Uterine electrical activity modeling

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1 Introduction

Our aim is to simulate uterine electrical activity at cell and tissue level within decent computation times. Two paths have been explored : –first, simple non-physiological models able to reproduce the bursts shape but without links to physiology, –secondly, simplified physiological models which keeps most of the physiological mechanisms but in simpler forms, leading to faster computations. We also explored the use of algorithmic optimizations in the integration methods of the ODEs.

This document describes the cell model to be used in the project.

2 Simplified physiological model

Parthimos et al. [PEG99] proposed a model of calcium oscillators in smooth muscle cells in arteries. This model describes the oscillations of membrane potential, intracellular calcium concentration and their coupling. It expresses the ionic flux through the cell membrane and with the sarcoplasmic reticulum. They also proposed a link with force generation via the intracellular calcium concentration.

The contribution of Koenigsberger et al. [KSL+04] is an extension of [PEG99]. It describes calcium dynamics in smooth muscle cells by means of two coupled oscillators: the intracellular calcium concentration $[Ca^{2+}]$ and the electrical potential of the cell membrane v_i. This work is also focused on vascular smooth muscle. It takes into account both electrical and chemical stimulation of cells. It also provides a model of interaction and synchronization between cells.

2.1 Methods

The strategy used to define this simplified model was to take the reduced uterine model (6 variables instead of 10) and use Python's profiling tools to track the most computational intensive mechanisms. As expected, the computation of I_{Ca} represents most of the computation time as it uses 3

of the 6 variables. This current represents the calcium entrance in the cell. This is mainly due to *VOC* channels, so we replaced it's former expression by the one proposed by Parthimos et al. This leads to a 3 variables reduced model (*Red3* model) and saves most of the computations of the exponential function.

The resulting model is described by the following equations :

$$\begin{aligned} \frac{dV_m}{dt} &= \frac{(I_{stim} - I_{Ca} - I_K - I_{KCa} - I_L)}{C_m} \\ \frac{dn_K}{dt} &= \frac{h_{K\infty} - n_K}{\tau_{n_K}} \\ \frac{d[Ca^{2+}]}{dt} &= f_c * (-\alpha I_{Ca} - K_{Ca}[Ca^{2+}]) \end{aligned} \tag{1}$$

The currents are defined as follows:

I_{Ca} Voltage dependent calcium channels current: $J_{back} - G_{Ca}(V_m - E_{Ca}) \frac{1}{1+\exp\left(\frac{V_{Ca}-V_m}{R_{Ca}}\right)}$

I_K Voltage dependent potasium channels current: $G_k n_k (V_m - E_k)$

I_{KCa} Calcium dependent potasium channels current: $G_{kCa} \frac{[Ca^{2+}]^2}{[Ca^{2+}]^2 + k_d^2} (V_m - E_k)$

I_L Leak current: $G_L(V_m - E_L)$

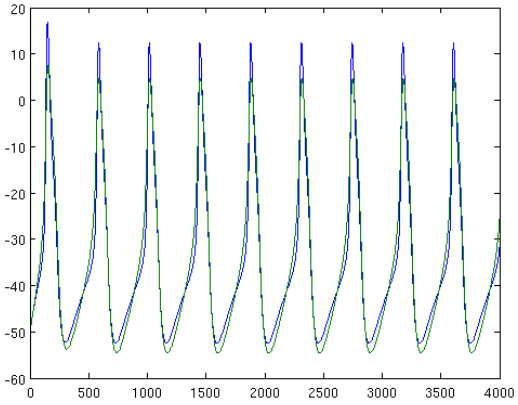
Finally, the expression of E_{Ca}, $h_{K\infty}$ and τ_{n_K} are:

$$\begin{aligned} E_{Ca} &= \frac{RT}{2F} \ln\left(\frac{[Ca^{2+}]_0}{[Ca^{2+}]}\right) \\ h_{K\infty} &= \frac{1}{1 + \exp\left(\frac{4.2 - V_m}{21.1}\right)} \\ \tau_{n_K} &= 23.75 \exp\left(\frac{-V_m}{72.15}\right) \end{aligned} \tag{2}$$

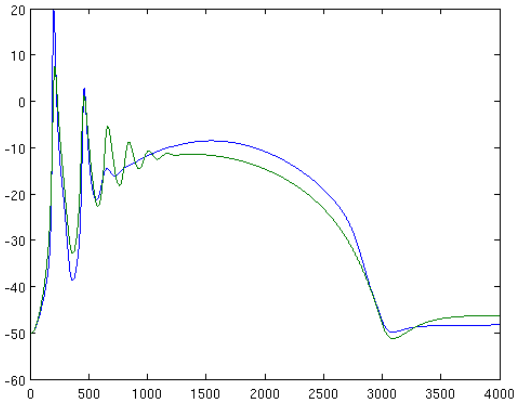
The model structure remains close to the uterine activity model. Parameters of the new I_{Ca} are then optimized using direct search methods to match the output of uterine activity model.

2.2 Results

Figure 1 shows the model output for two different stimuli, the VOCC parameters have been optimized in each case.



(a) Labor type signal.



(b) Pregnancy type signal

Figure 1: Blue: 10 variables uterine activity model, Green: *Red3* model.

We obtain rather good match for both signals, in term of time course and also in the frequency of the oscillations. In opposite to FHN model, it is possible to obtain non-stationary outputs. Computation time shows significative improvements and will be addressed in detail later on.

3 Conclusion

In this work, we explored different strategies for reducing the simulation time of the uterine activity in two different stages of pregnancy. It should allow us to simulate 2D and even more 3D physical uterine muscle activity in a relatively small amount of time. Here we try to use more simple models, i.e. with less variables to integrate, and to work on algorithmic optimization of the integration step.

Regarding simpler physiological models, our first approach using a modified Parthimos model has been unsuccessful. This model showed the basic behavior we wished, generating oscillatory or plateau-like signals. Unfortunately, we couldn't optimize its parameters it a way to match the uterine activity model satisfyingly. The latest work on the *Red3* model is promising. The first optimization results show that it is able to match the uterine activity model fairly well and there is a important improvement on computation times for big grids of cells. On going work focuses on determining how well the links to physiology are preserved in the simplifications and which size of grid we can simulate with this model in a decent amount of time.

References

[KSL+04] Michèle Koenigsberger, Roger Sauser, Mathieu Lamboley, Jean-Louis Bény, and Jean-Jacques Meister. Ca2+ dynamics in a population of smooth muscle cells: modeling the recruitment and synchronization. *Biophys J*, 87(1):92–104, Jul 2004.

[PEG99] D. Parthimos, D. H. Edwards, and T. M. Griffith. Minimal model of arterial chaos generated by coupled intracellular and membrane ca2+ oscillators. *Am J Physiol*, 277(3 Pt 2):H1119–H1144, Sep 1999.

[RTGM09] Sandy Rihana, Jeremy Terrien, Guy Germain, and Catherine Marque. Mathematical modeling of electrical activity of uterine muscle cells. *Medical and Biological Engineering and Computing*, 47:665–675, 2009. 10.1007/s11517-009-0433-4.

A Parameters values

Table 1: Identified parameters for calcium dynamics

Variable	Value	Description
I_{Bck}	0.029	Background calcium current (μA/cm^2)
G_{Ca}	0.022	VOCC conductance (mS/cm^2)
V_{Ca_2}	-24.88	Half-point of the VOCC activation sigmoid (mV)
R_{Ca}	4.81	Maximum slope of the VOCC activation (mV)

Table 2: Parameters taken from [RTGM09]

Variable	Value	Description
G_k	0.064	Potasium channels conductance (mS/cm^2)
G_{kCa}	0.08	Potasium/Calcium channels conductance (mS/cm^2)
G_L	0.0055	Leak channels conductance (mS/cm^2)
k_d	0.01	Half-point potasium concentration (μmol)
f_c	0.4	calcium influx propability
α	4e-5	current conservation factor (molcm^2/μC)
k_{Ca}	0.1	Ca extraction factor (ms^{-1})
E_L	-201	Leak nerst potential (mV)
E_K	-83	Potasium nerst potential (mV)
R	8.314	gas constant (JK^{-1}mol^{-1})
T	295	Temperature (K)
F	96.487	Faraday constant (kCmol)
$[Ca^{2+}]_0$	3	Extracellular calcium concentration (μmol)