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ANALYSIS OF PRIOR INFORMATION FOR THE BAYESIAN ESTIMATION OF PARAMETERS IN HODGKIN-HUXLEY´S MODEL

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Abstract. *The classical model of Hodgkin and Huxley for the action potential in excitable cells, such as axons or Purkinje fibers, is addressed in this paper. Hodgkin and Huxley proposed that the action potential be modeled in terms of an electric circuit with capacitance and ionic electrical currents. Sodium and Potassium ions are the most influential 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, the coefficients of which are given in terms of functions of the applied potential, and involve several empirical parameters. One important point about such parameters is their variability, like from one individual to another. In this paper, we apply the Markov Chain Monte Carlo (MCMC) method for the estimation of a parameters appearing in Hodgkin-Huxley´s model, by using simulated measurements of the action potential. For the application of the MCMC method, an analysis is performed regarding the prior distribution used for the unknown parameter. Among the priors examined in this paper we have Uniform, Gaussian, Log-normal and Rayleigh distributions.*

Keywords: *Action Potential, Hodgkin-Huxley, Estimation of the parameters, Markov Chain Monte Carlo (MCMC)*

1. INTRODUCTION

It has been long known that our neurological system propagates signals via ionic changes across the neurons membranes [1]. The resulting electric potential between the intracellular and extracellular media has been denoted as the action potential [1]. Failures or abnormalities in the ionic changes and in their resulting action potentials can be associated to several neurological disturbs, like epilepsy, Parkinson's and Alzheimer's diseases [2].

A typical normal action potential in neurons is presented in figure 1, where the periods corresponding to the occurrence of different physico-chemical phenomena are designated by numbers [1]. Such periods can be described as follows [1]:

Period 1 – Rest: In this period, the action potential is practically stable.

Period 2 – Un-polarization: During this period, the cell membrane allows the transfer of positive charges from the extracellular medium. The sodium ion is the most likely to cross the membrane at this period, due to its larger concentration gradients. As a result, the action potential undergoes a fast increase.

Period 3 – Re-polarization: As the maximum potential is reached, the sodium channels across the cell membrane gradually close and the potassium channels gradually open. Due to the concentration gradients of the potassium ion across the cell membrane, it is transferred towards extracellular region and the action potential is reduced. The cell is then re-polarized. Depending on how fast this period takes place, the next period might occur or not.

Period 4 – Hyper-polarization: This period occurs when the re-polarization period is too fast, and the slow potassium channels do not close in time sufficient for the potential to reach the stable level of the first period (rest). As a result, the potential becomes smaller than that of the first period.

Period 5 – Action of the Ionic pumps: The final period of the potential variation involves the pumping of sodium and potassium ions across the cell membrane in order to restore their initial concentrations in the intracellular and extracellular media. This period brings the action potential back to the levels of the first period (rest), so that another cycle can be started.

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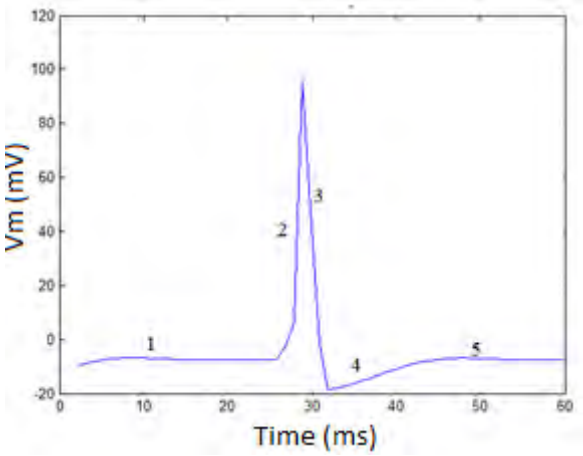

Fig. 1. Action potential in neurons.

Hodgkin and Huxley [3] proposed a model for the action potential, in terms of an electric circuit with a capacitance current and ionic currents. The model involves a non-linear system of four ordinary differential equations, whose coefficients are given in terms of functions of the applied potential and involve several parameters. This paper deals with the estimation of parameters appearing in Hodgkin-Huxley's classical model, by using measurements of the action potential. An analysis of the sensitivity coefficients is performed in order to verify possible small magnitudes of such quantities and linear dependence among the parameters [4-6]. The inverse parameter estimation problem is solved within the Bayesian framework, by applying the Metropolis-Hastings implementation of the Markov Chain Monte Carlo (MCMC) method [6-8]. Different prior probability functions are examined for the parameter of interest in this work, which is the capacitance of the equivalent electric circuit. The examined priors include the following probability functions: Gaussian, Rayleigh, Uniform and Log-Normal. The priors for the other parameters were modeled in terms of Gaussian distributions [7,8].

The accurate estimation of state variables appearing in Hodgkin-Huxley's model might serve for the prediction of diseases. Other recent articles dealing with Hodgkin-Huxley's model, including some of its variations, as well as related inverse problems, can be found in references [9-15].

2. HODGKIN-HUXLEY´S MODEL

Hodgkin and Huxley, in their classical paper of 1952 [3], 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 observed that the conductance of some ions across the cell membrane, like sodium and potassium, varied with changes in the axon potential. The imposed electric current across the cell membrane was then modeled in terms of a capacitive current and ions' currents. Being the sodium and potassium ions recognized as the most important ones in this process, as discussed above, their currents were treated as separate from those of the other ions, which were quantified in a global manner and referred to as leakage current. Hodgkin and Huxley [3] then proposed their model based on the electrical circuit depicted in figure 2. For the model, the transfer of ions towards the cell interior was assumed as positive.

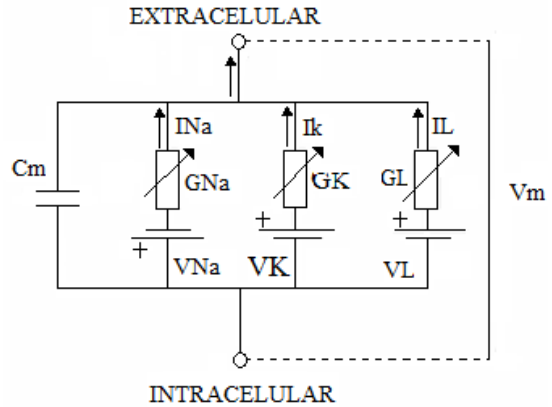

Figure 2. Electric circuit for Hodgkin-Huxley's model [3]

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The current across the cell membrane is then given by:

$$I = I_{ions} + C_m \frac{dV_m(t)}{dt} \tag{1}$$

where C_m is the cell capacitance. The ions current is given by:

$$I_{ions} = I_{Na} + I_k + I_L \tag{2}$$

The ionic currents are modeled by the conductances of the channels corresponding to each ion. Such conductances for the sodium and potassium ions were experimentally determined and written as [3]:

$$G_{Na} = G_{Na}^{max} m^3 h \tag{3}$$
$$G_k = G_k^{max} n^4 \tag{4}$$

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 equations (3) and (4), G_{Na}^{max} and G_k^{max} refer to the maximum sodium and potassium conductances, respectively. The electric currents resulting from the sodium and potassium ions flowing across the cell membrane are thus respectively given by

$$I_{Na} = G_{Na}^{max} m^3 h \left(V_m - V_{Na}\right) \tag{5}$$
$$I_k = G_k^{max} n^4 \left(V_m - V_k\right) \tag{6}$$

where V_{Na} and V_k give the equilibrium potential for the sodium and potassium ions, respectively.

Similarly, the electric current resulting from the flow of the other ions is given by:

$$I_L = G_L \left(V_m - V_L\right) \tag{7}$$

By substituting equations (5)-(7) into equations (1) and (2) we obtain

$$I = C_m \frac{dV_m}{dt} + G_{Na}^{max} m^3 h \left(V_m - V_{Na}\right) + G_k^{max} n^4 \left(V_m - V_k\right) + G_L \left(V_m - V_L\right) \tag{8}$$

Hodgkin and Huxley [3] proposed the following ordinary differential equations to describe the ion channels opening/closing dynamics:

$$\frac{dm}{dt} = \alpha_m \left(1 - m\right) + \beta_m m \tag{9}$$
$$\frac{dh}{dt} = \alpha_h \left(1 - h\right) + \beta_h h \tag{10}$$
$$\frac{dn}{dt} = \alpha_n \left(1 - n\right) + \beta_n n \tag{11}$$

where the coefficients α and β in each equation are given functions of V_m [3]. While the coefficients α represent the inflow of ions towards the cell interior, the coefficients β represent the opposite effect. The following expressions were proposed by Hodgkin and Huxley [3] for the axon studied in their experiment:

$$\alpha_m = \frac{0.1\left(25 - V_m\right)}{\exp\left[0.1\left(25 - V_m\right) - 1\right]} \qquad \beta_m = 4\exp\left[-\frac{V_m}{18}\right] \qquad \alpha_h = 0.07\exp\left[-\frac{V_m}{20}\right] \tag{12-14}$$

$$\beta_h = \frac{1}{\exp\left[0.1\left(30 - V_m\right) + 1\right]} \quad \alpha_n = 0.01\frac{\left(10 - V_m\right)}{\exp\left[0.1\left(10 - V_m\right) - 1\right]} \quad \beta_n = 0.125\exp\left[-\frac{V_m}{80}\right] \tag{15-17}$$

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where V_m is given in milivolt. The initial conditions for the cases addressed herein were taken as $V_m(0)$ = -5 mV, m = 0, n = 0.33 and h = 0.5 [16]. Other parameters appearing in the model were measured by Hodgkin and Huxley [3]; such parameters are presented in table 1.

Table 1. Parameters for Hodgkin-Huxley's model for an axon

Parameter	Value	Parameter	Value
$C_m\left(\mu F\right)$	1	$V_k\left(mV\right)$	-12
$G_{Na}^{max}\left(\mu S\right)$	120	$G_L^{max}\left(\mu S\right)$	0.3
$V_{Na}\left(mV\right)$	115	$V_L\left(mV\right)$	10.6
$G_k^{max}\left(\mu S\right)$	36	$I(mA)$	6

3. INVERSE PROBLEM

Inverse problems can be broadly defined as those dealing with the estimation of unknown quantities appearing in the mathematical formulation of any kind of process, by using measurements of some dependent variable of the problem (observable response of the system) [4-8].

In the direct problem associated with Hodgkin-Huxley's model given by equations (8) to (17), all the parameters and initial conditions are known; the objective of the direct problem is then to determine the time evolutions of the action potential, $V_m(t)$, as well as of the sodium and potassium channel dynamics represented by m, h and n.

On the other hand, the inverse problem under analysis in this work involves the use of measurements of the action potential, $V_m(t)$, to recover parameters appearing in Hodgkin-Huxley's model. Such parameters include $C_m, G_{Na}^{max}, G_k^{max}$ and G_L, as well as the empirical constants appearing in equations (12) to (17), yielding a maximum of twenty parameters. We denote the vector of parameters appearing in the formulation as

$$\mathbf{P}^T \equiv [P_1, P_2, ..., P_N] \tag{18}$$

where N is the number of parameters.

The vector containing the measured action potential is denoted as:

$$\mathbf{Y}^T = \left(Y_1\ ,\ Y_2\ , \ldots , Y_I\right) \tag{19}$$

where $Y_i \equiv Y(t_i)$, $i = 1, \ldots, I$.

By assuming that the measurement errors are Gaussian random variables, with zero means and known covariance matrix $\mathbf{W}$ and that the measurement errors are additive and independent of the parameters $\mathbf{P}$, the *likelihood function* can be expressed as [4, 5, 6,8]:

$$\pi(\mathbf{Y}|\mathbf{P}) = (2\pi)^{-I/2} \left|\mathbf{W}\right|^{-1/2} \exp\left\{-\frac{1}{2}[\mathbf{Y} - \mathbf{V}_m(\mathbf{P})]^T \mathbf{W}^{-1}[\mathbf{Y} - \mathbf{V}_m(\mathbf{P})]\right\} \tag{20}$$

where $\mathbf{V}_m(\mathbf{P})$ is the solution of the direct (forward) problem with known $\mathbf{P}$, that is,

$$\mathbf{V}_m^T(\mathbf{P}) = \left[\mathbf{V}_m(t_1;\mathbf{P}), \mathbf{V}_m(t_2;\mathbf{P}), ..., \mathbf{V}_m(t_I;\mathbf{P})\right] \tag{21}$$

The likelihood function gives the relative probability density of different measurement outcomes $\mathbf{Y}$ with a fixed $\mathbf{P}$ [6,7,8]. A very common approach for the solution of inverse problems, dealing with the estimation of the parameters $\mathbf{P}$ with the measurements $\mathbf{Y}$, is to maximize the likelihood probability density, Eq. (20). This can be accomplished through the minimization of its exponent, resulting in the popular *maximum likelihood objective function*. One important remark is that such classical approach for the solution of parameter estimation problems is not based on the modeling of prior information and related uncertainty about the unknown parameters. On the other hand, in approaches based on Bayesian statistics, the probability distribution models for the measurements and for the unknowns are constructed separately and explicitly.

The solution of the inverse problem within the Bayesian framework is recast in the form of statistical inference from the posterior probability density, which is the model for the conditional probability distribution of the unknown parameters given the measurements. The measurement model incorporating the related uncertainties is called the likelihood, given in this work by equation (20). The model for the unknowns that reflects all the uncertainty of the parameters without the information conveyed by the measurements, is called the prior model [6-8].

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The formal mechanism to combine the new information (measurements) with the previously available information (prior) is known as the Bayes' theorem [6-8].Therefore, the term Bayesian is often used to describe the statistical inversion approach, which is based on the following principles [8]: 1. All variables appearing in the model are random; 2. The randomness describes the degree of information concerning their realizations, which is coded in probability distributions; and 3. The solution of the inverse problem is the posterior probability distribution, from which distribution point estimates and other statistics are computed.

Bayes' theorem is stated as [6-8]:

$$\pi_{posterior}(\mathbf{P}) = \pi(\mathbf{P}\big|\mathbf{Y}) = \frac{\pi(\mathbf{P})\pi(\mathbf{Y}\big|\mathbf{P})}{\pi(\mathbf{Y})} \tag{22}$$

where $\pi_{posterior}(\mathbf{P})$ is the posterior probability density, $\pi(\mathbf{P})$ is the prior density, $\pi(\mathbf{Y}|\mathbf{P})$ is the likelihood function and $\pi(\mathbf{Y})$ is the marginal probability density of the measurements, which plays the role of a normalizing constant.

Sampling of the posterior distribution by using Markov Chain Monte Carlo (MCMC) methods is the most general technique for the computation of estimates within the Bayesian framework. The most common MCMC technique is the Metropolis-Hastings algorithm [6-8]. The implementation of the Metropolis-Hastings algorithm starts with the selection of a proposal distribution $p(\mathbf{P}^*,\mathbf{P}^{(t-1)})$ which is used to draw a new candidate state $\mathbf{P}^*$, given the current state $\mathbf{P}^{(t-1)}$ of the Markov chain. Once the proposal distribution has been selected, the Metropolis-Hastings sampling algorithm can be implemented by repeating the following steps:

1. Sample a *Candidate Point* $\mathbf{P}^*$ from the proposal distribution $p(\mathbf{P}^*,\mathbf{P}^{(t-1)})$.
2. Calculate the acceptance factor:

$$\alpha = \min\left[1, \frac{\pi(\mathbf{P}^* \mid \mathbf{Y})\, p(\mathbf{P}^{(t-1)}, \mathbf{P}^*)}{\pi(\mathbf{P}^{(t-1)} \mid \mathbf{Y})\, p(\mathbf{P}^*, \mathbf{P}^{(t-1)})}\right] \tag{23}$$

3. Generate a random value U which is uniformly distributed on (0,1).
4. If $U \leq \alpha$, set $\mathbf{P}^{(t)} = \mathbf{P}^*$. Otherwise, set $\mathbf{P}^{(t)} = \mathbf{P}^{(t-1)}$.
5. Return to step 1.

In this way, a sequence is generated to represent the posterior distribution and inference on this distribution is obtained from inference on the samples $\{\mathbf{P}^{(1)}, \mathbf{P}^{(2)}, \ldots, \mathbf{P}^{(n)}\}$. However, we note that values of $\mathbf{P}^{(i)}$ must be ignored while the chain has not converged to equilibrium (the burn-in period).

4. RESULTS

Generally, the timewise variations of the sensitivity coefficients must be examined before a solution for the inverse problem is attempted. For stable and accurate solution of the inverse parameter estimation problems, the sensitivity coefficients are required to be linearly-independent and with large absolute values [4-6]. We focus in this work on the analysis of the sensitivity coefficients for the parameters $C_m, G_{Na}^{max}, G_k^{max}$ and G_L, by using in the analysis their nominal values presented in table 1. The sensitivity coefficients were computed in this work by central finite-differences.

Figure 3.a presents the reduced sensitivity coefficients with respect these parameters, as well as the action potential. The reduced sensitivity coefficients were obtained by multiplying the original sensitivity coefficients by their corresponding parameters. Hence, they have the same units of the action potential, which can then be used as a reference to identify small magnitudes and linear dependence of the sensitivity coefficients. Since some sensitivity coefficients attain very large values in the un-polarization period, figure 3.b was prepared with a zoom of figure 3.a in the region where the action potential variations take place. An analysis of figure 3.b shows that the sensitivity coefficient with respect to G_L exhibits small magnitudes for the case under analysis. Furthermore, this figure shows a strong linear dependence of the sensitivity coefficients with respect to all parameters. Therefore, the parameters $C_m, G_{Na}^{max}, G_k^{max}$ and G_L cannot be simultaneously estimated by using measurements of the action potential.

Based on the foregoing analysis of the sensitivity coefficients, this work will consider the estimation of one single parameter, by assuming the others as known from theoretical predictions or from other experiments. In the classical approaches for parameter estimation based, for example, on the minimization of the maximum likelihood objective function, these judged "known" parameters would be considered as deterministic quantities in the inverse analysis, although their degrees of nuisance might be limited to their mean values and to some measure of their uncertainties. On the other hand, with a technique within the Bayesian framework, the uncertainties in the judged "known" parameters can be appropriately taken into account through their prior probability functions.

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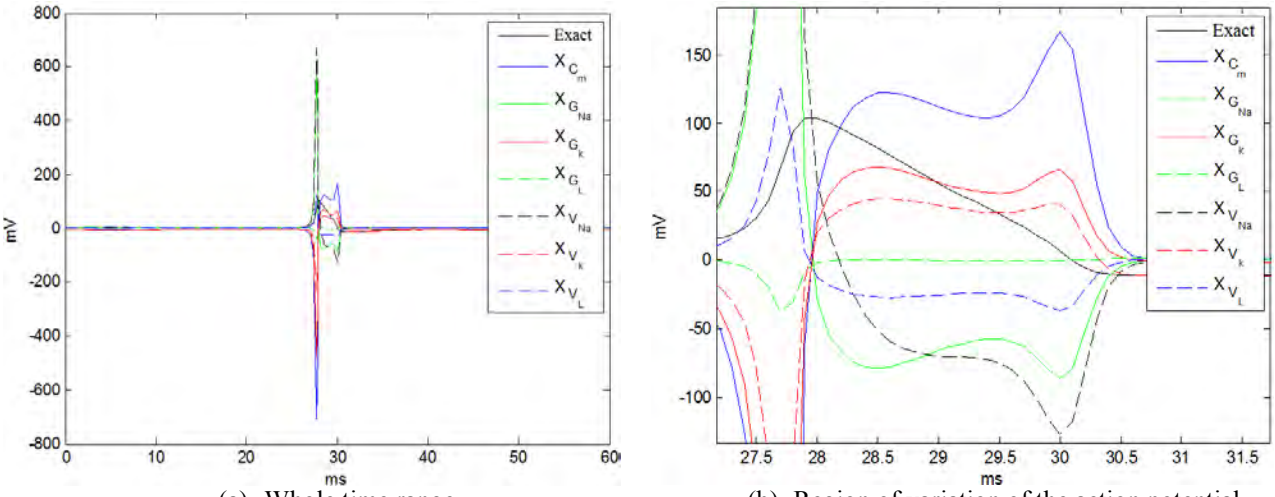

(a) Whole time range (b) Region of variation of the action potential

Fig.3. Reduced Sensitivity Coefficients.

Since the capacitance of the equivalent electrical circuit, C_m, exhibits a sensitivity coefficient of large magnitude (see figures 3.a,b), that is, the action potential response is severely affected by changes on such parameter, we will consider its estimation in this work. This paper is focused on the analysis of the prior distributions for this unknown parameter. The following prior distributions are examined (written for a random variable x): Uniform, Gaussian, Lognormal and Rayleigh, which are respectively given by:

$$p(x) = \begin{cases} \dfrac{1}{b-a}, \text{ if } a < x < b \\ 0 \ , \text{ otherwise} \end{cases} \tag{24.a}$$

$$p(x) = \frac{1}{\sqrt{2\pi\sigma^2}} e^{\left(-\frac{(x-\mu)^2}{2\sigma^2}\right)} \tag{24.b}$$

$$p(x) = \frac{1}{x\sigma\sqrt{2\pi}} e^{\left(-\frac{(Ln(x)-\mu)^2}{2\sigma^2}\right)} \tag{24.c}$$

$$p(x) = \frac{x}{b^2} e^{\left(-\frac{x^2}{2\sigma^2}\right)} \tag{24.d}$$

For the sake of comparison, the Uniform, Gaussian and Lognormal distributions have means given by the nominal value presented in table 1, that is, $C_m = \bar{C}_m = 1\mu F$. The bounds for the uniform distribution are given by $\bar{C}_m \pm 0.2\bar{C}_m$ and the standard-deviations of the Gaussian and Lognormal distributions are $0.2\bar{C}_m$. The mode of the Rayleigh distribution is given by $C_m = \bar{C}_m = 1\mu F$. These four prior distributions are presented in figure 4.

For the results presented below, a Gaussian prior was used for the other parameters appearing in Hodgkin-Huxley's model. The means for these priors were taken as the nominal values presented in table 1, and the standard-deviations as 1% of the nominal values. The parameters were assumed as independent.

The capacitance of the equivalent electrical circuit, C_m, was estimated by using simulated measurements of the action potential. Such measurements were obtained from the solution of the direct problem with the nominal values presented in table 1 and with the coefficients given by equations (12) to (17). The measurement errors were simulated by an additive Gaussian noise, with zero mean and a constant standard deviation given by 5% of the maximum potential. The numerical solution of the Hodking-Huxley's model and the simulated measurements are presented in figure 5.

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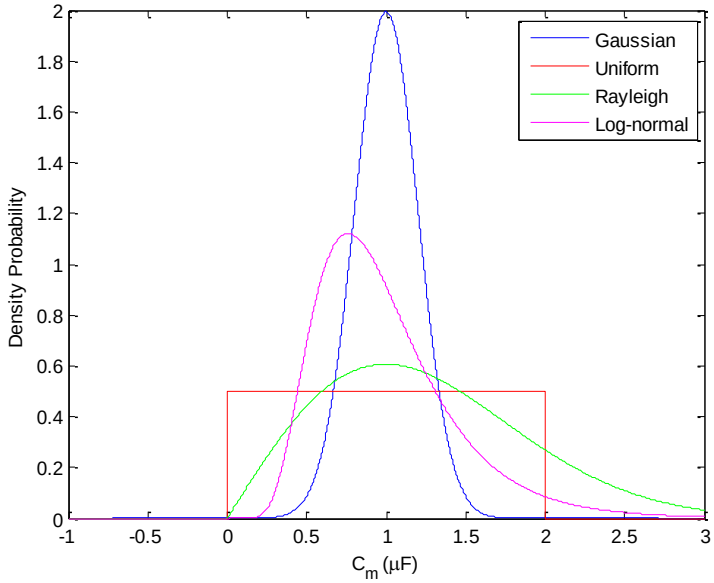

Fig. 4. Prior distribution examined for C_m

The Markov chains for the capacitance were started at values 50% larger than the nominal value of $\bar{C}_m$. The chains for all the other parameters were started at values 50% larger than their nominal values. The proposals were taken as Gaussian distributions with standard-deviations given by 0.2% of the current parameter value in the chain.

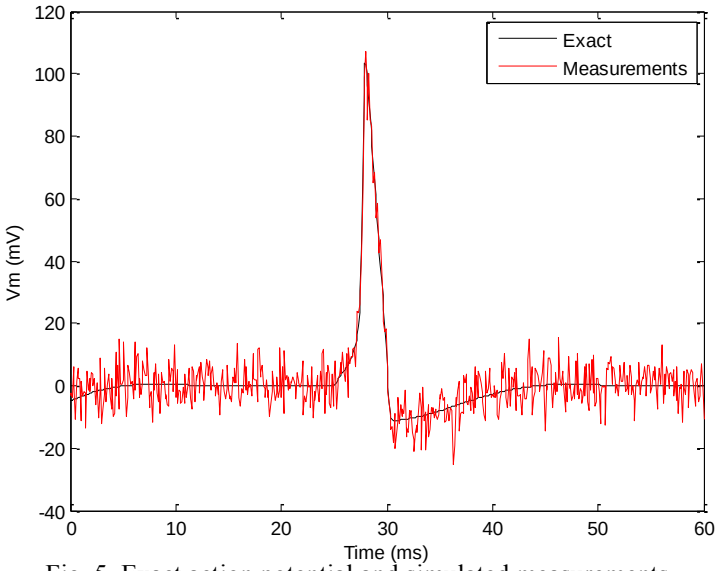

Fig. 5. Exact action potential and simulated measurements

The Markov chains for C_m, obtained with the four different prior distributions examined for this parameter, are presented in figures 6.a,b. Figure 6.b shows a magnification of figure 6.a in the region up to 550 states in the chain, where convergence is achieved for the Gaussian, Lognormal and Rayleigh distributions. On the other hand, figure 6.a shows that the chain resulting from the Uniform prior does not converge to the actual parameter, even after 4000 states. Such behavior results from the fact that the Uniform prior used in this work does not provide any information about the region of higher probability for the parameter, since all values in the interval $0 < C_m < 2$ are equally probable. The acceptance ratios of the states of the Markov chains were around 23% for the Gaussian, Lognormal and Rayleigh prior distributions, but the acceptance ratio for the Uniform prior was of 10%, due to the same reason given above for its lack of convergence for the chain.

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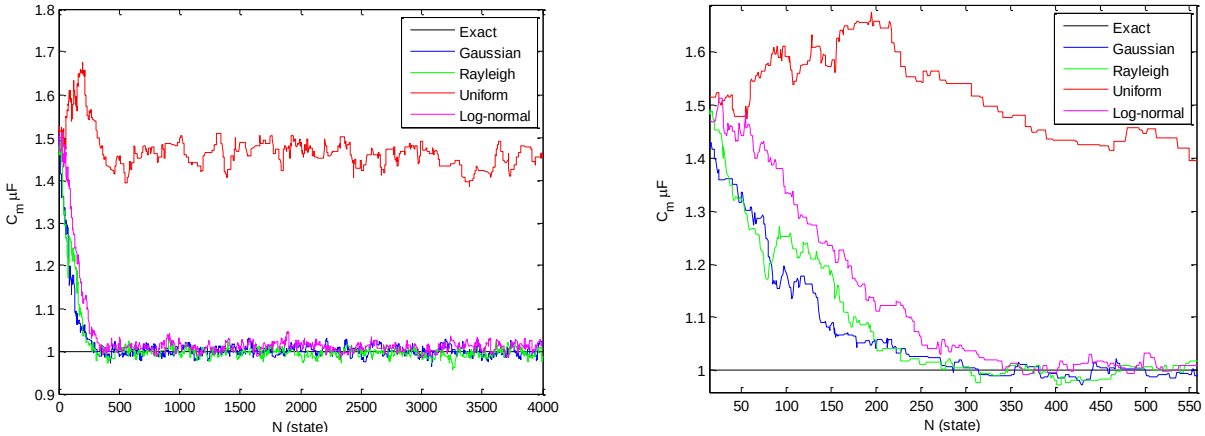

(a) Whole range of states (b) First 550 states

Fig.6. Markov chains with Gaussian, Uniform, Rayleigh and Lognormal priors.

The marginal means obtained for the parameters C_m, $G_{Na}^{máx}$, $G_k^{máx}$ and G_L, with each of the prior distributions examined in this work are presented in table 2, together with their associated uncertainties at 99% confidence levels (inside parentheses). Os valores estimados e as incertezas associadas com nível de confiança de 99%, que é apresentada entre parênteses, são apresentados na Tabela 4. For the Gaussian, Lognormal and Rayleigh distributions, the estimated means are in excellent agreement with the exact values of the parameters and the associated uncertainties are realtively small.

Tabela 4. Marginal means and uncertainties at the 99% confidence levels

	$C_m\ (\mu F)$	$G_{Na}^{máx}\ (\mu S)$	$G_k^{máx}\ (\mu S)$	$G_L\ (\mu S)$
Exact	1.000	120.000	36.000	0.300
Uniform	1.458(0.065)	113.965(3.173)	37.325(0.743)	0.304(0.007)
Gaussian	1.001(0.027)	119.672(3.338)	36.133(0.857)	0.301(0.001)
Lognormal	1.010(0.026)	119.914(2.833)	36.112(0.927)	0.301(0.007)
Rayleigh	0.997(0.025)	120.201(2.937)	35.918(0.907)	0.299(0.008)

5. CONCLUSIONS

The Metropolis-Hastings algorithm was applied for the estimation of parameters in Hodgkin-Huxley's model, by using simulated measurements of the action potential. An analysis of the sensitivity coefficients reveals parameters with strong correlation, so that the inverse problem was focused on the estimation of the capacitance of the equivalent electrical circuit, C_m. For this parameter, four different prior distributions were examined, namely: Gaussian, Uniform, Rayleigh and Lognormal . The Uniform, Gaussian and Lognormal distributions have means given by the nominal value of C_m. The bounds for the uniform distribution are given by $\bar{C}_m \pm 0.2\bar{C}_m$ and the standard-deviations of the Gaussian and Lognormal distributions are $0.2\bar{C}_m$. The mode of the Rayleigh distribution is given by the nominal value of C_m. The priors for the other judged "known" parameters were taken in the form Gaussian distributions. The means for these priors were taken as the nominal values for the parameters, and the standard-deviations as 1% of the nominal values. All the parameters were assumed as independent.

The Markov chains converged for the exact value of C_m with the Gaussian, Lognormal and Rayleigh prior distributions. On the other hand, the chain resulting from the Uniform prior does not converge to the actual parameter, even after 4000 states. Such behavior results from the fact that the Uniform prior used in this work does not provide any information about the region of higher probability for the parameter. The acceptance ratios of the states of the Markov chains were around 23% for the Gaussian, Lognormal and Rayleigh prior distributions, but of only 10% for the Uniform prior.

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7. REFERENCES

1. Guyton, A.C., Hall, J.E., "*Tratado de Fisiologia Médica"***,** 11 ed. Rio de Janeiro, Elsevier Editora Ltda, 2006.
2. Estumano, D. C., Orlande, H.R.B., Colaço, M. J., "*Estimativa do Potencial de Ação de Células Utilizando o Modelo de Hodgkin-Huxley e Filtro de Partículas"*, In: 7º Congresso Nacional de Engenharia Mecânica, São Luís, (2012).
3. Hodgkin, A.L., Huxley, A.F., "*A Quantitative Description of Membrane Current and It's Application to Conduction and Excitation in Nerve***,** *Journal of Physiology*", vol. 117, p. 500-544, (1952).
4. Beck, J.V., Arnold, K.J., "*Parameter Estimation in Engineering and Science"*, Wiley-Interscience, New York, 1977.
5. Özisik, M.N., Orlande, H.R.B., "*Inverse Heat Transfer"*, New York : Taylor & Francis, 2000.
6. Orlande, H., Fudym, F., Maillet, D., Cotta, R., 2011, *Thermal Measurements and Inverse Techniques*, CRC Press, Boca Raton.
7. Gamerman, D., "Markov Chain Monte Carlo**:** Stochastic simulation for Bayesian inference". First. ed. London: Chapman & Hall, 1997.
8. Kaipio, J.P., Somersalo, E., "*Computational and Statistical Methods for Inverse Problems"*, Springer, Berlin, (2004).
9. Malta, C., Pinto, R. D., Monbach J.C., Lenzi, H.L., Romanha W. S., Machado M.P., "*Modelagem Matemática do comportamento elétrico de neurônios e algumas aplicações"*, sociedade Brasileira de Matemática Aplicada e Computacional , vol. 13, São Paulo, Brasil, (2004).
10. Riera ,J., R., Hatanaka, T.Ozaki, Kawashima, R., "*Modeling the spontaneous* Ca^{2+} *oscillations in astrocytes: Inconsistencies and usefulness"*, Journal of Integrative Neuroscience, vol. 10, pp. 439-473, (2011).
11. Riera, J., Wan, X., Jimenez, J. C., Kawashima, R., "*Nonlinear Local Electrovascular Coupling. I: A Theorical Model"*, Human Brain Mapping, vol. 27, pp. 896-914, (2006).
12. Cepeda, C., André , V. M., Vinters H. V., Levine, M. S., Mathern, G. W., "*Are Cytomegalic Neurons and Balloon Cells Generators of Epileptic Activity in Pediatric Cortical Dysplasia?"*, Epilepsia - International League Against Epilepsy, vol. 82, pp. 82-88, (2005).
13. Meng, L., Kramer, M. A., Eden, U. T.*, "A sequential Monte Carlo approach to estimate biophysical neural models from spikes"*, journal of neural, vol. 8, Nº 6, (2011).
14. Buhry, L., Pace, M., Saïghi, S., "*Global Parameter Estimation of an Hodgkin-Huxley Formalism Using Membrane Voltage Recording: Application to Neuro-Mimetic Analog Integrates Circuits*", Neurocomputing, vol. 81, pp. 75-85, (2012).
15. Estumano, D.C, Orlande, H.R.B, Colaço, M.J., *"State Estimation Problem for Hodgkin-Huxley's Model: A Comparision of Particle Filter Algorithms"*. 4º Inverse Problems, Design and Optimization Symposium, Albi, France, 2013.
16. Soriano, D.C., Ricardo, R.A., Bassani , J.W.., *"Resolvendo o Modelo de Hodgkin-Huxley: uma proposta didática, XX Congresso brasileiro de engenharia biomédica"*, pp. 29-32, (2006).

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