23rd ABCM International Congress of Mechanical Engineering
December 6-11, 2015, Rio de Janeiro, RJ, Brazil

APPLICATION OF THE MARKOV CHAIN MONTE CARLO METHOD TO PARAMETER ESTIMATION IN A MODEL REPRESENTING THE CALCIUM INDUCED CALCIUM RELEASE MECHANISM IN NEURONS

Diego C. Estumano*, Eric Benk†, Raphael C. Carvalho*, Helcio R.B. Orlande*, Marcelo J. Colaço*, Jorge J. Riera†

*Department of Mechanical Engineering, Federal University of Rio de Janeiro, Brazil
diegoestumano@ufrj.br, raphael.costa.carvalho@poli.ufrj.br, helcio@mecanica.coppe.ufrj.br,colaco@ufrj.br
†Department of Biomedical Engineering, Florida International University, USA
jrieradi@fiu.edu, ebenk001@fiu.edu

Abstract. *It is a challenge for researchers to uncover the value of parameters they wish to use in their mathematical models. In this work we made use of the Markov Chain Monte Carlo Method (MCMC) to estimate parameters in a mathematical model of a neuron. Our main goal was to quantify the calcium concentration in a particular neuron and ultimately describe a complex mechanism in which the intracellular concentration of calcium fluctuates in response to various stimuli. This mechanism is known as calcium induced calcium release (CICR). The reduced sensitivity coefficients were calculated in order to examine which parameters in the model could be estimated. The estimation of parameters was performed with simulated measurements, by using a Gaussian prior distribution with the mean equal to the parameters of reference and standard deviation equal to 75% of the parameters of reference.*

Keywords: *Markov Chain Monte Carlo Method, Calcium induced calcium release model, parameter estimation.*

1. INTRODUCTION

Some biologic processes are based on ionic transfer, such as the ones happening in the excitable cells of Purkinje fibers and Purkinje neurons (Guyton and Hall, 2006). The estimation of electrophysiological properties in the human body is of fundamental importance to predict the onset of some diseases, such as epilepsy and Parkinson's disease (Cepeda *et al*., 2005, Surmeier *et al*., 2012). Many ions, such as sodium, potassium and calcium, are vital in maintaining biological homeostasis, which keeps physiological systems working well.

In this study, although several ionic systems are present in the neuron, we considered only the ion of calcium in a calcium induced calcium release (CICR) mechanism. This mechanism is controlled by two factors. The calcium transport from the endoplasmatic reticulum to cytosol is controlled by the presence of a specific protein, called inositol 1,4,5 – triphosphate (IP_3). On the other hand, the flux of calcium from cytosol to the endoplasmatic reticulum is governed by an ionic pump (Dupont and Erneux, 1997).

Dupont and Erneux (1997) proposed a mathematical formulation intended to represent how the calcium oscillation in neurons occurs. This formulation has several parameters, which are difficult to be directly measured. Because of this difficulty to evaluate such parameters, in this work we used a Markov Chain Monte Carlo Method via the Metropolis-Hastings algorithm for their estimation (Gamerman, 1997, Orlande et al, 2011, Kaipio and Somersalo 2004). Parameter estimation within the Bayesian paradigm of statistics is accomplished through two basic key factors: the model for the prior distributions of the parameters and the model for the measurement error of observed state variables (in this case, the calcium concentration). A Gaussian distribution was assumed to represent the prior, with a mean value taken from the literature, and a standard deviation equal to 75% of such a value. For the measurements, synthetic data was used for the calcium concentration, where a Gaussian noise was included, with zero mean and standard deviation equals to 0.1 μM.

The major aim of this study is to verify if the Markov Chain Monte Carlo (MCMC) Method is able to estimate the parameters of interest, making use of calcium concentration measurements taken from the cytosol of neurons. The main benefit of this study is to demonstrate that it is possible to estimate some unknown parameters, which are difficult to be measured, using only feasible calcium concentration measurements.

2. CALCIUM DYNAMIC MODEL

The model used in this study was early proposed by Dupont and Erneux, 1997. This model focuses on proposing a mechanism to explain the calcium oscillation in the cytosol of neurons. It is composed by four ordinary differential equations. Each equation describes the time evolution of some state variables. Such variables are: fraction of receptors

desensitized (R_{des}); calcium concentration in the cytosol (C_{cyto}); concentration of inositol 1,4,5 – triphosphate concentration (IP_3); and concentration of inositol 1,3,4,5 – thetraphosphate (IP_4).

The time evolution of R_{des} is given by:

$$\frac{dR_{des}}{dt} = k_{-}\left(\left(\frac{C_{cyto}}{k_{inh}}\right)^{n_i}\frac{1-R_{des}}{1+\left(\frac{C_{cyto}}{k_{act}}\right)^{n_a}} - R_{des}\right) \tag{1}$$

where k_{-} is a constant of dissociation of receptor , k_{inh} and, k_{act} are constants of activating and inhibiting sites , n_i and n_a are the so-called Hill coefficients.

The time evolution of calcium concentration (C_{cyto}) is modeled by Eq. (2.a). The calcium concentration is mainly influenced by two processes: the concentration of IP_3, which is responsible for leading calcium from endoplasmic reticulum to the cytosol; and the ionic pump, which is responsible for leading calcium from the cytosol to endoplasmic reticulum. The influence of IP_3 is represented by the first term in Eq. (2.a), while the second term represents the ionic pump.

$$\frac{dC_{cyto}}{dt} = k_1\left(b + I_{ra}\right)\left(Ca_{tot} - C_{cyto}\left(\alpha+1\right)\right) - V_{MP}\frac{C_{cyto}^{n_p}}{k_p^{n_p} + C_{cyto}^{n_p}} \tag{2.a}$$

where

$$I_{ra} = \left(1 - R_{des}\right)\frac{IP_3}{k_{ip} + IP_3}\frac{1}{1+\left(\frac{k_{act}}{C_{cyto}}\right)^{n_a}} \tag{2.b}$$

In Eqs. (2.a,b), k_1 is a kinetic constant, b is a basal efflux, Ca_{tot} is total calcium concentration, α is the ratio between the volumes of the intracellular store and cytosol, V_{MP} is a maximum velocity of pump, k_p is a constant for half-maximal activity, n_p is a Hill coefficient, k_{ip} is the equilibrium dissociation constant of IP_3 and k_{act} is a constant of inhibiting sites.

The kinetics of IP_3 is represented by Eq. (3.a). In this model, we consider three mechanisms that directly influence the concentration of IP_3. The first mechanism, shown by Eq. (3.b), represents how IP_3 is produced as a result of the phospholipase (PLC) activation. The second and third ones show how IP_3 is degraded via 3-kinase, Eq. (3.c), and 5-phosphalipase, Eq. (3.d). This latter mechanism has as major consequence, as will be shown by Eqs. (4), which is the production of inositol 1,3,4,5 – thetraphosphate (IP_4).

$$\frac{dIP_3}{dt} = v_{plc} - v_{3k} - v_{5p} \tag{3.a}$$

$$v_{plc} = \gamma V_{plc} \tag{3.b}$$

$$v_{3k} = V_k\frac{IP_3}{K_k + IP_3}\frac{C_{cyto}^{n_d}}{k_d^{n_d} + C_{cyto}^{n_d}} \tag{3.c}$$

$$v_{5p} = V_{p1}\frac{IP_3}{k_{p1}\left(1+\frac{IP_4}{k_{p2}}\right) + IP_3} \tag{3.d}$$

In the above equations, γ represents the level of external stimulation, V_{plc} is the maximal velocity of IP_3 synthesis by PLC, V_k is the maximum velocity of IP_3 degradation by 3-kinase, n_d is a Hill coefficient, K_k is a Michaelis constant, k_d is a threshold constant, V_{p1} is the maximum velocity of degradation of IP_3 by 5-phosphatase, while k_{p1} and k_{p2} are Michaelis constants.

The kinetics of IP_4 is modeled by Eq. (4.a). It is influenced by three mechanisms. The first one, which is represented by Eq. (3.c), is the production of IP_4 due to the degradation of IP_3. The second one, the degradation of IP_4

via 5-phosphatase is represented by Eq. (4.b), and the last one, represented by the last term of Eq. (4.a), is a small linear degradation of IP_3.

$$\frac{dIP_4}{dt} = v_{3k} - v'_{5p} - kIP_4 \tag{4.a}$$

$$v'_{5p} = V_{p2}\frac{IP_4}{k_{p2}\left(1+\frac{IP_3}{k_{p1}}\right)+IP_4} \tag{4.b}$$

In equations (4.a,b), V_{p2} is the maximal velocity of degradation of IP_4 by 5-phosphalipase. Table 1 shows typical values for all parameters appearing in Eqs. (1)-(4), found in the literature, and Table 2 shows the initial conditions used in this work for Eqs. (1)-(4).

Table 1. Parameters of the calcium oscillation model (Dupont and Erneux, 1997).

Parameter	Unit	Value	Parameter	Unit	Value
V_k	μMs^{-1}	0.5000	k_{p1}	μM	10.0000
K_k	μM	1.0000	k_{p2}	μM	2.0000
k_d	μM	0.3000	V_{p2}	μMs^{-1}	0.2000
$k\_$	s^{-1}	0.5000	b	s^{-1}	0.0001
k_{inh}	μM	0.1500	α	dimensionless	0.1000
k_{act}	μM	0.5600	Ca_{tot}	μM	80.0000
k_{ip}	μM	1.0000	k	s^{-1}	0.0100
γ	dimensionless	0.2000	n_a	dimensionless	3
V_{plc}	μMs^{-1}	1.3000	n_d	dimensionless	2
V_{MP}	μMs^{-1}	4.0000	n_i	dimensionless	4
k_p	μM	0.3500	n_p	dimensionless	2

Table 2. Initial conditions used in Eqs. (1)-(4)

State Variable	Initial Condition
R_{des}	0.8
C_{cyto} μM	0.1
IP_3 μM	0.55
IP_4 μM	0.415

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) (Beck,1997, Özisik and Orlande, 2000, Orlande, 2011, Kaipio and Somersalo 2004).

In the direct problem associated with the calcium oscillation model given by equations (1) to (4), all the parameters and initial conditions are known; the objective of the direct problem is then to determine the time evolution of the calcium concentration, $C_{cyto}(t)$, the fraction of receptors desensitized, R_{des}, and the concentrations of IP_3 and IP_4.

On the other hand, the inverse problem analyzed in this work involves the use of simulated calcium concentration measurements to recover some parameters appearing in the calcium oscillation model, given by Eqs. (1)-(4). The vector of parameters appears in the inverse problem formulation can be represented as:

$$\mathbf{P}^T \equiv \left[P_1,...,P_N \right] \tag{5}$$

where N is the number of parameters P.

The vector containing the transient calcium concentration measurements is denoted as:

$$\mathbf{Y}^T \equiv \left[Y_1,...,Y_I \right] \tag{6}$$

where $Y_i \equiv Y\left(t_i\right), i = 1,....,I$, and I is the total number of measurements.

By assuming that the measurement errors as Gaussian random variables, with zero means, known covariance matrix **W,** and the measurement errors are additive and independent of the parameters **P**, the *likelihood function* can be expressed as (Beck,1997, Orlande et al, 2011, Kaipio and Somersalo 2004):

$$\pi(\mathbf{Y}|\mathbf{P}) = (2\pi)^{-I/2} \left|\mathbf{W}\right|^{-1/2} \exp\left\{-\frac{1}{2}[\mathbf{Y} - \mathbf{C}_{cyto}(\mathbf{P})]^T \mathbf{W}^{-1}[\mathbf{Y} - \mathbf{C}_{cyto}(\mathbf{P})]\right\} \tag{7}$$

where $\mathbf{C}_{cyto}(\mathbf{P})$ is the vector with the solution of the direct (forward) problem at each time t_i, $i = 1, \ldots, I$, obtained with the vector of parameters **P**.

The likelihood function gives the probability density of different measurement outcomes **Y** with a fixed **P** (Gamerman, 1997, Orlande et al, 2011, Kaipio and Somersalo 2004). A very common solution of inverse problems, dealing with the estimation of the parameters **P** with the measurements **Y**, is to maximize the likelihood probability density, Eq. (7). 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 (Kaipio and Somersalo, 2004).

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 Eq. (7). 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 (Gamerman, 1997, Orlande et al, 2011, Kaipio and Somersalo 2004). The formal mechanism to combine the new information (measurements) with the previously available information (prior) is known as the Bayes' theorem (Gamerman, 1997, Orlande et al, 2011, Kaipio and Somersalo 2004). Therefore, the term Bayesian is often used to describe the statistical inversion approach, which is based on the following principles (Kaipio and Somersalo 2004): 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 (Gamerman, 1997, Orlande et al, 2011, Kaipio and Somersalo 2004):

$$\pi_{posterior}(\mathbf{P}) = \pi(\mathbf{P}|\mathbf{Y}) = \frac{\pi(\mathbf{P})\pi(\mathbf{Y}|\mathbf{P})}{\pi(\mathbf{Y})} \tag{8}$$

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 (Gamerman, 1997, Orlande et al, 2011, Kaipio and Somersalo 2004). 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:

$$AF = \min\left[1, \frac{\pi(\mathbf{P}^* \mid \mathbf{Y})\, p(\mathbf{P}^{(t-1)}, \mathbf{P}^*)}{\pi(\mathbf{P}^{(t-1)} \mid \mathbf{Y})\, p(\mathbf{P}^*, \mathbf{P}^{(t-1)})}\right] \tag{9}$$

3. Generate a random value U which is uniformly distributed on (0,1).

4. If $U \leq$ AF, set $\mathbf{P}^{(t)} = \mathbf{P}^*$. Otherwise, set $\mathbf{P}^{(t)} = \mathbf{P}^{(t-1)}$.

5. Return to step 1 while some convergence criteria is not satisfied.

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). In this work, the proposal was taken as a random-walk in the form:

$$\mathbf{P}^* = \mathbf{P}^{(t-1)} + w\mathbf{P}^{(t-1)}\boldsymbol{\varepsilon} \tag{10}$$

where $\boldsymbol{\varepsilon}$ is random vector with a standard normal distribution, i.e., $\boldsymbol{\varepsilon} \sim N(0,1)$.

For the solution of the inverse problem, an analysis of the sensitivity coefficients reveals which parameters are possible to estimate. For stable and accurate solutions of parameter estimation problems, the sensitivity coefficients are required to be linearly-independent and with large absolute values (Beck, 1997, Özisik and Orlande, 2000, Orlande et al, 2011, Kaipio and Somersalo 2004). The reduced sensitivity coefficients, J_{Pj}, with respect to parameter P_j, j=1,…,N, are defined as

$$J_{P_j} \equiv P_j \frac{\partial C_{cyto}}{\partial P_j} \tag{11}$$

4. RESULTS

The analysis of the reduced sensitivity coefficients revealed that the absolute values of such quantities with respect to the parameters V_{p2}, k and α are very small. Therefore, their estimation might be very difficult; hence, in this work typical values found in the literature were used for such parameters (Dupont and Erneux, 1997). The other parameters, except k_{inh} and Ca_{tot}, were found to be linearly dependent and, therefore, cannot be estimated simultaneously. For these linearly dependent parameters, typical values were also taken from the literature (Dupont and Erneux, 1997). Figure 1 shows the reduced sensitivity coefficients of k_{inh} and Ca_{tot}, as well as the direct problem solution, for the case examined in this work. Notice in figure 1 that the sensitivity coefficients with respect to k_{inh} and Ca_{tot} are of large magnitudes and are linearly independent.

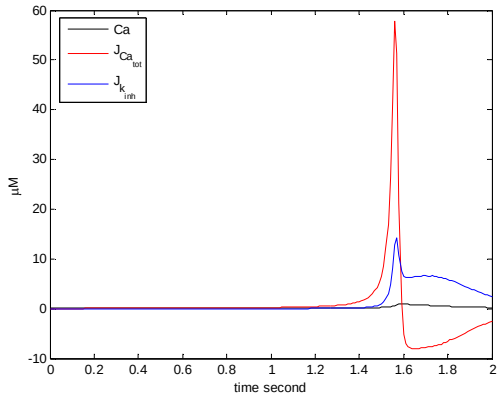


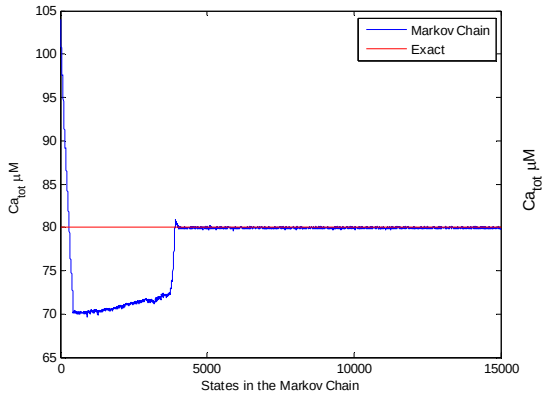
Figure 1: Relative coefficient sensitivity of parameters Ca_{tot} and k_{inh}

Based on the foregoing analysis of the reduced sensitivity coefficients, this study will consider the estimation of two parameters, k_{inh} and C_{atot}. The input data used for the Markov Chain Monte Carlo Method are shown in Table 3.

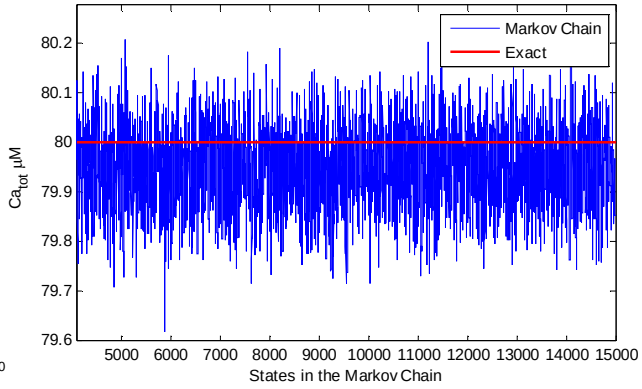
Table 3. Input data for the Markov Chain Monte Carlo Method

N	Number of states in the Markov Chains	15000
w	Step of proposal distribution	0.002
Ca_{tot}	Initial Estimation	104.00
k_{inh}	Initial Estimation	0.195
$\mu_{Ca_{tot}}$	Mean from prior distribution (Gaussian)	80.00
$\sigma_{Ca_{tot}}$	Standard-deviation from prior distribution (Gaussian)	60.00
$\mu_{k_{inh}}$	Mean from prior distribution (Gaussian)	0.1500
$\sigma_{k_{inh}}$	Standard-deviation from prior distribution (Gaussian)	0.1125
σ_{meas}	Standard-deviation from likelihood function (Gaussian)	0.1

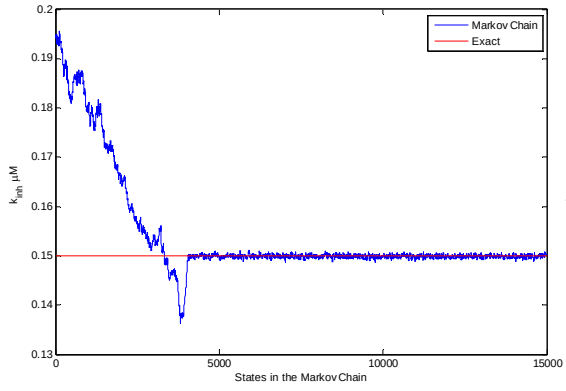
Results are shown in Figures 2-5 and Table 4. First, we performed an analysis of the Markov Chains evolutions, which are shown in Figure 2. This figure shows that the Markov Chains reached equilibrium after approximately 5000 states, for both k_{inh} and C_{atot}.



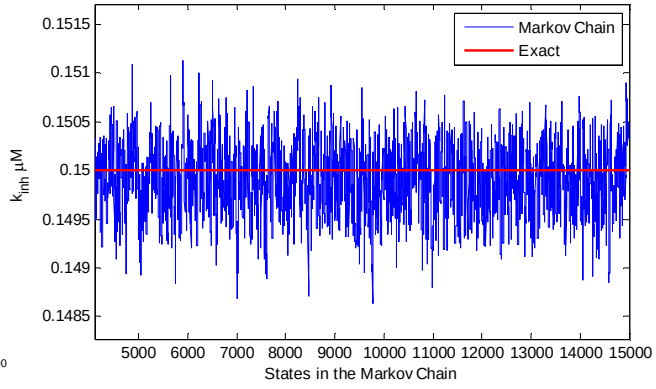
(a)Whole Markov Chain



(b) Range for posterior distribution analysis



(c)Whole Markov Chain



(d) Range for posterior distribution analysis

Figure 2: Evolution of Markov Chain.

Figure 3 shows the evolution of accepted states. From 15000 states, 6536 states were accepted, which results in an acceptance ratio of 43.57 %. The large acceptance ratio results from the small step use for the proposal distribution, and is also evidenced from figures 2.b and 2.d.

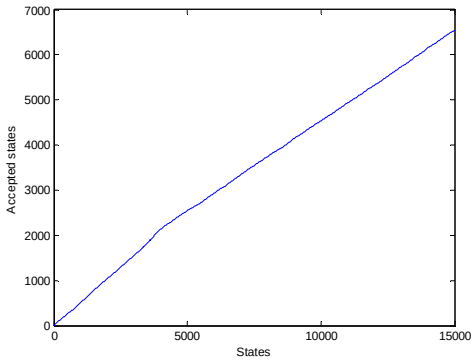


Figure 3: Acceptance of states from Markov Chain

The histograms of the marginal posterior distributions for Ca_{tot} and k_{inh} are presented in figures 4. The marginal posteriors resemble Gaussian distributions, since the likelihood is Gaussian and the priors are Gaussian with large standard-deviations (thus approaching uniform distributions). The means of the marginal posteriors are clearly in in excellent agreement with the exact parameters, despite the fact that the Markov chains are started quite far from the exact values. Such is the case because the exact parameters are used as the means in the Gaussian priors. Table 4 shows the comparison between the exact and estimated values, which is excellent in the case examined in this paper.

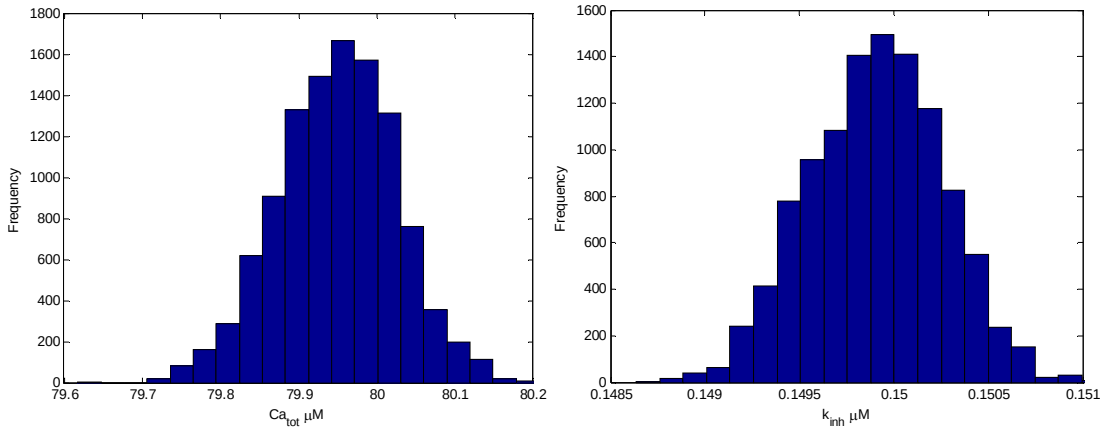


Figure 4: Histogram of posterior distribution to parameters Ca_{tot} and k_{inh}.

Table 4. Output analysis of parameters estimated.

Parameter	Unit	Exact Value	Initial Estimation	Mean	99% Conf. Int.
Ca_{tot}	μM	80.0000	104.00	79.9496	(79.7550;80.1442)
k_{inh}	μM	0.1500	0.1950	0.14990	(0.1490; 0.1580

Finally, Figure 5 shows a comparison between the measured and estimated calcium concentration. These quantities are in excellent agreement.

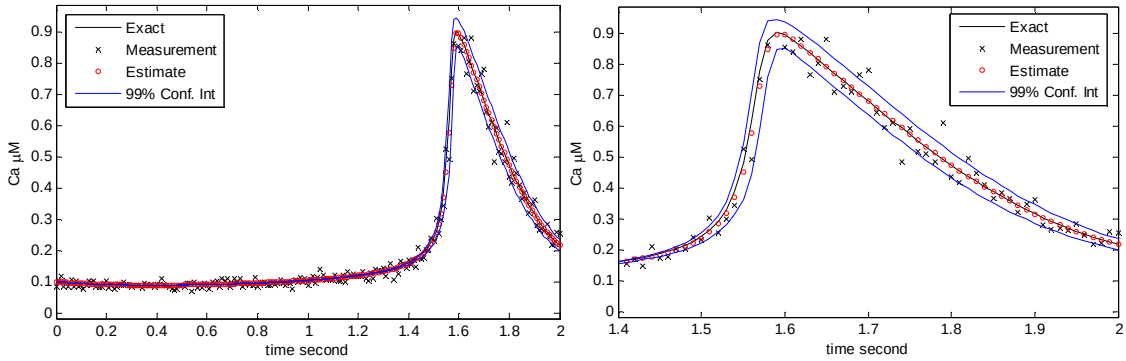


Figure 5: Comparison between the measured and estimated calcium concentration.

5. CONCLUSIONS

The results obtained, by using the Markov Chain Monte Carlo Method via Metropolis-Hastings algorithm, are very accurate and promising for the estimation of parameters in the Calcium Induced Calcium Release model used in this work. These results were obtained using Gaussian prior distributions with the means equal to the exact values of the parameters, but a large standard deviation corresponding to 75% of these values.

The Markov Chains reached equilibrium with means very close to the exact values and with 43.57% of accepted states.

6. ACKNOWLEDGEMENTS

The authors would like to thank the Brazilian agencies for the fostering of science, *Conselho Nacional de Desenvolvimento Científico e Tecnológico* (CNPq), *Coordenação de Aperfeiçoamento de Pessoal de Nível Superior* (CAPES), *Fundação Carlos Chagas Filho de Amparo à Pesquisa do Estado do Rio de Janeiro* (FAPERJ) and ANP/PRH37 for the financial support for this work.

7. REFERENCES

Beck, J.V., Arnold, K.J., 1997, *"Parameter Estimation in Engineering and Science"*, Wiley-Interscience, New York.

Cepeda, C., André , V. M., Vinters H. V., Levine, M. S., Mathern, G. W., 2005, "Are Cytomegalic Neurons and Balloon Cells Generators of Epileptic Activity in Pediatric Cortical Dysplasia?", Epilepsia - International League Against Epilepsy, Vol. 82, pp. 82-88.

Dupont, G., Erneux, C., 1997, "Simulations of the Effects of Inositol 1,4,5-Triphosphate 3-Kinase and 5-phosphatase Activities on Ca^{2+} Oscillations", *Cell Calcium*, Vol. 22, p. 321 – 331.

Gamerman, D., 1997, " Markov Chain Monte Carlo: Stochastic simulation for Bayesian Inference". First ed. London: Chapman & Hall.

Guyton, A.C., Hall, J.E., 2006, *Textbook of Medical Physiology*, Elsevier, Philadelphia 11nd edition.

Kaipio, J.P., Somersalo, E., 2004, "*Computational and Statistical Methods for Inverse Problems"*, Springer, Berlin.

Orlande, H., Fudym, F., Maillet, D., Cotta, R., 2011, *Thermal Measurements and Inverse Techniques*, CRC Press, Boca Raton.

Özisik, M.N., Orlande, H.R.B., 2000, "*Inverse Heat Transfer"*, New York : Taylor & Francis.

Surmeier, D.J., Guzman, J.N., Sanchez, J., Schumacker, P.T., 2012, "Physiological Phenotype and Vulnerability in Parkinson Disease", Cold Spring Harbor Perspectives in Medicine, DOI : 101101.

8. RESPONSIBILITY NOTICE

The authors are the only parties responsible for the printed material included in this paper.