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# Dynamical Analysis of Uterine Cell Electrical Activity Model

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***Abstract*— The uterus is a physiological system consisting of a large number of interacting smooth muscle cells. The uterine excitability changes remarkably with time, generally quiescent during pregnancy, the uterus exhibits forceful synchronized contractions at term leading to fetus expulsion. These changes characterize thus a dynamical system susceptible of being studied through formal mathematical tools. Multiple physiological factors are involved in the regulation process of this complex system. Our aim is to relate the physiological factors to the uterine cell dynamic behaviors. Taking into account a previous work presented in [1] in which the electrical activity of a uterine cell is described by a set of Ordinary Differential Equations, we analyze the impact of physiological parameters on the response of the model, and identify the main subsystems generating the complex uterine electrical activity, with respect to physiological data.**

## I. INTRODUCTION

The electrophysiological modelling is an important tool that helps in the comprehension of physiological mechanisms of biological systems. Similarly to most excitable cells, the uterine cell exhibits different types of electrical activity shapes during pregnancy (a single Action Potential (AP), repetitive AP, burst of AP). Since no much information about myometrial ionic currents is available, and since uterine cell model considers a wide number of parameters, it seems important to analyze the dynamic of the model in order to understand the effect of each parameter in the system's global behavior. Such analysis can be done by means of bifurcation analysis. However when the number of parameters in the model is high, a technique to simplify the system is recommended. This simplification process is usually called model reduction and it is a topic which receives growing attention, both in the mathematics community and in various application areas. In this particular case study we apply this idea so that we can reproduce the behavior of the original system proposed in [1] with a smaller number of equations while respecting the major physiological processes. For this uterine cell model we present an algorithm to determine the sensitivity of the system to changes This useful strategy has shown to be very appropriate in biochemical networks and it was applied with success recently in [2] where the concepts of nonlinear systems and control theory were used to identify the components and feedback interactions that generate periodic oscillations in Xenopus cell cycle.

This contribution is organized as follows: In section II is presented the uterine cell model on which our work is based. The methodology to address the problem of sensitivity analysis applied to uterine electrical activity is presented in sections III and IV. Concluding remarks are given in section VI.

## II. THE UTERINE CELL MODEL

The following equations present the mathematical model for the uterine cell, which is based on the general Hodgkin-Huxley (HH) format [3] taking into account physiological parameters found in the literature such as in [4].

$$\begin{array}{c} dV/dt = (I_{stim} - \sum_i I_i)/C_m \\ dm_{Na}/dt = (m_{Na\infty}(V) - m_{Na})/\tau_{mNa}(V) \\ dh_{Na}/dt = (h_{Na\infty}(V) - h_{Na})/\tau_{hNa}(V) \\ dm_{Ca}/dt = (m_{Ca\infty}(V) - m_{Ca})/\tau_{mCa}(V) \\ dh_{1Ca}/dt = (h_{Ca\infty}(V) - h_{1Na})/\tau_{h1Ca}(V) \\ dh_{2Ca}/dt = (h_{Ca\infty}(V) - h_{2Na})/\tau_{h2Ca}(V) \\ dn_{K1}/dt = (n_{K1\infty}(V) - n_{K1})/\tau_{n_{K1}}(V) \\ dn_{K2}/dt = (h_{K2\infty}(V) - n_{K2})/\tau_{n_{K2}}(V) \\ dh_{K1}/dt = (h_{K1\infty}(V) - h_{K1})/\tau_{h_{K1}}(V) \\ d[Ca^{2+}]_i/dt = f_c(\alpha I_{Ca} - K_{Ca}[Ca^{2+}]_i) \end{array} \quad (1)$$

The main equation in (1) presents how the variation of transmembrane potential $V$ depends on the following currents : $I_{stim}$ the external stimulation current, $\sum_i I_i$ the total ionic current. $I_i$ corresponds to the sodium voltage dependent current $I_{Na(V)}$, the calcium voltage dependent current $I_{Ca(V)}$, the potassium current $I_K$ . This last one includes the voltage dependent current $I_{K(V)}$ composed by three components ($I_{K1(V)}$, $I_{K2(V)}$, $I_{K3(V)}$) where $n_{K3}$ reach quickly its steady state, and potassium calcium dependent current $I_{K(Ca)}$.

Each ionic voltage dependent current $I_i(V)$ is expressed by $I_i = g_i(V - E_i) = G_i m_i^x h_i^y (V - E_i)$ where $G_i$ is the maximum conductance when all ionic gates of ionic channel $i$ are open. $m^x.h^y$ denotes the probability of the conductivity state of an ionic channel. The variation of each gating variable $m$ or $h$ is expressed as follows :

$$dg/dt = (g_\infty - g)/\tau_g \quad (2)$$

In equation (2) $g$ represents either activation gates $m$ for sodium and calcium currents, $n$ for potassium voltage dependent current or inactivation gates $h$. The $\tau_g$ denotes relaxation time, $g_\infty$ denotes the in/activation steady state

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which follows the following Boltzman distribution.

$$g_\infty = 1/[1 + \exp(V_g - V)/S] \quad (3)$$

The activation kinetics are represented by $m_{Na}$, $m_{Ca}$, $n_{K1}$ and $n_{K2}$ whereas the inactivation kinetics are represented by $h_{Na}$, both $h_{1Ca}$, $h_{2Ca}$ calcium inactivation gates and $h_{K1}$.

The last equation $d[Ca^{2+}]_i/dt$ in (1) represents the temporal behavior dynamics of intracellular calcium concentration where $[Ca^{2+}]_i$ temporal variation depends on the inward calcium current, $I_{Ca}$, and on the sequestration of intracellular $Ca^{2+}$ ions by the intracellular compartments. $fc$ is the rate of calcium participating in calcium cytosolic concentration, $\alpha$ represents a factor that allows the conversion of current in cytosolic concentration and $K_{Ca}$ is a constant rate representing the effects of diffusion and buffering.

## III. BIFURCATION ANALYSIS

The bifurcation diagram gives an overview of the qualitative behavior of the uterine cell model and consequently makes possible the examination of how its dynamics are affected with the variation of specific parameters. The state variable $V$ which corresponds to the electrical activity of the uterine cell is considered as the main variable of interest in this system. Bifurcation diagrams describing the variation of this state variable in function of parameters variables has been obtained using XPPAUT [7]. Figure 1 shows $I_{stim}$ bifurcation diagram where $V$ is represented on the $y$ axis and the control parameter $I_{stim}$ on the $x$ axis. The black circles refer to stable orbits and the white circles refer to unstable orbits (limit cycles). The solid bold curves represent stable steady state solutions and dashed lines the unstable steady state. Note that the system presents oscillatory behavior for a $1.2-3.3\mu A/cm^2$ range of $I_{stim}$. These two values consist in the two Hopf bifurcations points. An example of the model response is presented in Figure 2 for $I_{stim} = 1.7\mu A/cm^2$

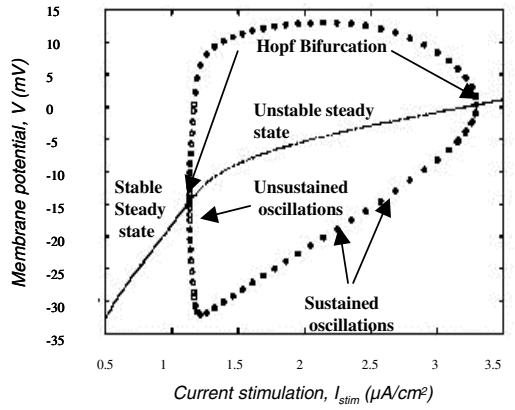


Fig. 1. Relation between uterine cell membrane potential ($V$) and current stimulation ($I_{stim}$) applied.

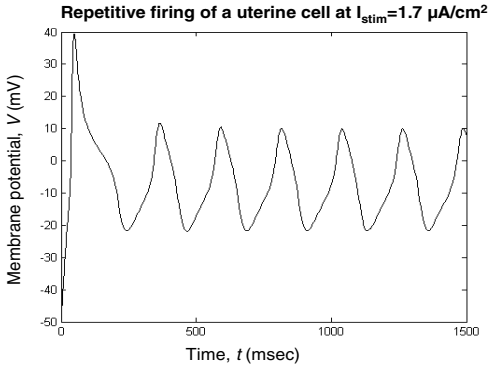


Fig. 2. Train of action potentials simulated for a stimulating current of $1.7\mu A/cm^2$

The stable limit cycle in Figure 1 indicates the maximum and minimum interval of the membrane potential oscillations presented in Figure 2. We highlight the fact that the bifurcations were observed also for the parameters $G_{Ca}$, $V_{mCa}$, $S_{hCa}$, $\alpha$ and $f$, $K_{Ca}$. Our analysis indicates the calcium as the main factor in myometrial excitability.

## IV. STABILITY ANALYSIS

Since the wide number of parameters in uterine cell model complicates the study, our aim is to determine the major variables and their interactions in order to simplify the model by determining the most important subsystems.

Our methodology is based on the work given in [5] which consists first in the analysis of the stability of the variables and their response upon an introduced perturbation. This technique is called sensitivity analysis and consists in the introduction of a perturbation to the Jacobian matrix corresponding the linearized system. This is possible by the fact that the local steady state stability of a nonlinear system can be determined from the linearization of the system around a particular equilibrium point. Additional information about it can be consulted in [6] where classical results related to stability of steady states are analyzed based on the linearization of the system in the vicinity of the bifurcation points.

We are interested in the nonlinear phenomena and limit cycles that occur in the nonlinear model that describe uterine cell oscillations. By analyzing the mechanisms that modify the nature of the steady state we can determine the parameters responsible for creating the limit cycle and as consequence, the appearance of periodic oscillations.

The linearized system is presented by the Jacobian matrix. Then we search for the smallest absolute value for which the stability is induced through a simple root analysis. This is done first for the elements of the main diagonal, which allows the determination of the main model's variables and then for the whole matrix elements to determine the main interactions between variables. The system of nonlinear equations (1)can be rewritten in the form :

$$\dot{x} = f(x, p) \quad (4)$$

The state vector $x$ of dimension 10 denotes the temporal derivative of uterine cell variables $(V, m_{Na}, h_{Na}, m_{Ca}, h_{1Ca}, h_{2Ca}, n_{K1}, n_{K2}, h_{K1}, [Ca^{2+}]_i)$. The system's parameters are represented by $p$. The vector-valued function $f = (f_1, .., f_{10})$ determines the dynamics of the system. Therefore the system is composed by ten small subsystems interconnected as presented in Figure 3.

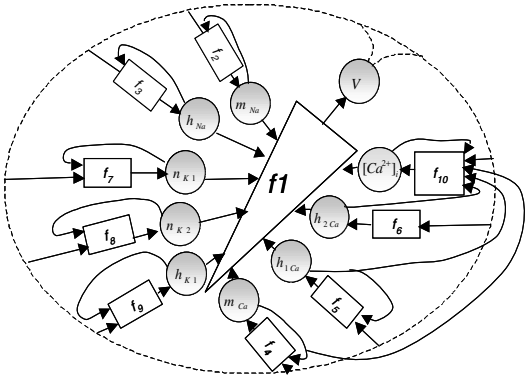


Fig. 3. Representation of the uterine cell model. Each subsystem $f_i$ corresponds to the ith ordinanary differential equation in the model (1). The outputs of the $f_2 \dots f_{10}$ affect the main subsystem $f_1$. The model's variables are represented by the circles. The dashed line represents the variable $V$, output of $f_1$, that serves as input to $f_2 \dots f_{10}$.The solid arrows represent the feedback and/or the interconnections lines between subsystems.

A step by step description of the algorithm used to compute the perturbation introduced to the linearized system in a small neighborhood of the equilibrium point $x^*$ is presented in the following. This algorithm consists in to apply a range of negative and positive values of perturbation to the linearized system. These perturbations can provide measures of performance of each feedback and interactions and their impact on the overall network stability.

Step 1−Figure 1, The $I_{stim}$ diagram bifurcation obtained by xppaut, shows limit cycle which underlies unstable steady states. By determining the mechanisms which modify the nature of the steady state, we could understand which mechanisms are responsible for creating the limit cycle.

The algorithm is started with the system in the unstable steady state zone as illustrated in Figure 1. Next we proceed to the sensitivity analysis by constructing an algorithm in Matlab® with the objective of introducing a perturbation to the linearized model described by the Jacobian matrix, showing variable sensitivity as follow :

$$J(f, x^*) = \left.\frac{\partial f}{\partial x}\right|_{x^*} = \left[\begin{array}{ccc} \frac{\partial f_1}{\partial x_1} & \cdots & \frac{\partial f_1}{\partial x_{10}} \\ \frac{\partial f_2}{\partial x_1} & \cdots & \frac{\partial f_2}{\partial x_{10}} \\ \vdots & \ddots & \vdots \\ \frac{\partial f_{10}}{\partial x_1} & \cdots & \frac{\partial f_{10}}{\partial x_{10}} \end{array}\right]\Bigg|_{x^*} \quad (5)$$

We start at an unstable steady state. Then a perturbation is added to the elements of the main diagonal (which correspond to the state variables) of the Jacobian matrix, then the perturbation is introduced to the elements in the off-diagonal (which corresponds to interactions among the variables) of the Jacobian matrix.

Step 2− The system is linearized around the unstable steady state $x^*$ near the bifurcation point by computing (5) and evaluate it at the operating point $x^*$ under consideration.

Step 3− For each element of the main diagonal of the Jacobian matrix, we add a perturbation $K_{ii}$, $J(f, x^*, K_{ii})$,and compute the smallest absolute value of $K_i$ (if it exists), such that the perturbed linearized system becomes stable, mean all eigenvalues of the Jacobian matrix must be in left hand side of the complex plane.

Step 4− Compare the absolute values of $K_{ii}$ for $i = 1, ...n$ and select those that are comparatively smaller than the others. The results are presented in Figure 4.

Step 5 − Add a perturbation $K_{ij}$ to the off-diagonal element $(i, j)$ of the Jacobian matrix $J(f, x^*, K_{ij})$ evaluated at the operating point $x^*$ and compute the smallest perturbation $|K_{ij}|$ which makes the Jacobian matrix stable.

Step 6 − Compare the absolute values of $K_{ij}$ for all $i$ and $j$. Those that are comparatively smaller than the others are selected. They correspond to the fundamental interactions in the complex behavior of interest.

As a result, the algorithm returns two arrays. The first one contains the minimum perturbations $|K_{ii}|$ values corresponding for main feedback loops, and the second one contains the smallest $|K_{ij}|$ values corresponding to the main interactions.

## V. Results

The response of the linearized system, after perturbation applied on $V$, shows a stable response which could be described by a plateau that may follow an action potential.

Figure 4 presents the smallest obtained absolute values of perturbation introduced to elements of the main diagonal of the Jacobian matrix. These values correspond to the minimum perturbation applied on the system necessary to stabilize the linearized model. They indicate therefore the state variables (in this case $V$ and $m_{Ca}$) considered as key in stabilizing process.

Based on the results we found that the reduced model, i.e., the minimum number of equations necessary to reproduce the repetitive periodic activity of the uterine cell shown in Figure 2, is the one composed of six equations corresponding to the variables $(V, m_{Ca}, n_{K2}, h_{1Ca}, h_{2Ca}, [Ca^{2+}]_i)$.It means that we can obtain with these six equations the same dynamic behavior obtained with the original system (1). Since the main state variables are determined, the second step is just to identify the main interactions among the states in the uterine cell model. The procedure is similar to the one described for the main feedback. We underline that in this case the algorithm must vary the perturbation into a range of values for all elements of the Jacobian matrix. The results are presented in figure 5. Note that the most important

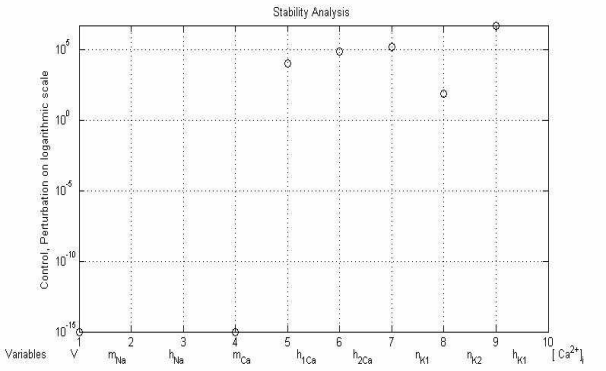


Fig. 4. Analysis of the model: magnitude of the perturbation,$|K_i|$,on each variable required to stabilize the steady state of the cell.

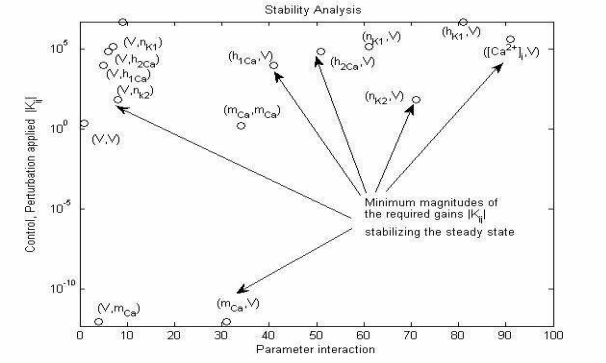


Fig. 5. Analysis of the model: magnitude of the perturbation,$|K_{ij}|$ required to stabilize the system via pairwise interactions, i.e. the influence of interaction of variable $i$ to variable $j$.

pairwise interactions correspond to the pairs ($V$,$m_{Ca}$), ($V$, $n_{K2}$), ($V$, $h_{1Ca}$), ($V$, $h_{2Ca}$) and ($V$,$[Ca^{2+}]_i$). These results confirm the minimum set of equations able to reproduce the train of APs in the uterine cell.

## VI. CONCLUSION

A study of the dynamics and feedbacks in the field of biomedical engineering dealing with uterine electrical activity has been exploited. The results obtained with help of tools from system theory have improved the determination of instrumental variables and their interactions in the physiological system.

The main idea of the approach is to introduce a perturbation in the elements of the Jacobian matrix evaluated in the vicinity of bifurcation points where phenomena of interest occurs. The smallest perturbation for which a stabilizing effect occurs underline the critical variables (diagonal elements of the Jacobian) and main interactions (off-diagonal elements of the Jacobian) which play a major role in the generation of oscillations.

The uterine cell model previously developed simulates the complex uterine electrical activity. Bifurcation analysis permitted us to have a general overview of the dynamic behavior of the model and evidenced the existence of a limit cycle, underlying an unstable steady state.

Since simpler models are easier to analyze, our efforts were focused on simplification of the model that can be able to reproduce the electrical activity of the uterine cell while respecting the main physiological factors. The applied method (linearization with a Jacobian matrix computed at the equilibrium) permitted us to determine the main variables in uterine cell model. The smaller is the perturbation introduced on each feedback variable to stabilize the system, the most important is the impact on the system behavior.

Figure 4 shows that the minimum perturbation values correspond to variables $(V, m_{Ca}, n_{K2}, h_{1Ca}, h_{2Ca})$. We underline that all these five variables modulate the temporal behavior of $[Ca^{2+}]_i$, figure 3. This explains why the $[Ca^{2+}]_i$ is also a key variable in the reduced system despite of the high required perturbation value necessary to stabilize the model and emphasizes the important role played by $[Ca^{2+}]_i$ as a main mechanism in the generation of sustained oscillations. In a qualitative way, the model has been reduced to six variables $(V, m_{Ca}, n_{K2}, h_{1Ca}, h_{2Ca}, [Ca^{2+}]_i)$ and this reduced system allow to reproduce the same repetitive periodic activity observed in uterine cell at term [8], with respect to physiological parameters found in the literature. This new subsystem will now serve to guide the research for the most important physiological parameters related to the evolution of uterine activity along pregnancy.

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