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An electro-mechanical multiscale model of uterine pregnancy contraction

Maxime Yochum *, Jérémy Laforêt, Catherine Marque

Sorbonne University,Université de technologie de Compiègne, CNRS, UMR 7338 Biomechanics and Bioengineering, Centre de recherche Royallieu, CS 60319-60203 Compiègne cedex, France

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ABSTRACT

Detecting preterm labor as early as possible is important because tocolytic drugs are much more likely to delay preterm delivery if administered early. Having good information on the real risk of premature labor also leads to fewer women who do not need aggressive treatment for premature labor threat. Currently, one of the most promising ways to diagnose preterm labor threat is the analysis of the electrohysterogram (EHG). Its characteristics have been related to preterm labor risk but they have not proven to be sufficiently accurate to use in clinical routine. One of the reasons for this is that the physiology of the pregnant uterus is insufficiently understood. Models already exist in literature that simulate either the electrical or the mechanical component of the uterine smooth muscle. Few include both components in a co-simulation of electrical and mechanical aspects. A model that can represent realistically both the electrical and the mechanical behavior of the uterine muscle could be useful for better understanding the EHG and therefore for preterm labor detection. Processing the EHG considers only the electrical component of the uterus but the electrical activity does not seem to explain by itself the synchronization of the uterine muscle that occurs during labor and not at other times. Recent studies have demonstrated that the mechanical behavior of the uterine muscle seems to play an important role in uterus synchronization during labor. The aim of the proposed study is to link three different models of the uterine smooth muscle behavior by using co-simulation. The models go from the electrical activity generated at the cellular level to the mechanical force generated by the muscle and from there to the deformation of the tissue. The results show the feasibility of combining these three models to model a whole uterus contraction on 3D realistic uterus model.

1. Introduction

Premature birth is 9.6% of all births worldwide making preterm birth one of the world's largest public health problems [1]. The highest rates of preterm birth are in Africa and North America (11.9% and 10.6% of all births, respectively) [1]. Premature birth leads to high morbidity and mortality of newborns and can also lead to long-term adverse consequences for baby's and parents' health [2]. Children born at term have lower rates of cerebral palsy, sensory deficits, learning disabilities and respiratory illnesses when compared with children who are born before term, which results in enormous physical, psychological and economic costs [3,4]. To prevent premature labor efficiently, it is important to detect preterm labor symptoms as soon as possible via some biochemical or biophysical indicator. The electrical activity of the uterus is one of the most promising tools for the detection of preterm labor signs [5–7]. The electrohysterogram (EHG), which is the uterine electrical activity recorded externally on a women's abdomen is representative of uterine contraction as it is directly related to the electrical activity of the muscle which is the trigger of the mechanical contraction [8,9]. The prediction of a preterm labor by processing the EHG is possible from the 28th weeks of gestation [10], time when preterm labor can be treated effectively if detected soon enough or the baby prepared for premature birth using steroids.

The uterine electrical activity detected on the abdomen's surface is generated at the cellular level. It passes through different kinds of tissue including muscle, fat and skin before reaching the abdominal electrode and being recorded as EHG.

A correlation clearly exists between the electrical and the mechanical activities of the uterine muscle [11]. The mechanical effect of the uterine contraction depends on the cells excitability, as well as on the synchronization of the uterine cell activities, which occurs for whole cells in a short time during labor. This uterine synchronization could be related to the appearance of communicating junctions (Gap Junction) and by electrical diffusion

* Corresponding author.
E-mail address: maxime.yochum@utc.fr (M. Yochum).

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through the extracellular medium, permitting thus the excitability to propagate over the uterus [12–14]. But, the electrical propagation over the tissue does not on its own explain this uterine global synchronization present during labor [15]. Recent studies suggest that this uterine synchronization is a key factor in developing efficiency of uterine contractions [16]. A new hypothesis has been proposed that explains this uterine synchronization by means of a hydrodynamic-stretch activation mechanism that involves the mechanical effects of contractions (Intra Uterine Pressure IUP increase, tissue stretching) as trigger of the electrical activity through a mechano/electric coupling [15].

Other links exist between the EHG and the mechanical effect of the contraction. These links are due to the tissue deformation resulting from the force generated by the smooth muscle cells (SMCs). The muscle contraction and the resulting tissue deformation modify the position of the cells. As the cells move due to these contractions the cells that are "seen" by the electrodes positioned on the skin change during contractions. This displacement of the electrodes with respect to the uterine muscle surface can cause artifacts on the EHG signal [17] and introduce nonlinearities in the signal. Another aspect that could be of interest is that the deformation of the tissue modifies the distance between adjacent cells, which may influence the electrical propagation by changing the tissue conductivity locally [18–20].

Furthermore, knowing in detail the forces generated by each active cell and their resulting tissue deformation will permit to compute the Intra Uterine Pressure which is another measure that physicians use during active labor to evaluate the uterus contractile activity. However, IUP cannot be used during pregnancy due to its invasiveness [21].

It has been proven that the electrical and the mechanical activities of smooth muscles cells (SMCs) are linked together [22]. It is widely admitted that the contraction of SMCs is initiated by the intracellular calcium concentration, named $[Ca_{2+}]i$, which links to the contractile elements of the SMC (actin and myosin proteins) [22]. It has also been proven that mechanical stretching of the SMC can induce modifications in the electrical behavior of the cell, especially through stretch-activated channels [23,24].

The aim of this paper is to present a novel model of the uterine smooth muscle behavior by means of the co-simulation of different models representing its different electrical and mechanical aspects. The objective is then to demonstrate the feasibility to combine three different models, at the uterine cell and tissue levels, in order to make a co-simulation of the contractile process at whole uterus level. This co-simulation could then allow us to link the EHG signal and the mechanical effects of contraction. The two major novelties of this study are that we use an electrical model with biophysical meaningful parameters instead of a simple neuron model (Fitzhugh-Nagumo), and that we applied this model on the geometry of a pregnant human uterus obtained from experimental data. The use of this geometry gives a more realistic simulation of the model.

The first model is an electrical one, dedicated to the cell/tissue level. It represents the ionic currents responsible for the uterine SMC activity, and its propagation over the tissue through electrical diffusion (simulating gap junctions). The second one is a force generation model at the cell level. It represents the mechanical force generated by a SMC due to the sliding of actin and myosin proteins. This force is related to the calcium concentration resulting from the calcium behavior modeled by the electrical model. The third one is a mechanical deformation model, which represents the modification of the uterine muscle shape due to the SMC forces generated by the second model. By combining these three models, the uterine behavior is modeled here in multi-scale (from the SMC to the whole organ) and with a multi-physics (chemical, electrical and mechanical) approach.

Simulation results are given for the behavior of: one cell, a 2D matrix of cells and a realistic 3D mesh of the uterine muscle, obtained from MRI images. Results show the feasibility of co-simulating uterine smooth muscle and its electrical, force and deformation aspects.

2. Materials and methods

The challenge in this work is to use several existing models and to couple them in order to model the uterine muscle contraction in its different physiological and physical aspects: chemical, electrical and mechanical. In this section, we present the three models used for this study: the electrical cell model, the force cell model and the whole uterus deformation model. These models are combined to form a multi-scale and multi-physic co-simulation of the uterine smooth muscle.

2.1. Electrical model

The electrical model used in this study is a reduction of the Rihana's model, a cellular model developed in our lab. All details can be found in [25,26]. The reduction of Rihana's original model (10 equations/cell) was a necessary step toward the modeling at the organ scale (whole uterine muscle) as all the equations in the cellular model for each cell have to be computed, at each sample time. Calculating this high number of equations is problematic when simulating several thousand of cells even for recent computer. The electrical model reduction, called *Red*3, uses only three variables [27]. This reduction is based on the change of the original I_{Ca} calcium current, which was the most time consuming in the original model, by the one proposed by Parthimos et al. [28]. The three variables of the simpler electrical model are described by the following equations:

$$\frac{dV_m}{dt} = \frac{1}{C_m}\left(I_{stim} - I_{Ca} - I_K - I_{KCa} - I_L\right), \tag{1}$$

$$\frac{dn_K}{dt} = \frac{h_{K_\infty} - n_K}{\tau_{n_K}}, \tag{2}$$

$$\frac{d\left[Ca^{2+}\right]_i}{dt} = f_c\left(-\alpha I_{Ca} - k_{Ca}\left[Ca^{2+}\right]_i\right), \tag{3}$$

where V_m is the transmembrane potential (initial condition is -50 mV), n_K is the potassium activation variable (initial condition is 0.079257), K_{Ca} is the Calcium extraction factor and $[Ca_{2+}]i$ the intracellular calcium concentration (initial condition is 0.1 mM). The ionic currents are I_{Ca} for the voltage dependent calcium channel current, I_K for the voltage dependent potassium channel current, I_{KCa} for the calcium dependent potassium channel current and I_{leak} for the leakage current. Equations for each current are then:

$$I_{Ca} = J_{back} + G_{Ca}(V_m - E_{Ca})\frac{1}{1 + e^{\left(\frac{V_{Ca} - V_m}{R_{Ca}}\right)}}, \tag{4}$$

$$I_K = G_K n_K (V_m - E_K), \tag{5}$$