Research Review Paper ■

BioModUE_PTL – Biophysical Modelling of the Uterine Electrical Activity for Understanding and Preventing PreTerm Labour

Branimir Leskošek, Drago Rudel

Abstract. We present the EraSysBio+ European project BioModUE_PTL (2010-2013), which addresses open questions regarding the actual contraction mechanisms of the uterus leading to onset of labour. Seven project partners from four EU countries (France, the Netherlands, Iceland, Slovenia) participate in the project, among them the authors' institution (Institute for Biostatistics, Faculty of Medicine, University of Ljubljana). Data standards for smooth muscle EMG and EHG digital recordings and preterm delivery models will be designed. The data, acquired from animal and human experiments, will be used to create a multiscale model of the behaviour of the uterus (cells, tissue, and organ). A database of the smooth muscle EMG/EHG activity signals will be designed based on an application profile agreed on the European level.

BioModUE_PTL – biofizikalni model električne aktivnosti maternice za razumevanje in preprečevanje prezgodnjega poroda

Izvleček. V prispevku je predstavljen evropski projekt BioModUE_PTL, eden izmed EraSysBio+ projektov, v okviru katerega raziskujemo (2010-2013) fenomen grozečega prezgodnjega poroda. Želimo razviti klinična orodja, s katerimi bi lahko zaznali in zabeležili prisotnost patološkega krčenja telesa maternice, ki vodi do prezgodnjega poroda. V projektu sodeluje sedem partnerjev iz štirih evropskih držav (Francije, Nizozemske, Islandije in Slovenije), med njimi domača institucija avtorjev. Cilji projekta so: na evropskem nivoju uskladiti podatkovni standard za EMG/EHG aktivnost maternice, na podlagi meritev pri ljudeh in živalih izdelati večnivojski matematični model maternice (celica, tkivo, organ) ter vzpostaviti podatkovno zbirko zapisov EMG/EHG aktivnost gladkega mišičja maternice, zgrajeno na evropskem nivoju.

■ **Infor Med Slov**: 2012; 17(1): 31-37

Institucija avtorjev / Authors' institution: IBMI, Medicinska fakulteta, Univerza v Ljubljani, Ljubljana, Slovenija.

Kontaktna oseba / Contact person: Branimir Leskošek, Medicinska fakulteta, Vrazov trg 2, 1000 Ljubljana. e-pošta / e-mail: brane.leskosek@mf.uni-lj.si.

Prejeto / Received: 01.06.2012. Sprejeto / Accepted: 26.06.2012.

Prispevek bo predstavljen na prihajajočem slovenskem kongresu medicinske informatike.

Background

Preterm birth, i. e., birth before the 37th week of gestation, is still a major cause of infant mortality and morbidity. In Europe and in other developed countries, the incidence of preterm birth is reported to be between 5% and 12%.[1] Preterm birth accounts for 75% of perinatal mortality and more than 50% of the long-term morbidity.[1] Infants born preterm are at increased risk for mortality as well as health and developmental problems.[1,2] Despite the improvement of technologies in high-care medical units, these problems still remain (EPIcure and EPIcure 2 studies).[2] Preterm birth can also bring considerable emotional and economic costs to families and society. The annual societal economic burden associated with preterm birth in the USA was more than $26.2 billion in 2005.[3] Despite an increased in understanding the risk factors and mechanisms related to preterm labour, and the improvements of obstetrical practice to reduce the incidence of preterm birth, preterm birth rate has risen in most industrialized countries.[1]

Many open questions remain regarding the actual mechanisms leading to onset of labour. When monitoring pregnancy contractions, the key issue is to differentiate preterm physiological contractions that are inefficient from the efficient contractions that will induce a progressive cervical dilatation leading to preterm delivery. As current obstetrical monitoring methods cannot discriminate between these two types of contractions, most obstetricians either treat all patients having preterm contractions or wait for cervical modifications. Administration of tocolytic treatment to all contractile patients entails risks for mother and fetus, due to the well-known side-effects of these agents, while delaying the diagnosis of preterm labour may results in lower efficacy of tocolytic drugs. Therefore, accurate prediction of preterm labour risk is fundamental for the reduction of fetal mortality and morbidity. The methods currently used for predicting preterm delivery are not accurate enough for an early diagnosis of preterm labour.

A promising non-invasive method for studying and monitoring the uterine contractility is the analysis of the electromyogram (EMG), called also electrohysterogram (EHG). The EMG/EHG is the signal recorded on the abdominal surface, which represents the electrical activity associated to the mechanical contraction of the myometrium. It has been demonstrated to be representative of the uterine electrical activity recorded internally.[4] 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, several teams have worked on the possible detection of preterm labour by means of external EMG/EHG recording and processing.[5,6] However, the obtained results have not shown sufficient reliability to provide an accurate tool for the detection of preterm labour.

Different hypotheses have been raised, from animal and human experiments, concerning the EHG evolution relatively to term and preterm labour, particularly on its relationship with an increase in either cell excitability or propagation of the electrical activity. Recent studies suggest that the uterine excitability and the propagation of action potentials are, in fact, key factors for the efficiency of the uterine contraction.[7,8]

BioMod UE_PTL project

BioModUE_PTL[9] is a European project (2010-2013) funded by the ERASysBio Plus consortium for Systems Biology.[10] The aim of the this project is to use a systems biology approach to better understand the links between the microscopic phenomena involved in uterine contractility leading to labour (term or preterm), and the macroscopic electrical activity observed on the abdomen of pregnant women (the EHG). The ultimate goal is to provide a clinical tool that can detect the presence of pathological uterine contractility leading to preterm labour. It addresses open questions regarding the actual contraction mechanisms of the uterus. Seven

project partners from four different EU countries participate in the project (France, the Netherlands, Iceland, Slovenia), among them the authors' institution (Institute for Biostatistics and Medical Informatics of the Faculty of Medicine, University of Ljubljana).

The BioModUE_PTL project is organized in seven work packages:

- Measurement standardisation
- EHG, magnetic resonance imaging (MRI) and ultrasound (US) data acquisition
- Multiscale modelling
- Data management system
- Dissemination
- IPR, legal and ethical issues
- Project Management

Several outputs are expected from the project. Data standards for smooth muscle EMG and EHG digital recordings and preterm delivery models will be designed. The data, acquired from animal and human experiments, will be used to create a model of the behaviour of the uterus, and to set up the first worldwide database of the smooth muscle EMG/EHG activity. We plan to create and manage a database of EHG signals, recorded in a standardized way, in different physiological and pathological situations in different European countries. This database, which will be opened to the whole EHG scientific community at the end of the project, will provide a unique opportunity and a very powerful tool for people working on preterm labour detection. The database will be provided through the uEMG Portal created during this project, as described below.

Data standards for smooth muscle EMG and EHG recordings

The uterine muscle, the myometrium, initiates contraction by the generation and propagation of electrical activity measured at the skin above the uterus. Currently, there are no data standards for smooth muscle EMG/EHG digital recordings and preterm delivery models. The different international research teams working on the analysis of the EHG use very different recording parameters.[11] The proposed measurement standard covers the application profile and the measuring protocol that will be set as the best practice of the partners in the BioModUE_PTL project consortium.

The application profile will be designed as a common subset of data and metadata used for EMG/EHG measurements by all project partners that perform such measurements in humans or in animals at the level of the subject, the uterus as an organ, or the uterine smooth muscle tissue.

The application profile will also focus on a specification of electrodes (size, type, position, spacing, configuration, skin preparation etc.), the analog signal pre-processing (filter bandwidth, amplification etc.) and the sampling frequency.

The EMG/EHG measurement protocol will be defined, aimed at defining a minimal standard for recording the uterine abdominal electrical activity in women (EHG) and animals in order to share a common EHG recording protocol in the different partner countries during the project. The partners will also use the same measuring set-up. The data will be sent to feed a common EMG/EHG database called uEMG database.

EMG/EHG measurements

EMG/EHG measurements that will be done within the project belong to two groups: measurements in humans and measurements in animals.

EMG/EHG measurements in humans should provide data for studies of preterm labour phenomena and for extracting information useful for modelling of the uterus.[5,12,13] Additionally, they will serve to develop a database of uterine EMG/EHG records from different European research groups that will use the agreed standardized protocol. The recordings will be made in three hospitals selected in the partners' countries in order to offer the variety of physiological and pathological situations needed to obtain a comprehensive and representative database. The new standardized protocol will be implemented. It would be used in accordance with local legal and ethical requirements. The measuring set-up for these recording will be the one developed within the project dedicated to the multi-lead recording of EMG/EHG signals during pregnancy and labour. The processing tools needed to quantify the uterine EHG will be developed for each specific purpose (quantification of propagation and/or excitability). These signals will be used to validate and/or improve the final EHG model by comparison of the simulated signals with the real signals.

In some cases it will be possible to combine US imaging wtih EHG recording, thus permitting the researchers to study the uterine-muscle and abdominal-wall structures. This will lead to an improved characterization of the link between electrical activity and mechanical contraction of the uterus muscle.

EMG/EHG measurements in animals will be performed mainly to provide additional data needed for the development of a multiscale model. The use of non-human primates will be crucial to investigate how soft tissues inside (placenta) and outside (digestive tract, fat, abdominal wall) the pregnant uterus affects the transfer function of the uterine EMG/EHG when recorded by external surface electrodes. The recordings will be made at one research institute.

Multiscale uterine modelling

The uterus is a very complex and dynamic system, which is controlled by a complex hormonal environment as well as by electric and by mechanical feedback systems. The only way to address the system is through multiscale modelling, starting from the biological phenomena involved in single uterine cell contractility, leading to the generation of EHG on the abdomen.[14,15] The proposed model will integrate the generation of contractile activity at the cell level, the communication between cells, tissue level (with the tissue being viewed there as a two-dimensional flat surface of multiple cells), a realistic 3D structure of the uterus (to reach the organ level, integrating specific anatomical structures associated with different propagation properties, such as the bundles), and then the propagation to the abdomen, i.e., the patient level, through the complex conduction volume associated to the abdomen.

In order to obtain the required information for the model parameters, as well as to validate the final model, we plan to acquire a new dataset of uterine electrical activity signals at different levels with a specific measurement protocols. For the cellular level, data available in the literature will be used. We plan to design animal experiments concerning the measurement of propagation at the tissue level, through uterine muscular strips and at the organ level (pregnant primate imaging for the anatomical 3D structure, exposed pregnant uterus for the electrical activity in vivo). The data acquired from animal and human experiments will be used to create a model of the behaviour of the uterus. The results obtained from the models will then be used to guide experimentation and to model the effects of pharmacological agents on the uterus.

EMG/EHG portal

Apart from disseminating results in the classical manner for scientific and technical research, the project aims at developing means to share the data and the results, both between the partners and with the larger scientific community. For this purpose, a web EMG/EHG portal will be designed, called uEMG. It integrates diverse EMG/EHG-related information spaces and offers an interactive collaborative environment for information providers as well as information users.

Within this framework, different services and tools will be offered. The most important service/tool will be the EMG/EHG databases (uEHG) with search and data processing tools. The framework will provide integration of resources of different providers in a single virtual infrastructure.

The uEMG portal will be based on the Drupal open source content management system (CMS),[16] enabling multilevel publication of content/information and user management. Additional modules will be added for publication of multimedia materials.

uEMG database

The EMG/EHG signal database called uEMG will be accessible through the uEMG portal. This database will provide the European scientific community interested in preterm delivery and/or pregnancy/labour monitoring with a complete set of signals representative of different physiological and/or pathological situations. Such a database exists for ECG.[17]

We know of only one smooth muscle EMG/EHG digital signal database, namely the Physionet's Term-Preterm EHG Database (TPEHG DB).[18] It consists of 300 uterine EMG/EHG records from 300 pregnancies recorded from 1997 to 2005 at the Department of Obstetrics and Gynaecology, University Medical Centre Ljubljana, Slovenia. As there are several research groups in Europe and USA using different measuring protocols and data standards, the BioModUE_PTL project has been developing a database (uEMG) that would have data recorded with an agreed multi-centre application profile (data standard) and an agreed measuring protocol.

The uEMG database will consist of three signal databases: DBT for signals recorded at the tissue level, DBO for signals recorded at the organ level, and DBP for signals recorded at the patient level. Other specific databases, such as those related to MRI imaging (DBUS) and ultrasound imaging (DBUS) should be added and accessed through a portal during the project.

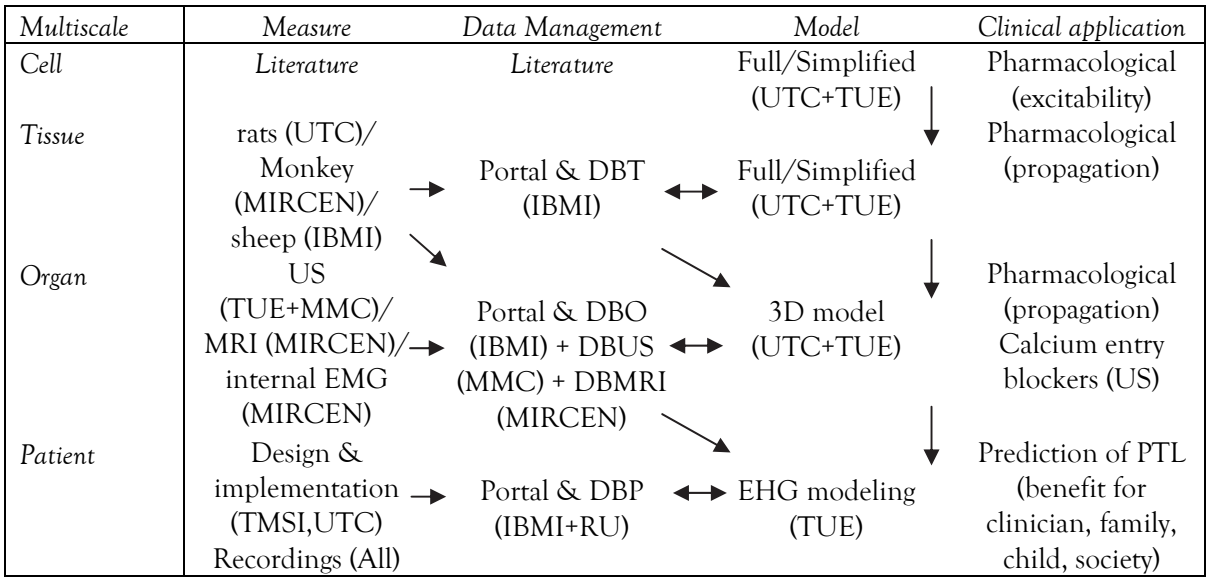

Figure 1 Organisation of the BioModUE_PTL project (UTC, MIRCEN, TUE , MMC, IBMI, RU and TMSI denote the different partners involved in each part of the work; "all" denoted all partners).

Conclusions

The aim of this paper is to review the activities within the BioModUE_PTL European project. An overview of the organisation of the project is given in Figure 1. Several results have already been produced and will be published separately. Many of the expected outputs were clearly defined in the project proposal but some have to be reshaped. In particular, the analytical part of the project and data presentation should be enhanced by implementing and applying dynamic interactive data visualization and visual analytics.

References

1. Goldenberg RL, Culhane JF, Iams JD, Romero R: Epidemiology and causes of preterm birth. *Lancet* 2008; 371(9606): 75-84.
2. Costeloe K: EPICure: facts and figures: why preterm labour should be treated. *BJOG* 2006, 113(S3): 10-12.
3. Behrman RE, Butler AS: *Preterm birth: causes, consequences, and prevention*. Washington 2007: National Academy Press.
4. Garfield RE, Maul H, Shi L, *et al.*: Methods and devices for the management of term and preterm labor. *Ann N Y Acad Sci* 2001; 943: 203-224.
5. Devedeux D, Marque C, Mansour S, Germain G, Duchêne J: Uterine electromyography: a critical review. *Am J Obstet Gynecol* 1993; 169(6): 1636-1653.
6. Maner WL, Garfield RE: Identification of human term and preterm labor using artificial neural networks on uterine electromyography data. *Ann Biomed Eng* 2007; 35(3): 465-473.
7. Garfield RE, Maner WL: Physiology and electrical activity of uterine contractions. *Semin Cell Dev Biol* 2007; 18(3): 289-295.
8. Euliano TY, Marossero D, Nguyen MT, et al.: Spatiotemporal electrohysterography patterns in normal and arrested labor. *Am J Obstet Gynecol* 2009; 200(1): 54.e1-54.e7.
9. *BioModUE_PTL – Biophysical Modelling of the Uterine Electromygram for understanding and preventing Preterm Labor*. https://unimed.mf.uni-lj.si/uemg/ (2012-06-11).
10. *ERASysBio Plus Initiative*. http://www.erasysbio.net/ERASysBio_PLUS_Projects (2012-06-11).
11. Terrien J, Marque C, Gondry J, Steingrimsdottir T, Karlsson B: Uterine electromyogram database and processing function interface: an open standard analysis platform for electrohysterogram signals. *Comput Biol Med* 2010; 40(2): 223-230.
12. Kavšek G. *Electromyographic activity of the uterus in threatened preterm delivery*. MSc thesis. Ljubljana 2001: Faculty of Medicine.

13. Marque C, Terrien J, Rihana S, Germain G: Preterm labour detection by use of a biophysical marker: the uterine electrical activity. *BMC Pregnancy Childbirth* 2007; 7 Suppl 1: S5.
14. Verdenik I: *Multilayer prediction model for preterm delivery*. PhD thesis. Ljubljana 2002: Faculty of Medicine.
15. Laforet J, Rabotti C, Terrien J, Mischi M, Marque C: Toward a multiscale model of the uterine electrical activity. *IEEE Trans Biomed Eng* 2011; 58(12): 3487-3490.
16. *Drupal – Open Source CMS*. http://drupal.org (2012-06-26).
17. Goldberger AL, Amaral LAN, Glass L, *et al.*: PhysioBank, PhysioToolkit, and PhysioNet: components of a new research resource for complex physiologic signals. *Circulation* 2000; 101(23): e215-e220. http://circ.ahajournals.org/cgi/content/full/101/23/e215 (2012-06-26)
18. *Physionet. The Term-Preterm EHG Database (TPEHG DB)*. http://www.physionet.org/physiobank/database/tpehgdb/ (2012-06-12).