. Then, samples are drawn from the importance density instead of the actual density (Kaipio and Somersalo, 2004; Arulampalam et al., 2001; Ristic et al., 2004; Doucet et al., 2001; Orlande et al., 2012).

The set of particles from time  $t_0$  to time  $t_k$  is denoted as  $\{\mathbf{x}_{0:k}^i, i = 0, K, N\}$  and their associated weights as  $\{w_k^i, i = 0, K, N\}$ , where  $N$  is the number of particles. The weights are normalized, so

that  $\sum_{i=1}^N w_k^i = 1$ . The sequential application of the particle filter might result in the *degeneracy*

*phenomenon*, where after a few states very few particles have negligible weight (Kaipio and Somersalo, 2004; Arulampalam et al., 2001; Ristic et al., 2004; Doucet et al., 2001; Orlande et al., 2012). An attempt to overcome this difficulty is to use a resampling step in the application of the particle filter, where particles with small weights are discarded and particles with large weights are replicated. In the *Sampling Importance Resampling* (SIR) algorithm, resampling is applied every time step (Arulampalam et al., 2001; Ristic et al., 2004). Although the resampling step reduces the effects of the degeneracy problem, it may lead to a loss of diversity and the resultant sample may contain many repeated particles, which is more likely to occur in the case of small state evolution noise (Kaipio and Somersalo, 2004; Arulampalam et al., 2001; Ristic et al., 2004; Doucet et al., 2001; Orlande et al., 2012). In addition, in the SIR algorithm the state space is explored without the information conveyed by the measurements at the specific instant that the state variables are sought. With the *Auxiliary Sampling Importance Resampling* (ASIR) algorithm an attempt is made to overcome these limitations, by performing the resampling step at time  $t_{k-1}$ , with the available measurement at time  $t_k$  (Arulampalam et al., 2001; Ristic et al., 2004). The resampling is based on some point estimate  $\mu_k^i$  that characterizes  $\pi(\mathbf{x}_k|\mathbf{x}_{k-1}^i)$ , which can be the mean of  $\pi(\mathbf{x}_k|\mathbf{x}_{k-1}^i)$  or simply a sample of  $\pi(\mathbf{x}_k|\mathbf{x}_{k-1}^i)$ . If the state evolution model noise is small,  $\pi(\mathbf{x}_k|\mathbf{x}_{k-1}^i)$  is generally well characterized by  $\mu_k^i$ , so that the weights  $w_k^i$  are more even and the ASIR algorithm is less sensitive to outliers than the SIR algorithm. On the other hand, if the state evolution model noise is large, the single point estimate  $\mu_k^i$  in the state space may not characterize well  $\pi(\mathbf{x}_k|\mathbf{x}_{k-1}^i)$  and the ASIR algorithm may not be as effective as the SIR algorithm.

We note that the functions  $\mathbf{f}_k(\cdot)$  and  $\mathbf{h}_k(\cdot)$ , in the evolution and observation models, respectively, contain several constant parameters, here denoted as the vector  $\boldsymbol{\theta}$ . However, in general, such parameters are not deterministic or might not be deterministically known. Therefore, the samples need to be extended to  $\{\mathbf{x}_k^i, \boldsymbol{\theta}_k^i : i = 0, K, N\}$  with associated weights  $\{w_k^i : i = 0, K, N\}$ . In this work, the algorithm developed by Liu and West (2001), and based on the ASIR algorithm, is used for the solution of the state estimation problem, with the vector of state variables given by equation (15) and the vector of parameters given by:

$$\boldsymbol{\theta}^T = [C_m, G_{Na}^{max}, G_{Na,l}] \quad (17)$$

Such parameters were selected for the present analysis because they are the ones with larger variabilities in the open literature.

The algorithms of the SIR and ASIR filters, as well as the one due to Liu and West, can be found in Kaipio and Somersalo (2004), Arulampalam et al. (2001), Ristic et al. (2004), Liu and West (2001), Orlande et al. (2012), Colaço et al. (2012) and are not repeated here for the sake of brevity.

## Results and Discussion

In this paper, the three algorithms described above are compared in terms of their RMS errors and computational times, for cases dealing with axons and Purkinje fibers. The CPU times correspond to a computational code running under the Matlab platform, in an Intel i5 CPU with 6 Gb of RAM memory. The RMS error is computed as

$$RMS = \sqrt{\frac{1}{M} \sum_{i=1}^M [x_{est}(t_i) - x_{exa}(t_i)]^2} \quad (18)$$

where the subscripts *est* and *exa* denote the estimated and exact values of the state variable  $x(t_i)$  at time  $t_i$ , while  $M$  is the number of time steps. A similar definition was used to compute the RMS errors for each parameter  $\boldsymbol{\theta}$ . The RMS errors were compared in terms of the means of 100 repetitions of the particle filter estimates, in order to avoid any bias resulting from different sets of simulated measurements used in the analysis (Hamilton et al., 2013).

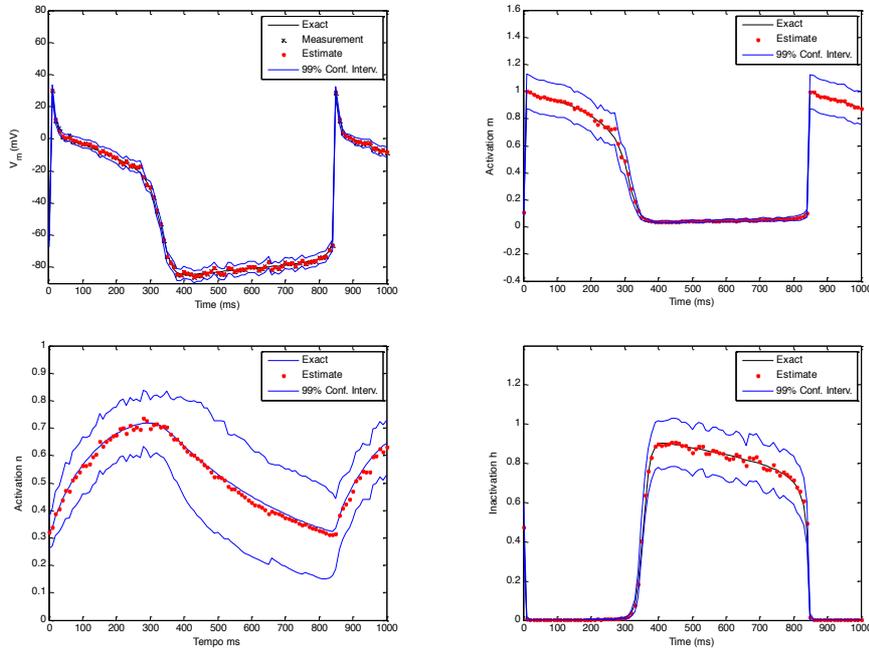
Simulated measurements of the cell potential,  $V_m$ , were utilized in the present work. Such measurements were generated from a numerical simulation of the deterministic dynamic problem for the Purkinje fibers. Errors in the simulated measurements were additive, uncorrelated, with a Gaussian distribution, zero mean and a constant standard deviation  $\sigma$ , so that the likelihood function at time  $t_k$  is given by

$$\pi(\mathbf{z}_k | \mathbf{x}_k) = \frac{1}{\sqrt{2\pi\sigma^2}} \exp \left\{ -\frac{1}{2\sigma^2} [V_m^{mod}(t_k) - V_m(t_k)]^2 \right\} \quad (19)$$

where the superscript *mod* refers to the measurement variable computed with the observation model given by Eq. (14). Simulated measurements were considered available in time intervals of 10 ms. For the results presented below, the parameters given by Eqs. (1) to (12) and Table 1 were used in the analysis. The initial conditions for these cases were taken as  $V_m(0) = -70mV$ ,  $m(0) = 0.079$ ,  $n(0) = 0.323$  and  $h(0) = 0.602$  (Estumano et al., 2013). The

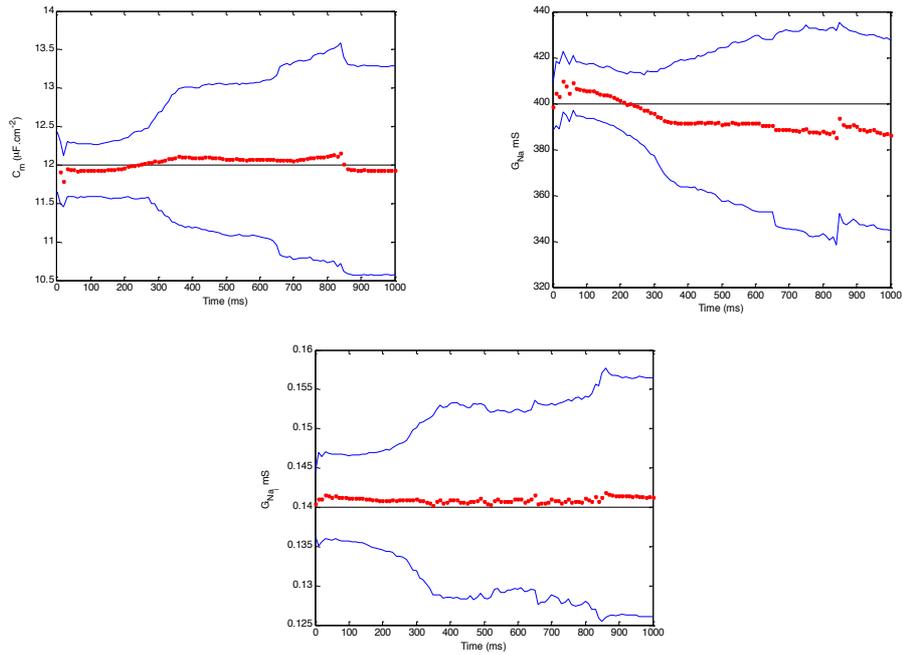
errors in the evolution model were additive, uncorrelated, with Gaussian distribution, zero mean and a constant standard deviation of 5% of the absolute value of the state variables at the initial time. The standard deviations of the measurements were taken as 5% of the maximum absolute value of the measured variable, that is,  $\sigma = 0.05|V_{m,max}|$ .

The results obtained for the estimation of the state variables and the model parameters with Liu and West's algorithm are presented in figures 2 and 3, respectively. Such results were obtained with 500 particles. Figure 2 shows an excellent agreement between exact and estimated state variables, even for those for which measurements are not available, such as  $m$ ,  $n$  and  $h$ . Similarly, uncertainties in the model parameters are appropriately taken into account as depicted from figure 3. Note in this figure that the exact values of the parameters fall within the confidence intervals of the estimates. Figures 2 and 3 reveals the robustness of Liu and West's algorithm as applied to the present problem, which was capable of accurately estimating state variables and model parameters, despite the large uncertainties in the evolution and measurement models, as well as in the model parameters.



**Figure 2: Estimation of the state variables**

Tables 2-4 present the RMS errors and the computational times for the three Particle filter algorithms examined in this work, for various numbers of particles ( $N_p$ ). Let us first examine tables 2 and 3, which present the results obtained with the SIR and the ASIR algorithms, respectively. Such algorithms deal only with the estimation of the state variables. These tables show, as expected, a reduction on the RMS errors, followed by an increase in the computational time, as the number of particles is increased. In addition, we notice in tables 2 and 3 that the RMS errors tend to approach a constant value as the number of particles is increased. According to tables 2 and 3, similar RMS errors were obtained with the ASIR algorithm by using less particles than those of the SIR algorithm. Although the ASIR algorithm is more expensive than the SIR algorithm in terms of computational time for the same number of particles, the ASIR algorithm is capable of providing accurate results with a much smaller number of particles. As a result, the computational times are smaller with the ASIR algorithm than with the SIR algorithm, for results of comparable accuracy.



**Figure 3: Estimation of the model parameters**

**Table 2: RMS errors and computational times for the SIR algorithm**

$N_p$	CPU Time (s)	$V_m$ (mV)	$m$	$n$	$h$
20	3.12	2.8126	0.0945	0.0806	0.0289
50	7.35	1.6984	0.0889	0.0743	0.0240
100	15.01	1.5899	0.0884	0.0698	0.0231
500	72.07	1.5811	0.0883	0.0669	0.0221
1000	140.08	1.5778	0.0882	0.0662	0.0221
2000	247.73	1.5769	0.0882	0.0662	0.0220

**Table 3: RMS errors and computational times for the ASIR algorithm**

$N_p$	CPU Time (s)	$V_m$ (mV)	$m$	$n$	$h$
50	15.91	1.4275	0.0902	0.0757	0.0191
100	48.00	1.4195	0.0901	0.0732	0.0182
200	111.03	1.4118	0.0900	0.0711	0.0174
300	205.77	1.4069	0.0900	0.0706	0.0173
400	332.19	1.4043	0.0900	0.0692	0.0170
500	485.80	1.4021	0.0900	0.0685	0.0170

The results obtained with Liu and West's algorithm (2001) are presented in table 4. A comparison of tables 3 and 4 reveal an increase on the computational time, for the same number of particles, when Liu and West's algorithm was used, caused by the simultaneous estimation of parameters and state variables. Anyhow, both state variables and parameters can be accurately estimated (see also figures 2 and 3) with this algorithm. In addition, the RMS error was reduced when the uncertainties on the parameters was taken into account, as compared to the original ASIR algorithm.

**Table 4: RMS errors and computational times for Liu and West's algorithm**

$N_p$	CPU Time (s)	$V_m$ (mV)	$m$	$n$	$h$	$C_m$ ( $\mu F cm^{-2}$ )	$G_{Na}$ (mS)	$G_{Na,l}$ (mS)
50	96.76	1.1360	0.0109	0.0133	0.0109	0.0621	5.2964	0.0003
100	191.55	1.1417	0.0111	0.0133	0.0129	0.0734	7.0376	0.0008
200	383.40	1.1373	0.0108	0.0132	0.0138	0.0662	8.6214	0.0007
300	574.81	1.2897	0.0108	0.0134	0.0173	0.0885	8.5989	0.0007
400	765.37	1.1356	0.0108	0.0133	0.0126	0.1613	9.3856	0.0009
500	957.93	1.1402	0.0109	0.0135	0.0135	0.0782	8.9281	0.0009

## Conclusions

Particle filter methods are the most general techniques for the solution of state estimation problems involving nonlinear and non-Gaussian models. In this paper, three different particle filter algorithms were applied to the estimation of state variables of the model proposed by Hodgkin and Huxley to describe the action potential in excitable cells. Cases involving Purkinje fiber are examined in the paper, by using simulated measurements of the action potential. Although the SIR and the ASIR algorithms are capable of accurately estimating the state variables, we notice that the more general algorithm by Liu and West allows the simultaneous estimation of the state variables and model parameters. Furthermore, such quantities can be estimated with better accuracy than those related to the estimation of only the state variables.

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