35th Annual International Conference of the IEEE EMBS
Osaka, Japan, 3 - 7 July, 2013

Preliminary global sensitivity analysis of a uterine electrical activity model.

Jeremy Laforet, *Member, IEEE* and Catherine Marque, *Member, IEEE*
Université de Technologie de Compiègne, CNRS UMR 7338, Biomécanique et Bioingénierie, France.

***Abstract*—A comprehensive multiscale model of the uterine muscle electrical activity would permit understanding the important link between the genesis and evolution of the action potential at the cell level and the process leading to labor. Understanding this link can open the way to more effective tools for the prediction of labor and prevention of preterm delivery.**

For better results, these models and tools should be adapted to each patient. The first step toward this patient specific adaptation is to define which of the parameters must be identified and what are the signal features most suitable to do so. The sensitivity analysis of the model will enable us to answer this question.

To study the sensitivity of the 26 model parameters, We use the principle of elementary effects as described by Morris [1] . We assume no prior knowledge of the possible variations of the parameters and use uniform distributions bounded by $\pm 20\%$ of their nominal value. As model output we considered not on the simulated EHG signal itself but 5 classical features extracted from the signal.

The results we obtain are the ranking of the model parameters in order of sensitivity. With 4 of the features the list of sensitive parameter is very consistent, however there are some differences in the rankings.

I. Introduction

In Europe, the incidence of preterm birth is 5-12% and it is the leading cause of perinatal mortality and morbidity [2]. It causes considerable emotional and financial burden to families and society as pre-term children require intensive care and may require long term special care.

A promising non-invasive method for studying and monitoring the uterine contractility is the analysis of the electrohysterogram or uterine EMG (EHG). The EHG is the signal recorded on the abdominal surface, which represents the electrical activity triggering the mechanical contraction of the myometrium. It has been demonstrated to be representative of the uterine electrical activity recorded internally. As it is related to the trigger of the uterine mechanical contraction, its analysis is a promising method for accurate early recognition of preterm contractions. During the last 15 years, many teams have worked on the possible detection of preterm labour by means of external EHG recording and processing.

The ERASysBio+ project model we propose to use follows this direction. It starts from a simplified model of the myometrial cell that keeps the link with the ionic phenomenon (in order to reduce the computational time and needed resources, but keeping the link with physiological interpretation). It then models the propagation at the tissue level (by using the simple cable model as used for cardiac tissue) for a 2D surface with thickness. Then a model representing the specific anatomy of pregnant woman's abdomen (Muscle, fat and skin layers), permits to obtain, from the propagated signal, a simulated EHG recorded by a chosen electrode configuration.

Using the proposed EHG model, we will first tailor it to a specific patient by determining the anatomical parameters (i.e. fat and skin layers, uterus dimensions) influencing the volume conductor. These parameters will be determined by means of ultrasound imaging performed on each patient. We will then identify, from the recorded EHG, the physiological parameters describing the uterine activity: cell excitability (i.e. in terms of ionic channel conductance) and propagation characteristics (i.e. tissue conductivity). We envisage this information (related to the physiology of uterine contraction), when fed into the diagnosis system, to be more efficient for clinical diagnosis than the features directly extracted from EHG processing. Indeed, these EHG features have no direct relationship with the contraction physiology, as opposed to the identified model parameters.

The first step toward this patient specific adaptation is to define which of the parameters must be identified and what are the signal features most suitable to do so. The sensitivity analysis of the model will enable us to answer this question. Indeed the most sensitive parameters are the ones which value are crucial for simulation accuracy, but they also will be the most efficiently identified.

As the computational cost of the multi-scale model is important (around 90 minutes each without parallelism), we choose to use a screening method as a first approach to a global sensitivity analysis. Screening methods aim to give an overview on the model sensitivity to parameters variation relying on few model runs.

In this paper, we'll first briefly summarize the multi-scale model (previous detailed in [3], [4]) and then describe the screening methodology we applied. Preliminary sensitivity analysis will be presented and discussed.

II. Methods

A. 2D multi-scale model

To model the generation of the electrical activity and its propagation within the myometrium we adopted a reaction-diffusion formalism. The reaction term corresponds to the

This work was funded by ANR, partner of the ERASysBio+ initiative supported under the EU ERA-NET Plus scheme in FP7.

model of cell excitability and the diffusion term to the communication between the cells.

In the present study the *Red3* model (*Red*uced *3* equations) will be used. It is a simplified version of the model from [5], based on Hodgkin-Huxley model. It takes into account the main ionic currents through the cell membrane. *Red3* is up to 60% faster with an acceptable accuracy [3].

The ODE system representing *Red3* can be expressed as follows:

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

with V_m the trans-membrane potential, n_K the potassium activation variable, and $[Ca^{2+}]$ the intracellular calcium concentration.

At the tissue scale, the communication between the myometrial cells through gap-junctions is modeled by the spatial diffusion of the electrical potential over the cells.

The cells are arranged into a Cartesian grid, which can be 0D (a single cell), 1D (a cable-like line of cells), 2D (a flat surface), or 2.5D (a flat surface with non-null thickness). The grid is modeled by a N-dimensional state array where each element represent a cell which is electrically coupled with its direct neighbors (2, 4 or 6 depending on the dimensions).

Finally, we add a two-layer padding on the borders to avoid side effects of the spatial filtering. These 'ghost cells' have a coefficient of diffusion 10^4 times lower than the other cells to efficiently attenuate the signals at the borders.

Certain elements of the cell/tisue model were kept constant in this study. We simulate the myometrium area directly under the electrode grid, so we use a 7cm by 7cm square (140+4 cells in each direction). Each cell is considered to be a square of 50μm side. And the stimulation is applied to a pacemaker area of 4 by 4 cells at the center of the surface. The figure 1(a) shows an example of such simulation conditions.

To simulate the effect of the tissues interposed between the myometrium and the recording surface, we adopt the model proposed in [6], which allows modeling the surface EHG in the spatial frequency domain as the product between an electrical source, at the myometrium, and an analytical expression representing the effect of the volume conductor. To improve the volume conductor model described in [6] and in [3], we extended it to two dimensions.

The electrical source is the transmembrane potential V_m, previously computed at the tissue level using a 2D Red3 model.

The volume conductor is considered as made of parallel interfaces separating the different abdominal tissues, namely, the myometrium, where the source is placed at a depth $z = z_0$, the abdominal muscle, fat, and skin. The volume conductor effect depends on the tissue thicknesses, their conductivities, and the source depth, z_0. All these tissues are assumed to be isotropic with the exception of the abdominal muscle. For the tissue conductivities, the values reported in the literature are used for simulating a signal propagating along the direction parallel to the vertical line of the abdomen. Finally, we assume the source to be close to the myometrium-abdominal muscle interface, i.e., $z_0 \to 0$.

In order to visualize a simulated EHG similarly to a recorded one, we simulated the surface EHG in the spatial domain for subsequent time instants and then reconstructed the time samples from the spatial ones. Indicating by CV the conduction velocity, a sampling frequency $f_t = 200$ Hz was chosen, in time, in order to verify the relation $f_t < f_z \cdot$ CV, to avoid artifacts due to aliasing in the reconstruction of the signal in the time domain.

We include a simple model of electrode grid to generate EHG signals similar to the ones recorded experimentally. It is flexible, and has been designed to reproduce the different type of arrays we may use in human or animal experiments. Finally, white Gaussian noise can be added to the signals to match the typical SNR of recorded signals (5 to 10 dB). This noise addition is useful in order to test the noise reduction stages of signal processing tools and robustness to noise of the extracted features.

In this study, we use the grid shape of 4 by 4 electrodes, each spaced by 1.75cm (center to center). We present in figure 1(b) an example of simulated monopolar EHG signals obtain with a such grid. This example is shown without additon of noise.

B. Sensitivity Analysis

To study preliminarily the sensitivity of the model parameters we use the principle of elementary effects as described by Morris [1]. This screening method is based on a "one factor at a time" design. It uses local variations (the elementary effects) but averages them over several points in the parameters space.

As we have an large number of parameters (26) and each run of the model is time consuming (around 90 minutes per run), we based our study on the work of Saltelli et al. [7]. This enabled us to obtain two elementary effects per parameter with only a total of 64 runs of the model while aiming at a good covering of the parameters space.

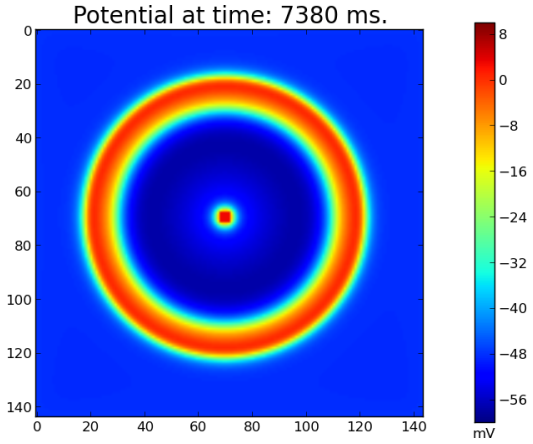
The elementary effects are computed this way:

$$EE_i(X) = \frac{f(X_1, \ldots, X_i + \Delta, \ldots, X_n) - f(\mathbf{X})}{\Delta} \tag{2}$$

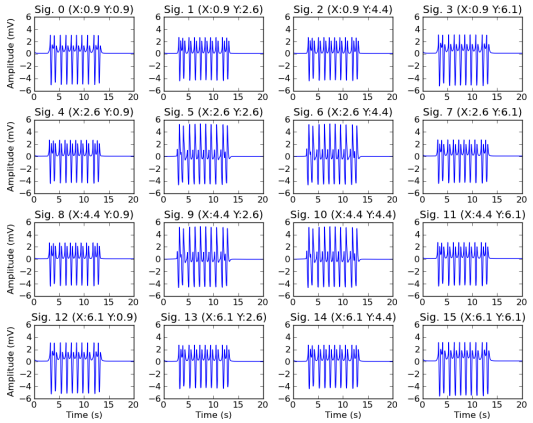
with $\mathbf{X} = X_1, \ldots, X_i, \ldots, X_n$ the vector of parameters and f the model.

As suggested by [8], we computed the 3 indicators μ^*, μ and σ as follows for parameter i:

$$\begin{aligned} \mu_i^* &= \frac{1}{r}\sum_{j=0}^{r}\left|EE_i(X^{(j)})\right| \\ \mu_i &= \frac{1}{r}\sum_{j=0}^{r} EE_i(X^{(j)}) \end{aligned} \tag{3}$$



(a) Simulated electrical activity at the myometrium level, amplitude is color-coded.



(b) Simulated EHG signals as recorded by the standard grid at the skin level, without addition of noise.

Fig. 1. Simulated signals obtained with the multi-scale model (a), both an tissue and organ scales (b).

$$\sigma_i = \sqrt{\frac{1}{r-1}\sum_{j=0}^{r}\left(EE_i(X^{(j)}) - \mu_i\right)^2}$$

with r the set of runs of the model on which the elementary effect is computed.

The parameters of the multi-scale model to be studied in the sensitivity analysis are summarized in table I with their variation ranges.

We assume no prior knowledge of the possible variations of the parameters, hence we use uniform distributions bounded by $\pm 20\%$ of their nominal value. The temperature (T) and signal to noise (snr) are the only exceptions as we were able to set more realistic bounds. The nominal values of the parameters were taken from [5], [3], [6].

Finally, to reduce the global computational time of this study the model simulations are run in parallel on a dedicated workstation. We used 24 threads and one simulation per thread.

C. Signal features

Each simulation of the model produces a 16 channel signal, 20 seconds long and sampled at 200Hz to match the characteristics of the recorded EHG signals.

We computed the elementary effects not on the multichannel signals themselves but on features extracted from these signals. For the present study we used 5 different features among the ones considered to treat EHG signals:

- RMS amplitude of signal Y : $rmsA(Y) = \sqrt{\frac{1}{n}\sum_{j=0}^{n} Y(j)^2}$,
- time reversibility of signal Y: $trev(Y) = \left(\frac{1}{n}\sum_{j=0}^{n} Y(j) - Y(n-j)\right)^3$,
- peak frequency ($f_{peak}(Y)$) is the frequency of the highest peak of the power spectrum of signal Y,
- $r^2(X,Y)$ is the square of the Pearson linear correlation coefficient between signals X and Y,
- $h^2(X,Y)$ is the non-linear correlation coefficient between signals X and Y as defined in [9].

The first three are computed for each channel of the signal and then averaged to obtain one value per feature and per signal. The correlations are computed on all possible pairs of channels and then averaged as well. These features were selected for this preliminary study as they cover a wide variety of signal properties: amplitude, frequency, non-linearity and correlations between channels.

III. Results

The computations were performed on a dedicated workstation (2x8 cores Intel Xeon 2.40Ghz with hyperthreading, 64Gb Ram, Ubuntu 12.04 64bits). The 64 model simulations needed to compute the elementary effects of all parameters were obtained in 165 minutes.

We present in table I the list of most important parameters obtained for each signal feature by the elementary effect method previously described. They are ranked by their $\mu*$ value. Parameters were considered non significantly sensitive when their $\mu*$ value was 1000 times smaller than the maximum for the given feature.

It shows consistent results over the set of features. The ranking varies but the significant parameters always belong to the same subset : [a, alpha, Ek, El, ERay, fc, Gca2, Gk, Gkca, Gl, Iback, Kca, Kd, Rca, Sigma_m, snr, T, vca2] (here presented in alphabetical order).

In several cases we observed that the absolute value of μ_i was smaller than μ_i^*. This means that the sign of the different EE_i varies depending of where in the parameter space they are computed. For example parameter Vca2 for feature time reversibiliy: $|\mu|$= 4.2e-3 and μ^*= 5.8e-3. The change of sign points the non-monotony of the effect of these parameters or the existence of interaction effects.

Finally some parameters show high values of σ (Vca2, Gl and Eray for RMS amplitude and Ek for time reversibility). This shows their indirect effect on the features through interactions with other parameters.

IV. Conclusion and Discussion

This preliminary global sensitivity analysis shows promising results. Allowing studying the whole multiscale model at a reasonable computational cost.

Name	Description	Value range		Sensitivity Ranking				
		min	max	rmsA	trev	fpeak	r^2	h^2
a	abdominal muscle thickness	7.5e-3	1.1e-2	18	16	9	9	14
alpha	current conservation factor	3.2e-05	4.8e-05	11	13	5	5	10
Dx	Diffusion coefficient (x axis)	0.16	0.24	*	*	*	*	*
Dy	Diffusion coefficient (y axis)	0.16	0.24	*	*	*	*	*
EL	Leak nerst potential	-66.4	-99.6	6	2	*	11	5
EK	Potassium nerst potential	-160.8	-241.2	12	8	*	*	11
Eray	Electrode radius	0.64	0.96	1	1	*	2	1
f	fat tissue thickness	9.05e-3	1.36e-2	*	*	*	*	*
fc	calcium influx propability	0.32	0.48	16	14	7	4	6
GCa	VOCC conductance	0.0176	0.0264	8	6	*	14	15
Gk	Potassium channels conductance	0.0512	0.0768	15	11	*	13	17
GkCa	K/Ca channels conductance	0.064	0.096	9	12	6	7	13
GL	Leak channels conductance	0.0044	0.0066	5	9	3	15	4
Iback	Background calcium current	1.9e-2	2.8e-2	17	15	*	*	16
kCa	Ca extraction factor	0.08	0.12	10	17	10	8	8
kd	Half-point potasium concentration	0.008	0.012	14	7	1	12	18
RCa	Max. slope of the VOCC activ.	3.848	5.772	3	4	4	10	7
s	skin thickness	0.0016	0.0024	*	*	*	*	*
Sigma_ax	Abd. muscle conductivity (x axis)	0.16	0.24	*	*	*	*	*
Sigma_ay	Abd. muscle conductivity (y axis)	0.32	0.48	*	*	*	*	19
Sigma_f	fat tissue conductivity	0.032	0.048	*	*	*	*	*
Sigma_m	myometrium conductivity	0.16	0.24	4	3	8	6	9
Sigma_s	skin conductivity	0.4	0.6	*	*	*	*	*
snr	EHGsignal to noise ratio	0.0	5.0	7	*	*	1	2
T	Temperature	293.0	315.0	14	10	*	16	12
VCa2	Half-point of the VOCC activ.	-19.904	-29.856	2	5	2	3	3

TABLE I

PARAMETERS USED FOR SENSITIVITY ANALYSIS AND THEIR VARIATION RANGE. PARAMETERS ARE RANKED BY THEIR μ^* VALUE FOR THE CONSIDERED FEATURES. *1* INDICATES THE MOST SENSITIVE PARAMETERS, A STAR MARKS THAT THIS PARAMETER DID NOT SHOW SIGNIFICANT INFLUENCE.

Peak frequency shows a particular behavior, different of the other features. μ^* and σ are high for sensitive parameters and null for the others, also only 10 parameters are found sensitive. Hence, this would be useful only to identify few parameters of the model and will not be retain.

The other features show very consistent results: the significant parameters are the same, but show some differences in the rankings. This could be explained as the list of significant parameters depending on the properties of the model but their ranking depending more heavily on the properties of the features. Overall they offer good coverage of the physiological parameters of the model. However, the abdominal level parameters show poor sensitivity. This might be due to the chosen variation range which might be too small to show the impact of these parameters. Otherwise, it suggest the possible need to determine them by other means (ultrasound examination for example).

The main improvements to this preliminary study that will be addressed in the near future are :

- better defined parameters ranges to respect physiological bounds and probability distributions of the parameters values.
- the use of a more in depth sensitivity analysis method, based on latin hypercubes design or Fourier analysis.

For the last item, we plan to rely on the screening results to limit the number of parameters to study and on parallelization to address the problem of computational cost.

REFERENCES

[1] M. D. Morris, "Factorial sampling plans for preliminary computational experiments," *Technometrics*, vol. 33, no. 2, pp. pp. 161–174, 1991.

[2] R. L. Goldenberg, J. F. Culhane, J. D. Iams, and R. Romero, "Epidemiology and causes of preterm birth," *The Lancet*, vol. 371, no. 9606, pp. 75–84, May.

[3] J. Laforet, C. Rabotti, J. Terrien, M. Mischi, and C. Marque, "Toward a multiscale model of the uterine electrical activity," *IEEE Transactions on Bio-Medical Engineering*, vol. 58, no. 12, pp. 3487–3490, Dec. 2011, PMID: 21968708.

[4] J. Laforet, C. Rabotti, M. Mischi, and C. Marque, "Improved multi-scale modeling of uterine electrical activity," *IRBM*, vol. In Press, 2013.

[5] S. Rihana, J. Terrien, G. Germain, and C. Marque, "Mathematical modeling of electrical activity of uterine muscle cells," *Medical & Biological Engineering & Computing*, vol. 47, no. 6, pp. 665–675, Mar. 2009.

[6] C. Rabotti, M. Mischi, L. Beulen, S. Oei, and J. Bergmans, "Modeling and identification of the electrohysterographic volume conductor by high-density electrodes," *IEEE Trans. Biomed. Eng.*, vol. 57, pp. 519–527, 2010.

[7] A. Saltelli, F. Campolongo, and J. Cariboni, "Screening important inputs in models with strong interaction properties," *Reliability Engineering & System Safety*, vol. 94, no. 7, pp. 1149 – 1155, 2009, special Issue on Sensitivity Analysis.

[8] A. Saltelli, M. Ratto, T. Andres, F. Campolongo, J. Cariboni, D. Gatelli, M. Saisana, and S. Tarantola, *Global Sensitivity Analysis: The Primer*. Wiley, January 2008.

[9] M. Hassan, A. Alexandersson, J. Terrien, C. Muszynski, C. Marque, and B. Karlsson, "Better pregnancy monitoring using nonlinear propagation analysis of external uterine electromyography," *Biomedical Engineering, IEEE Transactions on*, vol. PP, no. 99, p. 1, 2012.