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Catalin Dumitru
Department of Obstetrics and Gynecology, "Victor Babes" University of Medicine and Pharmacy of Timisoara, Romania

Anghel Cernescu
Mechanics and Strength of Materials Department, Politehnica University Timisoara, Romania

Correspondence
Catalin Dumitru
Department of Obstetrics and Gynecology, "Victor Babes" University of Medicine and Pharmacy of Timisoara, Romania

Collaborative research on uterine contractions

Catalin Dumitru and Anghel Cernescu

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Abstract
Problem: Myometrium contraction is a complex process involving electrical, hormonal and mechanical phenomena. With all the effort, studies reported so far indicate that uterine contraction is not completely known.
Methods: In this paper, by presenting the current stage of uterine contraction research from the perspective of three approaches (medical, engineering and interdisciplinar), it is desired to encourage the collaborative research. An interdisciplinary research methodology is also presented in the paper, based on which outstanding issues on uterine contractions can be addressed in a common perspective.
Conclusion: Uterine contractions are a complex process that studied at different levels and from different perspectives involves principles and phenomena of anatomic-biological, mechanical, electrical, etc. This justifies an interdisciplinary approach to uterine contractions, and this paper is the first wrok that highlights this.

Keywords: Uterine contraction, interdisciplinary research, medical research, engineering research

1. Introduction
Interdisciplinary work has proven to be particularly effective in research. Complex phenomena are described, analyzed and modeled through an effective interaction and collaboration between different disciplines. Interdisciplinary research and collaboration can provide substantial benefits to researchers, practitioners and policy makers [1, 2], being predicted that the future of research is increasingly interdisciplinary [3]. The research funding bodies at European level but not only, emphatically support and promote the interdisciplinary research. By far, Biomechanics Engineering has proven to be the best example of interdisciplinary research, where engineering concepts are used along with medical practices and concepts to come up with solutions to various attempts of human nature. Mixed groups of researchers are successfully conducting work in areas such as: antimicrobial resistance, biomedical ultrasound, brain biomechanics, cancer biomechanics, cardiovascular biomechanics, manufacturing, materials, mathematical and computational modeling, pharmaceutics biomechanics, robotics, surgical methods and techniques and tissue engineering. Obstetrics and Gynecology is another area where although interdisciplinary research has proven its capabilities in a series of studies, some of which will be presented later, however, there is a certain need for even greater involvement. One of the subjects requiring even better interdisciplinary research is uterine contractions. Although, there is an important volume of studies in which a number of indicators, methods and analysis techniques of uterine contractions have been developed, current clinical studies highlights some ambiguities and contradictions. One of the uncertainties is revealed by W.R. Cohen [4], which moreover seems extremely important, being mentioned in other studies [5], that is not known precisely how the uterine contractions cause progress in labor. A contradictory discussion also exists about the methods of evaluating the uterine contractions. In order to come up with a solution to such problems, an interdisciplinary research activity is absolutely important and necessary.
This paper aims to strengthen the role of interdisciplinary research in Gynecology and Obstetrics for a complex approach to various problems, but also for finding complete solutions. Through concrete examples described and discussed in the paper also aim at highlighting and clarifying some aspects of uterine contractions, addressed from three different perspectives. The three approaches consist of strict clinical and medical research, engineering studies and interdisciplinary research respectively.

2. Approaches to research of uterine contractions

2.1. Clinical and medical research

In terms of clinical and medical perspective, the uterine contraction is an activity of the muscular tissue of the uterus that dilates the cervix and pushes the fetus out of the birth canal. The level of uterus contraction may determine when or not the actual birth is triggered. Also, high contraction of the uterus indicates that the uterine pressure is high enough to push the fetus out of the birth canal. Instead, low contraction of the uterus indicates that the fetus may not be pushed out of the birth canal that means an intervention is needed [6]. On the other hand, another effect of the uterine contractions is that they affect the heart rate of the fetus by causing deceleration. To date this effect is still unexplained.

An interesting review of the uterine contractility was made by Susan Wray [7], where the uterus is described as a smooth muscle which is spontaneously active. The paper describes on one hand the mechanism of myometrium contractility in conjunction with the rise of $[Ca^{2+}]_i$, and on the other hand a series of factors that influence the contractile activity of the myometrium are discussed. The descriptions within the paper, very explicit and well-reasoned, highlight a number of uncertainties leading to the idea that the uterine contraction and its control are still incomplete. In this respect, the paper outlines some directions from which research advances are expected, such as: characterization of myometrial receptor-operated channels, identification of myometrial G proteins and their effector pathways, elucidation of the role of intra- and extracellular Ca sources, understanding of the relation between pH_i, $[Ca^{2+}]_i$, and contraction, and pacemaker activity respectively. At the cellular level, the myometrium contraction is an electro-mechanical action where the muscular fibers respond to electrical stimuli. These occur as a result of the activity of calcium ions coming from two sources: intracellular Ca^{2+} stores and external Ca^{2+} entering across the plasma membrane. Despite all the efforts made so far, a better understanding of how the Ca^{2+} rise in the myometrial sarcoplasmic reticulum influences Ca^{2+} signalling and contractility, respectively the mechanisms linking the sarcoplasmic reticulum Ca^{2+} depletion to store operated Ca^{2+} entry, is needed. Hypothetically, it is known that agonist-induced Ca^{2+} from sarcoplasmic reticulum could activate store operated Ca^{2+} entry leading to depolarization of uterine smooth muscle cells [8, 9, 10, 11]. The complete knowledge of these intracellular mechanisms could lead to the development of medications to keep the uterine contractions under control and respectively prevent the premature births.

Given the clear role of the uterine contractions, another direction of research has focused over time on finding methods to identify and analyze them. In this respect, it is worth mentioning the Cohen's review [4], which presents the available techniques for evaluating the uterine contractions: manual palpation, intrauterine pressure (IUP) determination, tocodynamometry and electrohysterography (EHG). Although the IUP measurements are often a benchmark in comparison with other methods [12], however has a great disadvantage in that it increases the risk of infection and requires membrane rupture. Instead, a high potential for uterine contractions has EHG, showing to be more reliable than tocodynamometry, and much more effective than IUP measurements in providing an interpretable tracing [13]. Studies carried out by the Maner [14], Garfield [15] *et al*. or Lucovnik *et al*. [16] pointed out that the recording of the uterine electrical activity at the abdominal surface can diagnose and predict the term or preterm labor. But this involves computerized techniques for analyzing and interpreting the electrical signals that are not at hand. Interpretation of the results is crucial and can easily lead to false indications.

2.2. Engineering research

The engineering approach of uterine contractions is focused on the electro-mechanical activity of myometrium tissue that determines the intrauterine pressure. By engineering approach in this paper should be understood those studies/researches carried out by teams of engineer researchers. This section also aims to highlight the engineering perspective on the uterine contractions. Probably the most comprehensive and complete numerical study on uterine contractions is made by Cochran and Gao [17]. This numerical study involves an electro-mechanical model that includes intrauterine pressure as a function of tissue deformation. The myometrium tissue is considered to be composed of two families of fasciculi which are parallel to each other and parallel to the surface of the uterine wall. Fasciculi in the first family are aligned longitudinally with respect to the uterus and fasciculi in the second family are aligned circumferentially. The electrical activity is transposed to the tissue by a stress state consisting of two components: active and passive. The active stress is the stress due to cellular contraction and is oriented in the directions of the two families of fasciculi (respectively longitudinal and circumferential), and the passive stress is the mechanical stress caused by the deformation of the tissue. Also, the intrauterine pressure is related to the intrauterine volume that changes as a result of the evolution of the uterine contraction and the deformation of the tissue itself. The intrauterine pressure resulting from the simulation ranged from 51 to 55 mmHg, being within the range of the clinical variability observed. Also, a number of other significant observations are reported based on the numerical study such as the change of maximum active stress had the largest impact on the peak pressure and respectively a change of the two electrical properties, recovery rate and activation threshold, had the largest impact on duration of the peak pressure. An action potential initiated in the upper region of the uterus was propagated throughout the uterus in about 9 s, with a circumferential speed of 6.1 cm/s. Another observation is that during the uterine contraction, the uterus can be divided in two regions, in the wake of the action potential and respectively ahead of the action potential. In the wake of the action potential the active stress is high causing a compressive stress state both in the longitudinal and circumferential directions. Ahead of the action potential, the active stress is zero, there is no electrical activity and there is a predominance of mechanical tensile stress state due to intrauterine pressure, fig. 1.

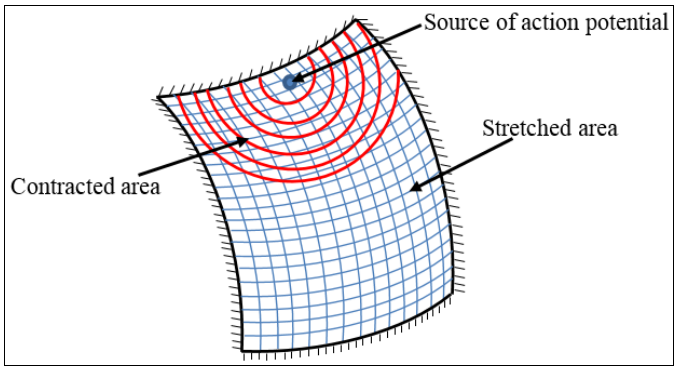

Fig 1: The propagation of action potential during a uterine contraction

Another direction of research underlying the engineering approach of uterine contractions is the mechanical behavior of

the myometrium tissue. The myometrium is a smooth tissue that can be spontaneously active, so an isolated part of the uterus will produce regular spontaneous contractions [18]. The uterine activity also increases gradually as the term approaches. In view of these, the mechanical behavior of the myometrium tissue should be investigated in correlation with these factors. However, one of the relevant studies on mechanical behavior of myometrium tissue was carried out by Pearsall and Roberts [19]. The passive mechanical behavior of human myometrium was experimentally analyzed by tensile and compression tests on samples taken from excised uterus. Samples were taken from upper uterus and fundus. The results presented in the form of true stress – true strain curves revealed a mechanical behavior similar to soft tissues with tensile strengths between 80 psi (0.551 MPa) and 300 psi (2.068 MPa) and the elastic modulus, determined at an applied stress of 10 psi (0.0689 MPa), in the range of 70 – 200 psi (0.4826 – 1.378 MPa). Similar results are also presented in Reference [20]. Applying the thin wall pressure vessel theory for an intrauterine pressure of 55 mmHg in the case of an average sized uterus corresponding to week 37 of pregnancy [17], results in a safety factor of the uterine wall of at least 8. This means that the circumferential passive stress in the uterine wall is at least 8 times smaller than the tensile strength. However, the uterine contraction is an active process that causes in the uterine wall a repeated stress superimposed over the passive stress state. Until this moment there are no data on the behavior of the myometrium tissue under cyclic loading. It is not known exactly whether the cyclic loading due to uterine contraction in the late of pregnancy results in residual strain or even damage of the tissue stiffness.

A concern of engineering research is also the registration and especially the processing and analysis of the signals emitted by the uterine contractions. An example might be the analysis of the Uterine Contractions Interference Signal (UCIS) from the combined fetal and mother transabdominal ECG signals, made by Walid Zgallai [21]. The UCIS is measured during peak contractions at 40 weeks of pregnancy using a wireless ECG sensor. The signal analysis is made using adaptive LMS- or LMF-based Volterra filters. The results revealed that the short-term data is non-Gaussian and the long-term data is nonlinear, deterministic and chaotic. Also, by employing a super-resolution Multiple Signal Classification routine would be possible to improve the fetal heartbeat detection.

2.3. Interdisciplinary research on uterine contractions

In this paper, interdisciplinary research on uterine contractions has been identified in two topics. On the one hand, the accuracy of uterine contractions based on electrohysterography was investigated using abdominal surface electrodes [22-24]. On the other hand, the numerical modeling technique is used to develop a biophysical model of electromyography (EMG) and magnetomyography (MMG) in order to quantify the uterine contractions [25]. In an experimental study developed by an interdisciplinary team, a simplified EHG recording protocol is proposed to predict deliveries in less than 7/14 days [26]. The EHG recording protocol consists of 4 electrodes vertically aligned with the median line of the uterus and tracking the evolution of global efficiency indexes (GEI), defined in the study based on the phenomena involved in the efficiency of uterine myoelectrical activity (intensity, excitability and synchronization).

3. Discussion

In this paper the research on uterine contractions was presented in terms of three approaches. Medical research includes studies and research directions conducted by specialists, clinicians and biologists with concerns about uterine contractions. A group of specialists who could bring a significant contribution to the research of uterine contractions are neurological researchers. Normally, the triggering moment of birth should also be seen from the perspective of nervous system involvement. The child feels that his need for feeding becomes higher than the ability of the placenta and the amniotic fluid, and thus sends signals to the mother's brain. This, in turn, acts through the vegetative nervous system on the sources of action potential. A similar action must also be present in the preterm births. A second approach of uterine contractions is engineering research. This mainly includes studies conducted by researchers with engineering background. Three main directions being identified as: numerical modeling of uterine contractions, the evaluation of mechanical behavior of myometrium tissue and respectively development and implementation of techniques for evaluation of uterine contractions based on electrical activity at the myometrium tissue level. The third approach to uterine contractions is interdisciplinary research in which there have been identified studies conducted by mixed teams of researchers with specialized medical background and engineering background, respectively.

Although interdisciplinary studies on uterine contractions are being initiated, compared with individual studies and the issues highlighted by each of these approaches, there is a need to further support the interdisciplinary research. Uterine contractions are a complex process that studied at different levels and from different perspectives involves principles and phenomena of anatomic-biological, mechanical, electrical, etc.

Interdisciplinary research has as a key element the creation of a mixed team. This involves identifying specialists and facilitating their meetings. Bridle *et al*., [1], also identify the importance of the team in interdisciplinary research and develop a concept of "cultivation" and "development" encounter. Cultivation encounter is a meeting designed to expose researchers who are not yet involved in interdisciplinary projects to other disciplines, help participants to understand what those disciplines have to offer and explore potential ways to work with them. Development encounters may involve people from outside academia to present a 'real-word' problem of industry or society. Once the team has been set up, the interdisciplinary research has to take place within a well-established strategy.

Tobi and Kampen [27], have developed a framework for methodology in interdisciplinary research that puts the common goal of researchers at the center, regardless of the diversity of their backgrounds. In their conception, the design of interdisciplinary research starts with "conceptual design" that aims to clarify the idea of research and which must be well understood by all team members. Another aspect clarified at this stage is the need of research, which often comes from the current practice. The conceptual design includes activities such as thinking, exchanging interdisciplinary knowledge, reading and discussing.

A second stage in the planning of interdisciplinary research is the "technical design", in which the team has to clarify how the problem will be solved. Aspects such as methods/techniques will be used, what instrumentation is needed and what data will be collected and how they will be processed, are elements that need to be clarified in the technical design. The methodology for planning interdisciplinary research provides also that the activities carried out in parallel to be integrated in order to achieve a common sense of the research. This is a third stage of

integrating different modules developed separately.

A last step is the scientific quality and ethical considerations that are particularly important in recognizing the research. The results and conclusions must be clear, concise, well supported by the obvious and related to the existing research on the problem addressed. Ethical criteria are also of particular importance in medical research and should be considered in all stages of interdisciplinary research.

A continuum concern for interdisciplinary research implies on the one hand the development of a practical and conceptual definition and on the other hand the development of indicators and methods for the measurement of interdisciplinary research. Abramo *et al*. [28], have tried to quantify the interdisciplinary research based on two approaches, the disciplinary diversity of references and the disciplinary diversity of the authors of a paper. The results of this analysis were not the clearest, but an increase in interdisciplinary research was observed as a result of the increase of the disciplines highlighted in the reference list of a paper. However, their analysis concluded with the need for a multi-perspective framework for measuring interdisciplinary combined with expert reviews and content interpretations. This paper is the first work that addresses the interdisciplinary research in terms of disciplinary diversity of the authors but also goes into a content review on a clear subject.

4. Conclusions

In this paper a series of studies on uterine contractions are presented, from the perspective of three approaches, with the main aim to support and encourage interdisciplinary research on this topic. It also highlights the state of the research and issues still unclear on this subject. There are two approaches discussed in this paper, namely medical-biological and engineering, which although they have their own research methods and techniques depending on the background, they have a common topic. This makes them suitable for interdisciplinary research. In addition, specialized medical research has the advantage of practical evidence that should bring to light the observed problems. Furthermore, the paper presents a clear interdisciplinary research methodology to strengthen the collaboration between the two approaches in achieving a common goal: fully understanding the mechanisms and process underlying uterine contractions and preventing as far as possible the premature births.

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