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APPLICATION OF APPROXIMATE BAYESIAN COMPUTATION FOR THE ESTIMATION OF PARAMETERS IN A MODEL FOR THE CALCIUM DYNAMICS IN NEURONS

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Abstract. *Ionic transfer plays an important role in several processes in the human body, in special in the electrophysiology of neurons, where the most important ions are those of potassium, sodium and calcium. The models for the dynamics of potassium and sodium are classical and well established in the literature. On the other hand, several models were proposed for the dynamics of calcium ions, such as those of Dupont and Erneux , 1997and of Dupont and Goldbetter ,1993. In fact, none of the proposed models for calcium dynamics is widely accepted and general to represent phenomena characteristic of anomalous behaviors observed in neurons, related, for example, to epilepsy. Due to the nonlinear character of these models, the values of their parameters strongly affect the predicted responses, like the transient ion concentrations, as well as the dynamics of several state variables, including the electrical current responses in voltage clamp experiments. Approximate Bayesian Computation (ABC) methods have been conceived for inferring posterior distributions where likelihood functions are computationally intractable, too costly to evaluate or not exactly*

known. In this work, we apply an ABC algorithm based on the Monte Carlo method (Toni et al., 2009) for the estimation of parameters appearing in the Calcium model proposed by Dupont and Goldbetter, 1993. Simulated measurements of the concentration of calcium ions in the cytosol are used for the parameter estimation.

Keywords: *Approximate Bayesian Computation, Calcium Induced Calcium Release Model, Parameter Estimation*

1 INTRODUCTION

The dynamics of Calcium ions play a fundamental role in the human body. Specifically in neurons, syndromes like Alzheimer's disease (AD), Parkinson's disease, and amyotrophic lateral sclerosis (ALS), among other neurodegenerative disorders, can be associated to misbehaviors of the calcium ions transfer processes (Bezprozvanny, 2009, Bezprozvanny et al., 2008, Mattson and Chan, 2003).

The objective of this paper is to examine the solution of a parameter estimation problem in a model for the calcium dynamics in neurons. Different models can be found in the literature for the calcium dynamics in cells such as neurons and muscles (Dupont and Erneux , 1997, Dupont and Goldbetter ,1993 , Goldbetter et al., 1990, Dupont et al., 1991) . In this work we used the model proposed by Dupont and Goldbeter, 1993 , which model the oscillations of the concentration of Calcium ions in the cytosol and in the endoplasmic reticulum. This model is based on the Calcium induced–Calcium release (CICR) mechanism: it is assumed that Ca^{2+} in the cytosol activates its own release from the intracellular region, after an increase in its concentration caused by the IP_3 (inositol 1,4,5-trisphosphate), where IP_3 is synthesized in response to an external stimulus (Dupont and Goldbeter, 1993). This mechanism works through the action of a calcium pump and IP_3, which causes the oscillation in the concentration of Ca^{2+} in the cytosol and in the endoplasmic reticulum (Goldbetter et al., 1990, Dupont et al., 1991) (see Figure 1).

The concentration of Ca^{2+} calcium ions in the cytosol can be measured by a fluorescence method (Cork et al., 1989, Riera et al., 2011). Therefore, such measurements can be used for the estimation of parameters appearing in the mathematical model for the calcium dynamics. Several parameter estimation techniques can be found in the literature. In this work, we applied an Approximate Bayesian Computation Technique (ABC), which does not require the model for the measurement errors (Likelihood function). The algorithm used in this work is that proposed by Toni et al., 2009, because it readily allows for extension to cases involving simultaneous model selection and parameter estimation.

2 PHYSICO-CHEMICAL PROBLEM

The physico-chemical problem considered here deals with the transfer of the calcium ion Ca^{2+} between the extracellular and intracellular regions of one single cell, as illustrated by Figure 1, where the intracellular region is subdivided into cytosol and endoplasmic reticulum. In response to the external stimulation, IP_3 is synthesized and binds to receptors located on the endoplasmic reticulum membrane. These receptors are responsible for the transformation of the stimulus into the production of IP_3. This production allows the liberation of Ca^{2+} into the cytosol. The increase of the Ca^{2+} in the cytosol activates the liberation of Ca^{2+} present in the endoplasmic reticulum through the Calcium induced – Calcium release (CICR) process. The calcium concentration in the cytosol is controlled through the action of the Calcium pump and extrusion from the cell. A new cycle of oscillations begins as soon as the level of Ca^{2+} in the cytosol reaches the threshold for CICR.

In Figure 1 the term "signal" refers to the extracellular signal that activates the CICR process, while the term "receptor" refers to the receptor of the cell.

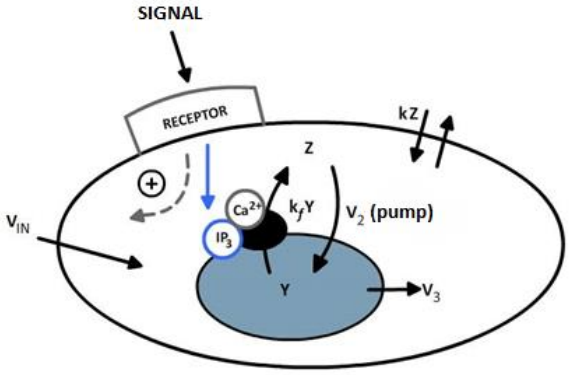

Figure 1: Representation of the chosen model adapted from Dupont and Goldbeter, 1993

2.1 Mathematical Formulation

The mathematical model used here to represent the physical chemical phenomena described above is that proposed by Dupont and Goldbeter, 1993. It is given by the following system of ordinary differential equations:

$$\frac{dZ(t)}{dt} = V_{in} - V_2(t) + V_3(t) + k_f Y(t) - kZ(t) \tag{1}$$

$$\frac{dY(t)}{dt} = V_2(t) - V_3(t) - k_f Y(t) \tag{2}$$

where

$$V_{in} = v_0 + v_1\beta \tag{3}$$

$$V_2(t) = V_{M2}\frac{Z(t)^n}{K_2^n + Z(t)^n} \tag{4}$$

$$V_3(t) = \beta V_{M3}\frac{Y(t)^m}{K_R^m + Y(t)^m}\frac{Z(t)^p}{K_A^p + Z(t)^p} \tag{5}$$

In these equations, Z and Y represent the concentrations of Ca^{2+} in the cytosol and in the endoplasmic reticulum, respectively and V_{in} represents the entry of Ca^{2+} in the cytosol, which includes the passive influx v_0 from the extracellular medium to the cytosol and the term $v_1\beta$ representing the entry of Ca^{2+} from the extracellular medium due to the external stimulation. V_2 represents the pumping rate of Ca^{2+} from the cytosol to the endoplasmic reticulum, while V_3 is the rate of Ca^{2+} liberation from the reticulum sensitive to the calcium ions. V_{M2} and V_{M3} represent the maximum rates of pumping and liberation, respectively (Dupont and Goldbeter, 1993). K_2, K_R and K_A are the saturation constants for pumping.

liberation and activation concentrations, respectively, while n, m and p are the so-called Hill coefficients (Gesztelyi et al 2012, Weiss, 1997). $k_f Y$ and kZ are the passive effluxes from the endoplasmic reticulum and cytosol, respectively (Dupont and Goldbeter, 1993).

The direct problem, when the model parameters are all known, was solved using the parameters presented in the Table 1, with the following initial conditions: Z(0) = 0.37 μM and Y(0)= 1.87 μM (Dupont and Goldbeter, 1993) .The direct problem was solved with the Fourth Order Runge Kutta Method.

Table 1: Parameters used to solve the Model (Dupont and Goldbeter, 1993)

Parameter	Unit	Value
v_0	$\mu M min^{-1}$	3.40
v_1	$\mu M min^{-1}$	3.40
β	dimensionless	0.40
V_{M2}	$\mu M min^{-1}$	50.00
V_{M3}	$\mu M min^{-1}$	650.00
K_2	$\mu M min^{-1}$	1.00
K_R	μM	2.00
K_A	μM	0.90
K	min^{-1}	10.00
K_f	min^{-1}	1.00
n	dimensionless	2.00
m	dimensionless	2.00
p	dimensionless	4.00

3 INVERSE PROBLEM

The inverse problem addressed here deals with the estimation of the vector of parameters

$$\boldsymbol{\theta}^T = [v_0, v_1, \beta, V_{M2}, V_{M3}, K_2, K_R, K_A, K, K_f] \tag{6}$$

using transient measurements of the Ca^{2+} concentration in the cytosol, that is, $Z(t)$.The vector of measurements is denoted as **x**.

In this work, we apply an Approximate Bayesian Computation (ABC) technique for the estimation of the vector of parameters given by Eq. 6. Approximate Bayesian Computation

offers the advantage of not requiring the model for the measurement errors in the estimation procedure, at the same time that the prior information for the parameters is taken into account in the analysis. ABC was used in this work since the biological experimental data are often scarce and might not allow an appropriate model for the measurement errors.

For the present work, the ABC algorithm developed by Toni et al, 2009 for parameter estimation was used. The algorithm is based on a method of acceptance-rejection, where, for the particles to be accepted, the distance between the solution of direct problem using the candidate population and the measurement must be smaller than a user-prescribed tolerance.

3.1 The Algorithm

The algorithm used in this work can be summarized in terms of the following steps:

1. Set t =0, select the number of particles, $Dist_{CV}$, CV_1 and ε.

2. Set the particle indicator i=1

3. If t = 0, sample $\boldsymbol{\theta}^{**}$ independently from the prior distribution $\pi(\boldsymbol{\theta})$.

If t > 0, sample $\boldsymbol{\theta}^{*}$ from the previous population $\{\boldsymbol{\theta}^{(i)}_{t-1}\}$ with weights w_{t-1} and perturb the particle to obtain $\boldsymbol{\theta}^{**}\sim K_t(\boldsymbol{\theta}\,|\boldsymbol{\theta}^{*})$, where K_t is a perturbation kernel.

4. If $\pi(\boldsymbol{\theta}^{**}) = 0$, return to step 3

5. Calculate the solution of the forward problem (1), that is, $\mathbf{x}^{*}\sim\mathbf{f}(\mathbf{x}\,|\boldsymbol{\theta}^{**})$. If $d(\mathbf{x}^{*},\mathbf{x}) \geq \varepsilon$, return to step 3

6. Set $\boldsymbol{\theta}^{(i)}_t = \boldsymbol{\theta}^{**}$ and calculate the weight for the particle $\theta^{(i)}_t$

$$w_t^{(i)} = \begin{cases} 1 & \text{if } t = 0 \\ \dfrac{\pi(\boldsymbol{\theta}_t^{(i)})}{\sum_{j=1}^{N} w_{t-1}^{(j)} K_t(\boldsymbol{\theta}_{t-1}^{(j)}, \boldsymbol{\theta}_t^{(i)})} & \text{if } t > 0 \end{cases}$$

7. Normalize the weights.

8. If i < number of particles, let i = i+1 and go to step 3.

9. Let ε = median(**d**) and CV_2 = cv(**d**) , where cv = standard deviation of **d** divided by the mean of **d**

10. If $\|CV_1 - CV_2\| < Dist_{CV}$, then stop. Else, make $CV_1 = CV_2$, t=t+1 and go to step 2.

For the implementation of the ABC algorithm described above, the distance function $d(\mathbf{x}^{*},\mathbf{x})$ was chosen as the Euclidean norm between the vectors containing the measurements, **x**, and the estimated state variables, $\mathbf{x}^{*}$. The tolerance ε was adaptively selected, being set by the user for the first iteration (population) of the method. The adaptive selection of ε is proposed in the present work, together with the stopping criterion for the method, as given by steps 9 and 10 in the algorithm presented above. In step 9, the tolerance ε is set for the next iteration as the

median of the vector **d**, which contains the values of the distance functions $d(\mathbf{x}^*, \mathbf{x})$ for all particles. Therefore, as the iterations evolve and the estimated mean values for the parameters provide smaller distance functions $d(\mathbf{x}^*, \mathbf{x})$, the tolerance ε is gradually reduced. The stopping criterion in step 10 is based on the coefficient of variation of the vector **d**, which is also expected to reduce as the distance functions $d(\mathbf{x}^*, \mathbf{x})$ decrease when the iterations advance. A tolerance Dist_{CV} is established by the user for the coefficient of variation of **d**. We hope that this stopping criterion provide better approximations for the posterior distribution, instead of a criterion based on the convergence of the parameter means.

4 RESULTS

The results presented below were obtained with simulated measurements of the Ca^{2+} concentration in the cytosol. The simulated measurements were obtained from the solution of the direct problem, with the parameter values presented in Table 1, as

$$x(t) = Z(t) + \omega \tag{7}$$

where ω is a random variable with a normal distribution, zero mean zero and constant standard deviation. The measurement errors were simulated in this work with a standard deviation of 10% of the maximum value of the direct problem solution. The simulated measurements would be discarded if negative values were obtained for $x(t)$, but such was an event not very likely with the value used for the standard deviation. The simulated measurements were supposed to be available every 0.01 min, until the final time of 5 min. The results presented below were obtained with 1000 particles, with a tolerance ε fixed as 10^{10} for the first iteration, while the tolerance for the convergence of the coefficient of variation was fixed as Dist_{CV}=0.005. CV_1 was set to 10^{10} for the first iteration. The priors for each parameter were chosen as uniform distributions, in the range $[0.5\boldsymbol{\theta}_{exact}, 1.5\boldsymbol{\theta}_{exact}]$, where $\boldsymbol{\theta}_{exact}$ are the parameter values presented by Table 1.

Figures 2.a-j present the evolution of the histograms for each of the model parameters, respectively, at each iteration of the ABC algorithm used here. These figures clearly show a strong reduction of the variance of the estimated parameters as the iterations advance. Convergence is achieved in 11 iterations, by satisfying the convergence criterion established in step 10 of the algorithm, which is proposed in this work. We notice in figures 2.a-j that the histograms at the final iteration resemble uniform distributions, because the actual Gaussian likelihood was not used in the ABC algorithm. Instead, a distance function based on the vector Euclidian norm was used for the selection of particles that appropriately represent the measured data. Furthermore, the histograms at the final iteration exhibit quite small variances, despite the very large Gaussian errors considered for generating the simulated data.

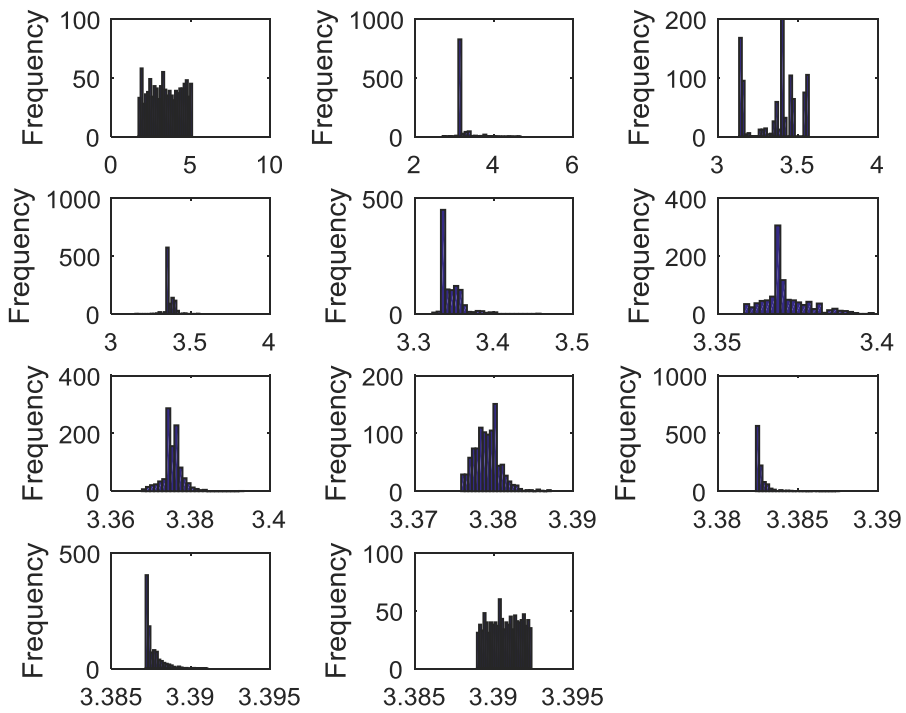

Figure 2.a Evolution of the histograms for the parameter v_0

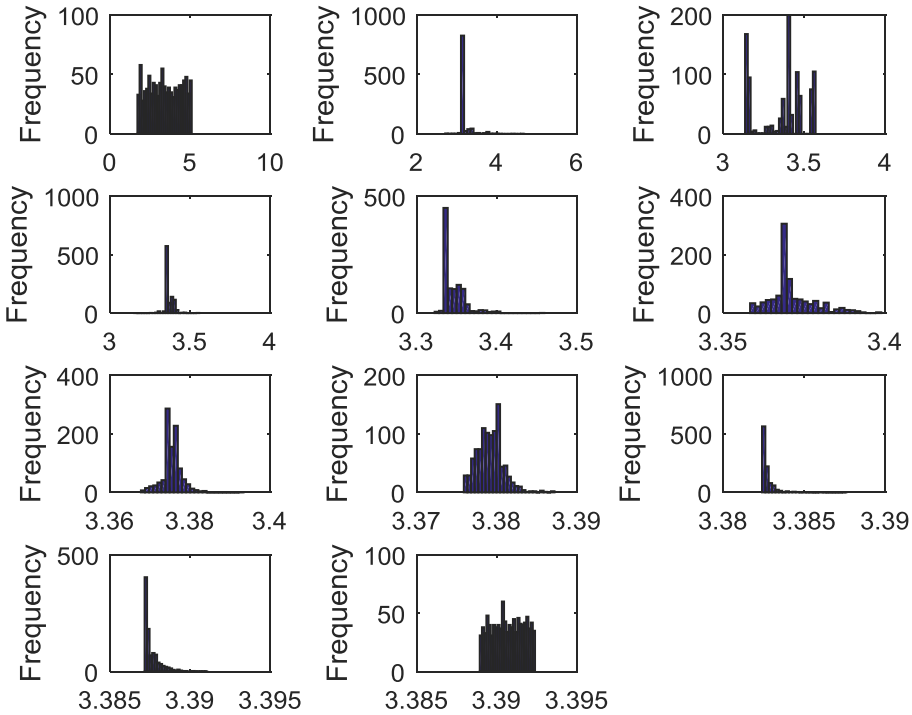

Figure 2.b Evolution of the histograms for the parameter v_1

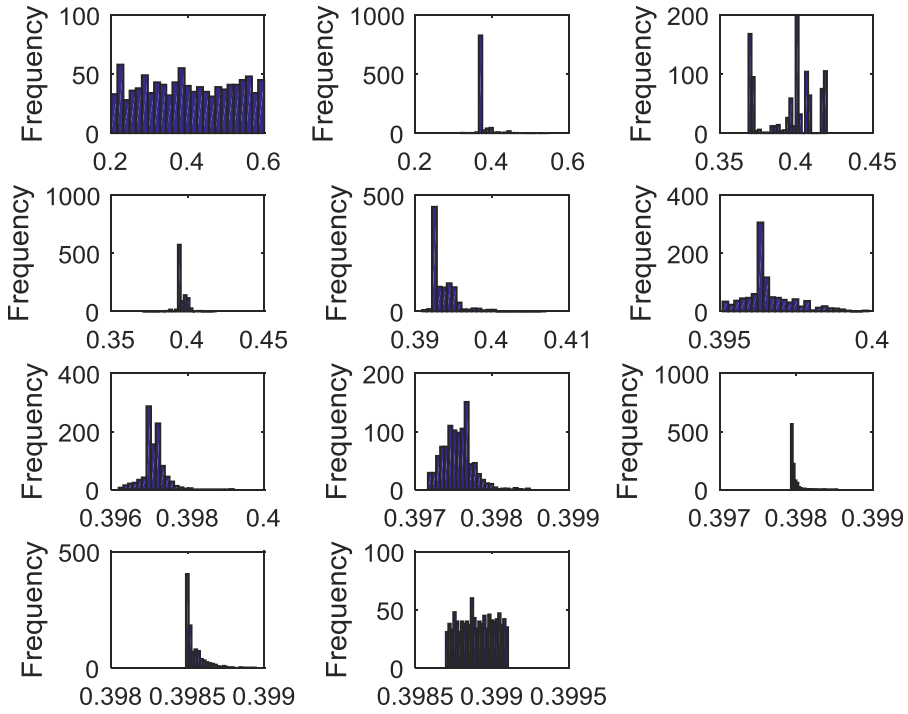

Figure 2.c Evolution of the histograms for the parameter β

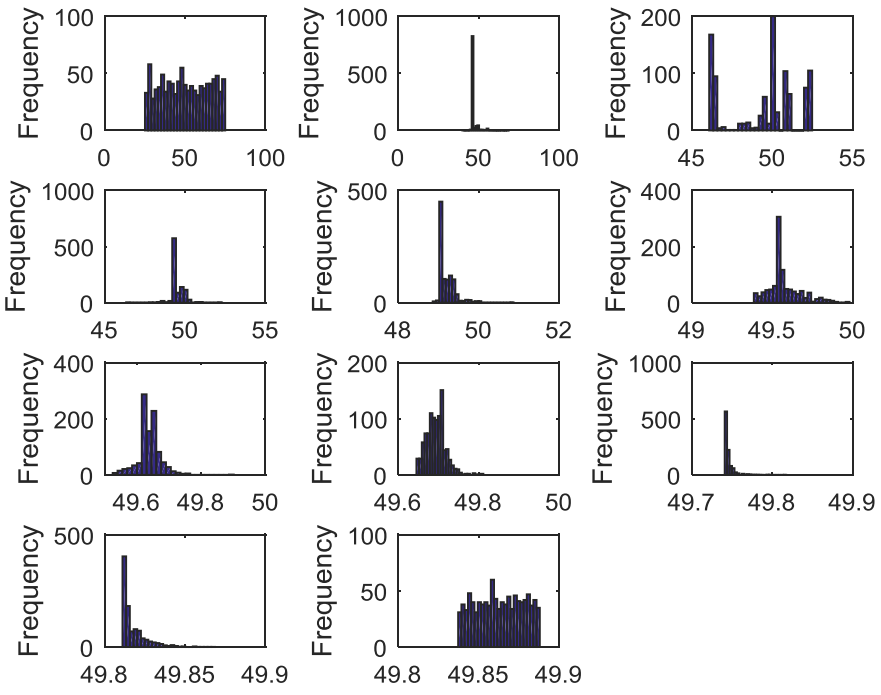

Figure 2.d Evolution of the histograms for the parameter V_{M2}

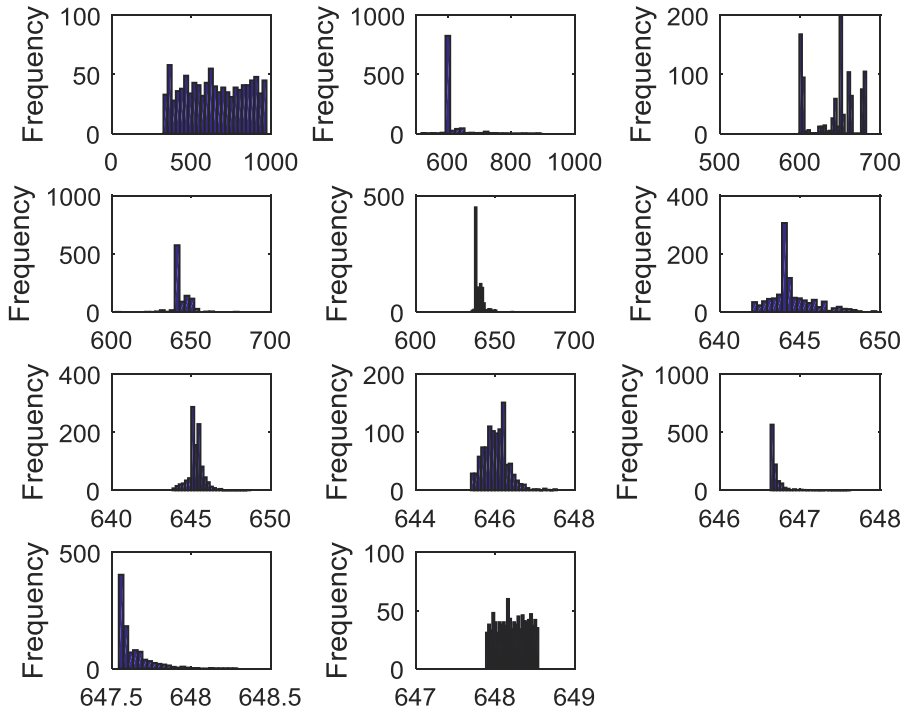

Figure 2.e Evolution of the histograms for the parameter V_{M3}

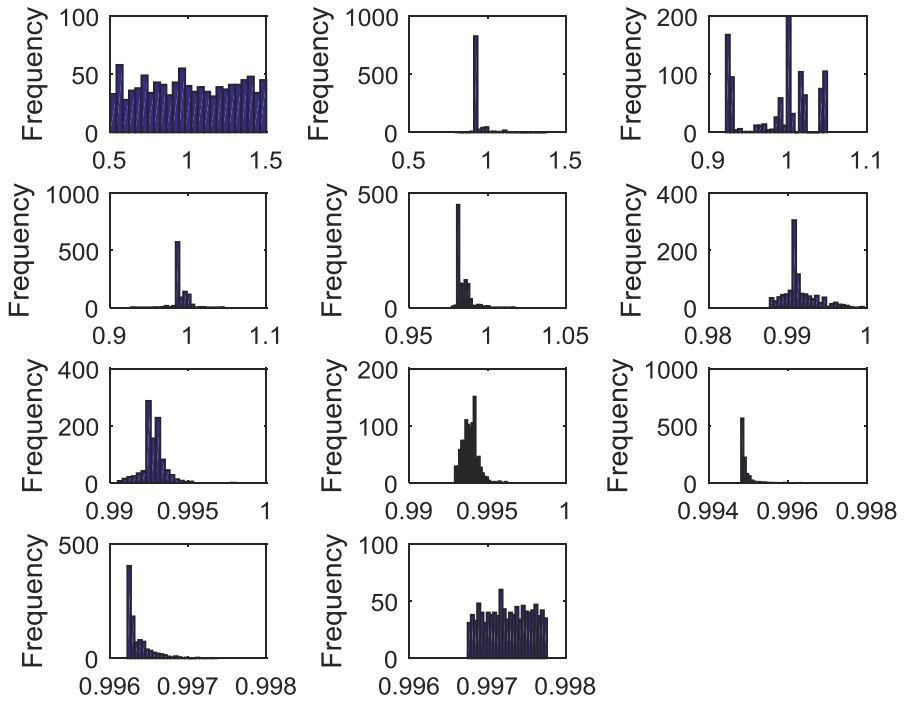

Figure 2.f Evolution of the histograms for the parameter K_2

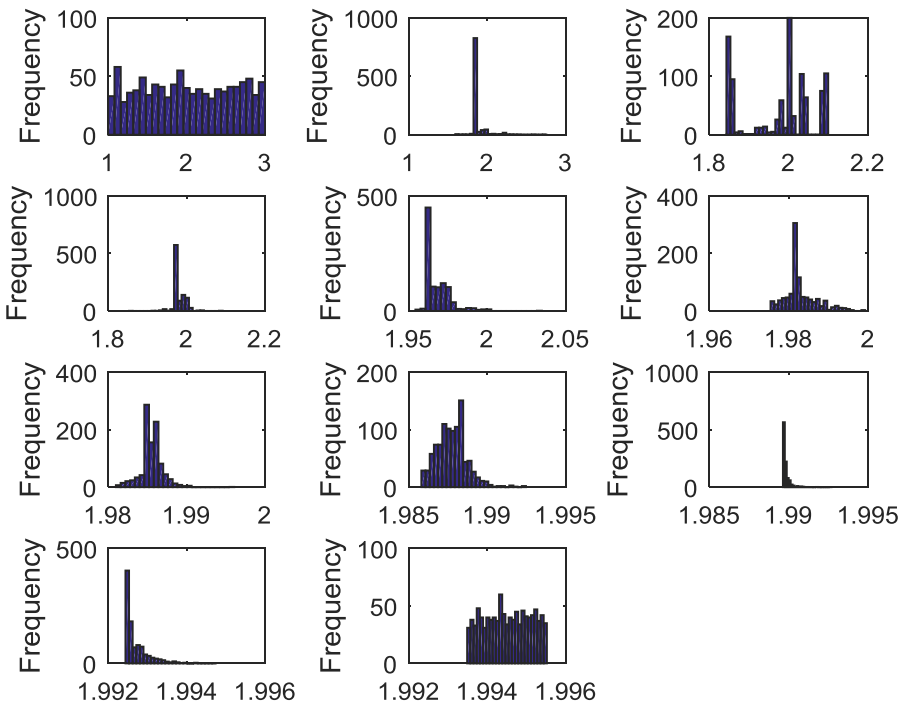

Figure 2.g Evolution of the histograms for the parameter K_r

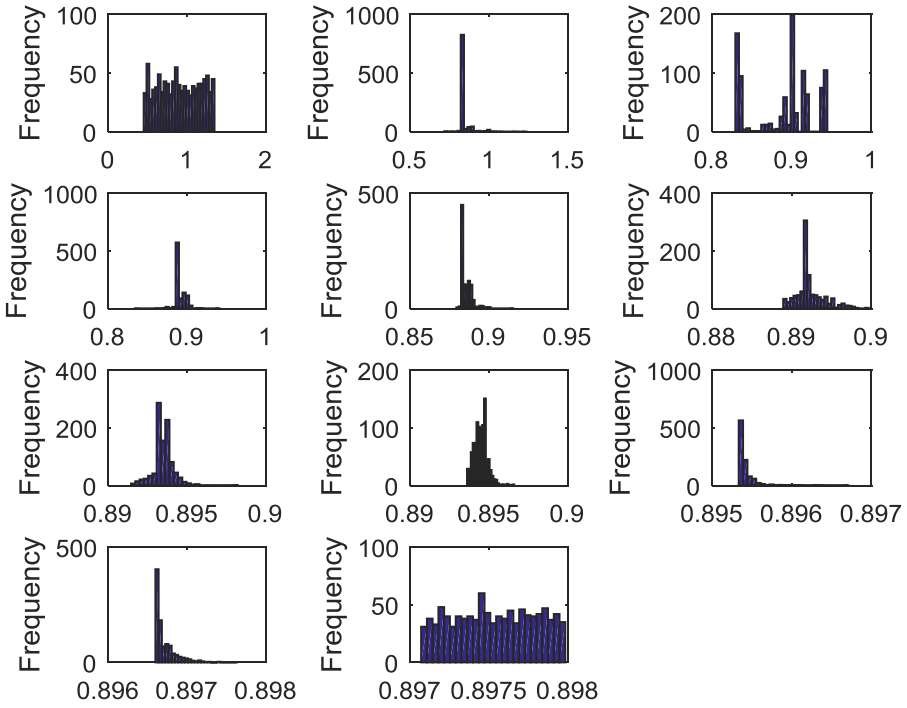

Figure 2.h Evolution of histograms for the parameter K_a

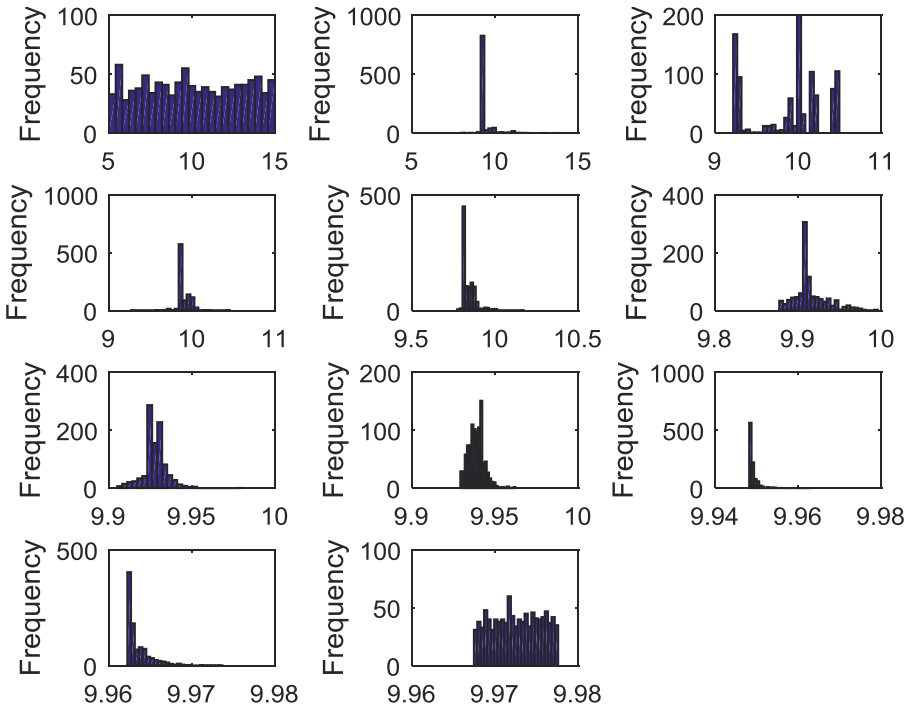

Figure 2.i Evolution of the histograms for the parameter K

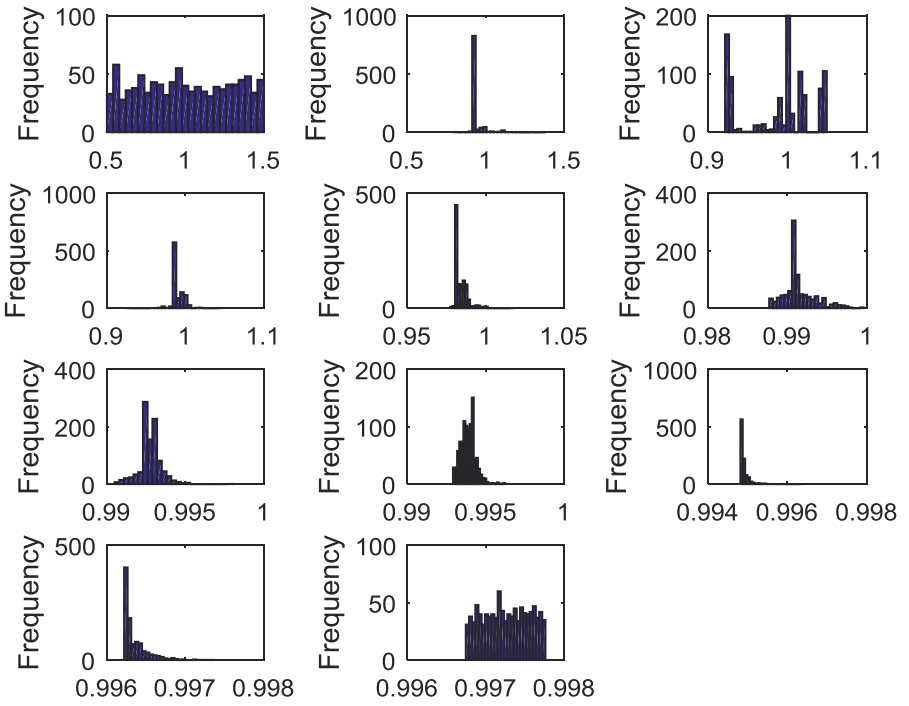

Figure 2.j Evolution of histograms for the parameter K_f

Figures 3.a,b exhibit the exact and estimated transient variations for the state variables $Z(t)$ and $Y(t)$, respectively. The simulated measurements are also presented in Figure 3.a. The estimated transient variations of these variables were obtained from the solution of the direct

problem with each sample of the converged marginal posteriors shown by Figures 2.a-j for each parameter. The agreement between estimated means and exact state variables is excellent. Furthermore, the 99% credible intervals resulting from this stochastic numerical simulation are quite small, due to the small variances of the converged marginal posteriors for each parameter.

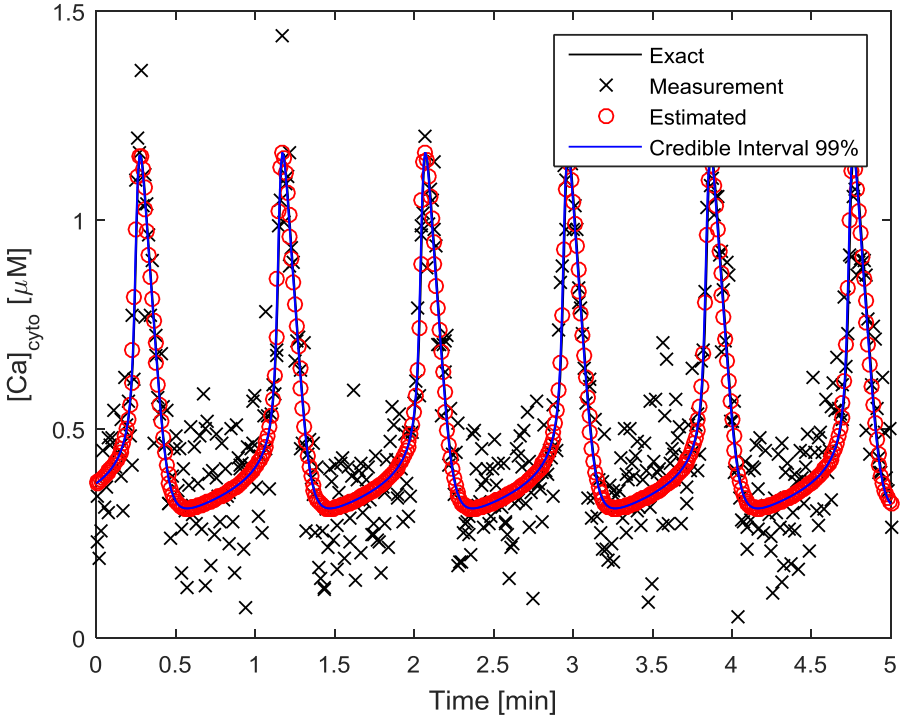

Figure 3.a Comparison of estimated and exact Z(t)

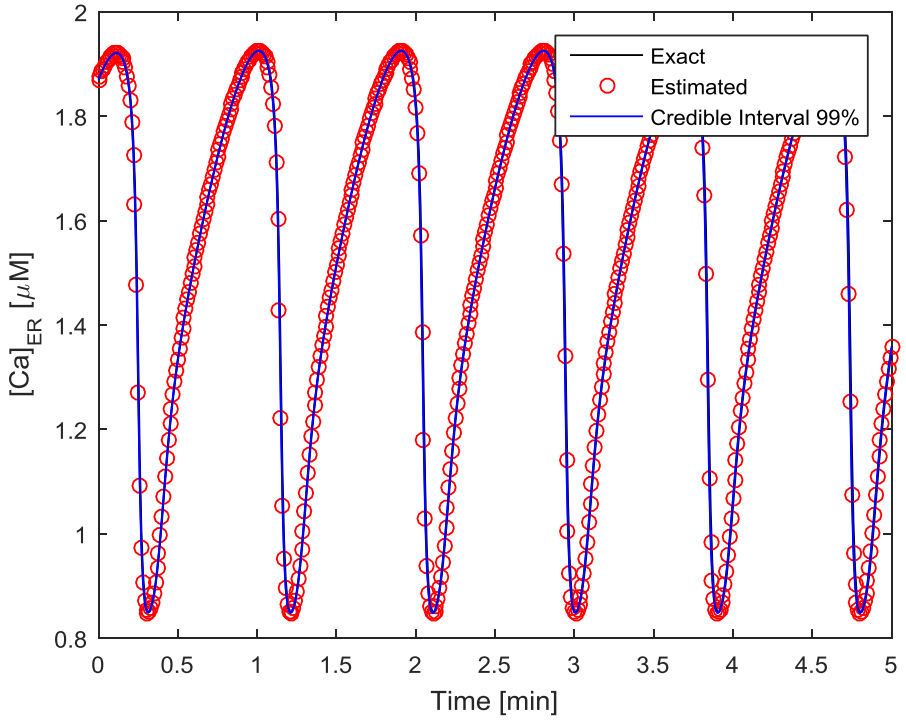

Figure 3.b Comparison of estimated and exact Y(t)

5 CONCLUSIONS

In this paper we applied an Approximate Bayesian Computation algorithm for the estimation of parameters in a Calcium Induced Calcium Release model for neurons. A procedure for the adaptive reduction of the tolerance for the acceptance of particles in the ABC algorithm was proposed in this work, together with a convergence criterion to stop the iterative procedure. Simulated measurements of the concentration of Ca^{2+} in the cytosol with quite large uncertainties were used in the inverse analysis. The results presented above reveal that the technique used in this paper is quite robust with respect to the measurement errors, being capable of significantly reducing the variances of each parameter as the iterations advance, even for uniform priors with large support. Results obtained with the stochastic simulation of the direct problem, by using samples of the parameters generated with the ABC algorithm at the final iteration, reveal that the state variables can be very accurately predicted with the present approach.

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