Uterus Modeling from Cell to Organ Level: towards Better Understanding of Physiological Basis of Uterine Activity

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DOI 10.1109/RBME.2020.3023535
ISSN 1937-3333

Publisher: IEEE

Uterus Modeling from Cell to Organ Level: towards Better Understanding of Physiological Basis of Uterine Activity

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***Abstract*—The relatively limited understanding of the physiology of uterine activation prevents us from achieving optimal clinical outcomes for managing serious pregnancy disorders such as preterm birth or uterine dystocia. There is increasing awareness that multi-scale computational modeling of the uterus is a promising approach for providing a qualitative and quantitative description of uterine physiology. The overarching objective of such approach is to coalesce previously fragmentary information into a predictive and testable model of uterine activity that, in turn, informs the development of new diagnostic and therapeutic approaches to these pressing clinical problems. This article assesses current progress towards this goal. We summarize the electrophysiological basis of uterine activation as presently understood and review recent research approaches to uterine modeling at different scales from single cell to tissue, whole organ and organism with particular focus on transformative data in the last decade. We describe the positives and limitations of these approaches, thereby identifying key gaps in our knowledge on which to focus, in parallel, future computational and biological research efforts.**

***Index Terms*—Uterus, uterine physiology, computational modeling, uterine activity**

I. Introduction

As a major hormone-responsive sex organ of the reproductive system, the uterus is of great importance with regard to hosting and facilitating fetal development in humans and other mammals. The uterus is a fibro-muscular organ which is pear-shaped with thick wall and in humans is of a simplex form as it is in some oft-used experimental animal models (*e.g.* sheep) but not all (*e.g.* rodents where it has a duplex form). The uterus is located in the pelvis and has two main anatomic parts: the corpus and the cervix [1], [2]. The uterus is formed by three distinct layers: the endometrium (inner), the myometrium (middle) and the perimetrium (outer) [1], [2]. A normal nulliparous uterus is $6-8.5$ cm long, $3-5$ cm broad and $2-4$ cm thick. Whereas, in multiparous women, the length of uterus increases to $8-10.5$ cm, and both the width and thickness increase to $4-6$ cm [3], indicating that despite involution following pregnancy, there may be features or organ remodeling persistent after pregnancy. Uterine weight increases approximately $6-8$-fold during pregnancy [4], [5] enabled in considerable part by myometrial cell hypertrophy and hyperplasia.

The uterus is a spontaneous and episodic contractile and motile organ. In the non-pregnant state the regulation of the extent of this contractile activity may be involved in menstruation (*e.g.* activation to aid the shedding of endometrial lining during menses) and reproduction (*e.g.* quiescence to facilitate of uterine receptivity of a blastocyst). In the pregnant state the discrete regulation of uterine contractile activity serves two main purposes. First, during much of gestation the role of the uterus is to host and protect the growing placenta and fetus and supply them with nutrients [1], [3]. This requires a period of relative quiescence. Second, at the end of gestation the uterus has to be activated to produce repetitive contractile efforts of sufficient strength and co-ordination to safely deliver the fetus and placenta safely through the cervix and vagina to the outside environment. Alteration in cervical compliance, or cervical shortening, is therefore also a crucial part of a successful labor process [6]–[10]. The importance of the timeliness of these uterine changes during pregnancy is evident from the clinical outcomes if these changes do not follow it. Inappropriately early activation of the uterus, especially if accompanied by premature shortening of the cervix, can result in preterm birth which affects an estimated 15 million babies every year reported by the World Health Organization (WHO), increases the risks of neonatal mortality (accounting for more than 50% of all neonatal deaths) and numerous health problems [11]–[15]. Insufficient uterine activation (dystocia) can also be a marked problem of pregnancy, *e.g.* resulting in post-date gestation (with increased risk of stillbirth or the likelihood of operative delivery) and postpartum hemorrhage [16]–[20].

It seems likely, therefore, that obtaining a comprehensive understanding of uterine contractile activation will assist efforts $-$ diagnostic or therapeutic $-$ This is where an important role for computational biology arises. The biological questions spawn experiments that may answer questions such as how does the electrical action potential increase intracellular calcium $[Ca^{2+}]_i$ and modulate contraction? Where does the electrical activity originate? What controls the frequency of spontaneous action potentials (and contractions) and how is this activity co-ordinated throughout the uterus? Approaches to answer these questions can involve sub-cellular molecular studies (mRNA, protein), single cell or tissue level physiological experiments or even whole organ recordings. Computational approaches often seek to merge complicated datasets

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into a quantitative model that serves to quantitatively describe extant data and predict new hypotheses for the structuring of new experiments. Often, a challenge, and one that is considerable for the uterus, is to construct quantitative models that integrate several systems. In this article, we review the success of computational biology to inform us about the mechanisms of uterine activation from cellular level to whole organ and whole body perspectives. In particular, we highlight key approaches from the last decade that hold promise for advancing the subject in the next decade. For each scale, key models are described and the data sources are introduced. The extent of validations of the models are described including new supporting information introduced in this review. We also highlight key gaps in our knowledge that may help draw attention to important questions for the computational biology community to focus their attention towards.

II. UTERUS MODELING AT DIFFERENT LEVELS

In order to gain physiological insight into the uterine contraction, many studies have focused on modeling the contraction in recent years [1], [21]–[33]. However, the existing modeling and measurement techniques suffer from limitations and their accuracy needs to be improved. The contractions and the propagation of electrical activity associated with the cellular action potential are highly interrelated. Therefore, understanding the mechanisms regarding, for example, the generation and propagation of, such electrical activity is of equal importance. A noninvasive measurement of uterine electrical activity is provided by the technique of electrohysterogram (EHG) which is the electromyogram (EMG) recorded externally on the abdomen [34], [35]. Many groups, thus, have proposed methods for predicting preterm parturition by feature extraction of EHG signals during recent years [36]–[46]. The question that naturally arise is that whether the EHG signal is thoroughly understood. Indeed, we lack the knowledge of underlying electrophysiology of EHG signal such as where it starts during contractions and how it propagates to motor units and then the surface. Modeling the uterus, on one hand, can produce useful information with respect to the source and propagation of EHG signal. On the other hand, an accurate uterus model is an alternative of the uterus in living body for the experiments related to the physiology of uterus, and thus can solve the ethical issue brought by the experiments on human beings and animals.

This section lays emphasis on the studies of the last decade. From year 2010 till now, the studies regarding uterus modeling have focused on different scales of the model. Different fields including those which are electrical, electromagnetical, mechanical, chemical, and geometrical have been considered. Both animal and human models have been investigated. In vivo, ex-vivo and in-virtro data have been used for developing model and/or model validation. Data were always recorded noninvasively from a living person or sometimes invasively from animals so as to obtain useful signals with less noise [47], [48]. Subsequently, the studies on uterus modeling at different levels are reviewed, from cellular level, at which the generation of action potential and/or force is described.

A. Model at Cellular Level

Uterine modeling at cellular scale involves electrical, mechanical and/or chemical aspects and has been developed for exploring the ionic mechanisms of uterus in humans. Electrical properties are described based on previous models of electrical activity [23], [49]–[51] to represent the action potential generation [26], [27], [29]–[31], [33], [52]–[55]. The chemical activities are described in [27], [29]–[31], [33] by the Hai-Murphy model [56] or the modified Hai-Murphy's model [57] regarding the kinetics of myosin phosphorylation, where the intracellular mechanical contraction is the result of the cross-bridge interactions [56], [57]. An advanced mathematical platform for single rat uterine cell modeling was developed by Tong *et al.*, in 2011, for the purpose of describing uterine excitation-contraction coupling quantitatively [23]. This study has provided later investigations with physiological and pathophysiological mechanisms that dominate labors. They then built on their own model with some more potassium channels in 2014, enabling simulations of the long-lasting bursting action potentials, which were further used to investigate how these components work in terms of the cellular excitability of uterus [58]. Later, their model was used as the basal model by Testrow *et al.* for developing a model of electrical, electro-chemical and mechanical activities for single uterine myometrial cell [30]. The elementary diagram of a single myometrial cell model developed in [23] is shown in Fig. 1 as an example for cellular-scale modeling. In 2016, a comprehensive electrophysiological model for human uterine myometrial cell was developed by Atia *et al.*, which relies upon extrapolation of mRNA abundances to protein and thence to channel activity [53]. These cellular-level models have advanced our understanding of the electrophysiological behavior of uterine cell.

Only one of the publications in the last decade mentioned above includes validation of the cell model with their own experimental data rather than literature data or without model validation [53]. In vitro data (Ca^{2+} imaging and current clamp recordings) from both women and mice, whose gestational age was $37-40$ weeks and $15-18$ days, respectively, were used for model validation. The mRNA expression data from previous literature [59] were used for determining the species of potential conductance in myometrial smooth muscle cell [53]. Some studies regarding multi-scale modeling also contain the model validation [26], [52], [55], [60]. Whereas, the validation was conducted at the whole uterus level instead of specifically at cellular level. The model validation with respect to the multi-scale models is discussed in Section II-C.

Modeling at cellular level, which helps to discover physiological mechanisms of uterine activity, was suggested to be useful for the evaluation of the efficacy of drugs [23], [30], [51], [61]. Novel methods of cellular modeling were also proposed with tissue model and organ model for predicting uterine contraction so as to aid the diagnosis of preterm labor and other disorders [24], [26], [27], [29], [31], [33], [52], [54], [55], [60].

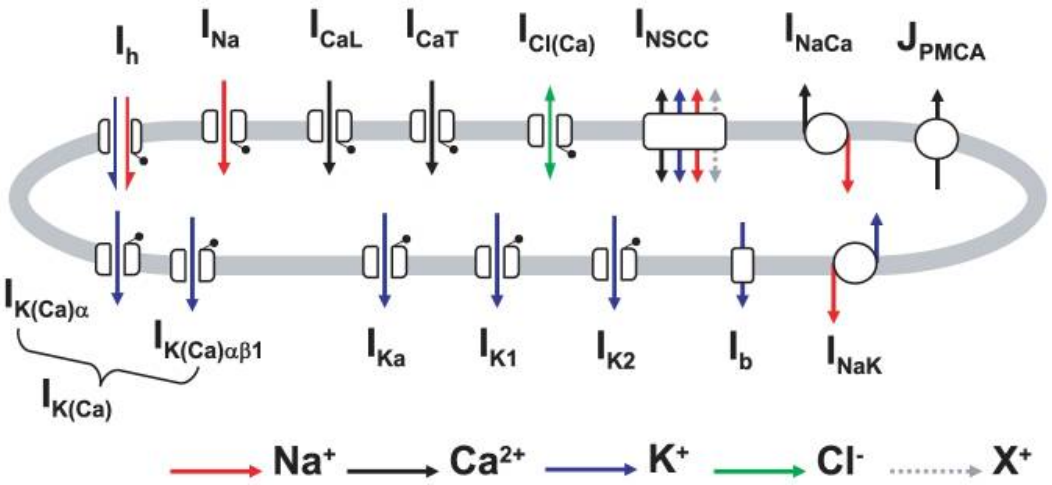


Fig. 1. Uterine smooth muscle cell model [23]. A single cell is composed of 14 ion channels for various types of currents I_h, I_{Na}, I_{CaL}, I_{CaT}, $I_{Cl(Ca)}$, I_{NSCC}, I_{NaCa}, J_{PMCA}, I_{NaK}, I_b, I_{K1}, I_{K2}, I_{Ka}, $I_{K(Ca)}$.

B. Model at Tissue Level

At tissue level, mechanical model is normally developed, which describes the connection between neighboring cells or collagen fiber dispersion and orientation. There are publications that consider the electrical model of the muscular tissue, which is related to the diffusion tensor, as well as mechanical model at tissue level [25], [29], [31], [52]. The mechanotransduction can then be investigated by considering also the electrical and mechanical behavior at cellular level, which was taken as a first step towards a better understanding of global uterine synchronization by Yochum *et al.* [29], [31]. Fig. 2 shows the diagram of an example of uterus model, which involves both mechanical and electrical models at tissue level [31]. In order to reveal the role of collagen fibers in the prevention of preterm birth, Myers *et al*. proposed a material model of collagen fiber ultrastructure of human cervical tissue [62]. Optical coherence tomography (OCT) data has been used for estimating fiber orientation and distribution. An example of OCT fiber orientation maps of an axial cervical slice is shown in Fig. 3.

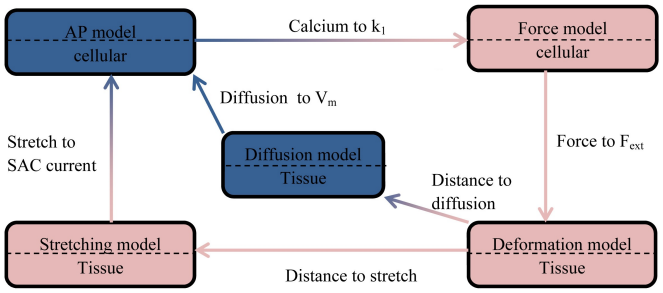
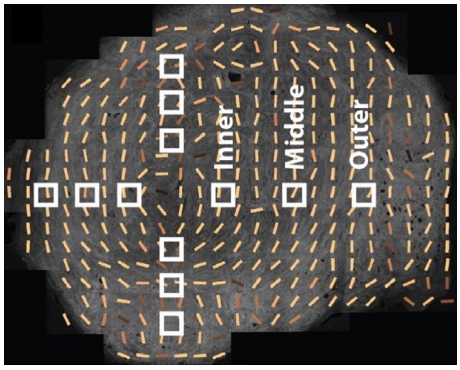
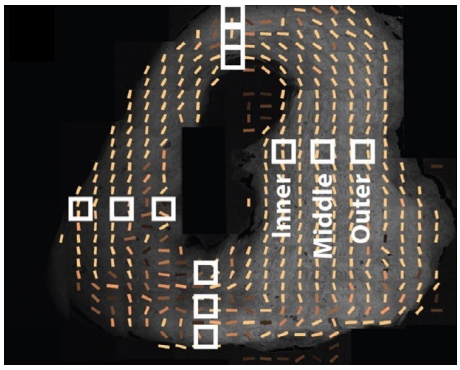


Fig. 2. Diagram of uterus model [31]. The dark blue boxes indicate the electrical models and the pink ones indicate the mechanical models. V_m represents the transmembrane potential which is the output of AP model, $k1$ is the phosphorylation rate dependent on Ca^{2+}, F_{ext} is the external force introduced in the deformation model, and the stretch activated channel is represented by SAC.

None of the recent studies conducted model validation at tissue level using their original experimental data. Because of the ethical restrictions, there are very limited data for characterizing the mechanical response of myometrial tissues in humans and animals. Uterus model at tissue level was usually built on the ex vivo data from uterus removed by hysterectomy [63]. Myers *et al* used their previous experimental data for modeling [62], which were collected from the hysterectomy specimens of hysterectomy patients [64], [65].



(a)



(b)

Fig. 3. Fiber orientation maps of an axial cervical slice produced by optical coherence tomography (OCT) data from (a) a nonpregnant patient and (b) a pregnant patient with hysterectomy [62]. The squares indicate the measurement locations.

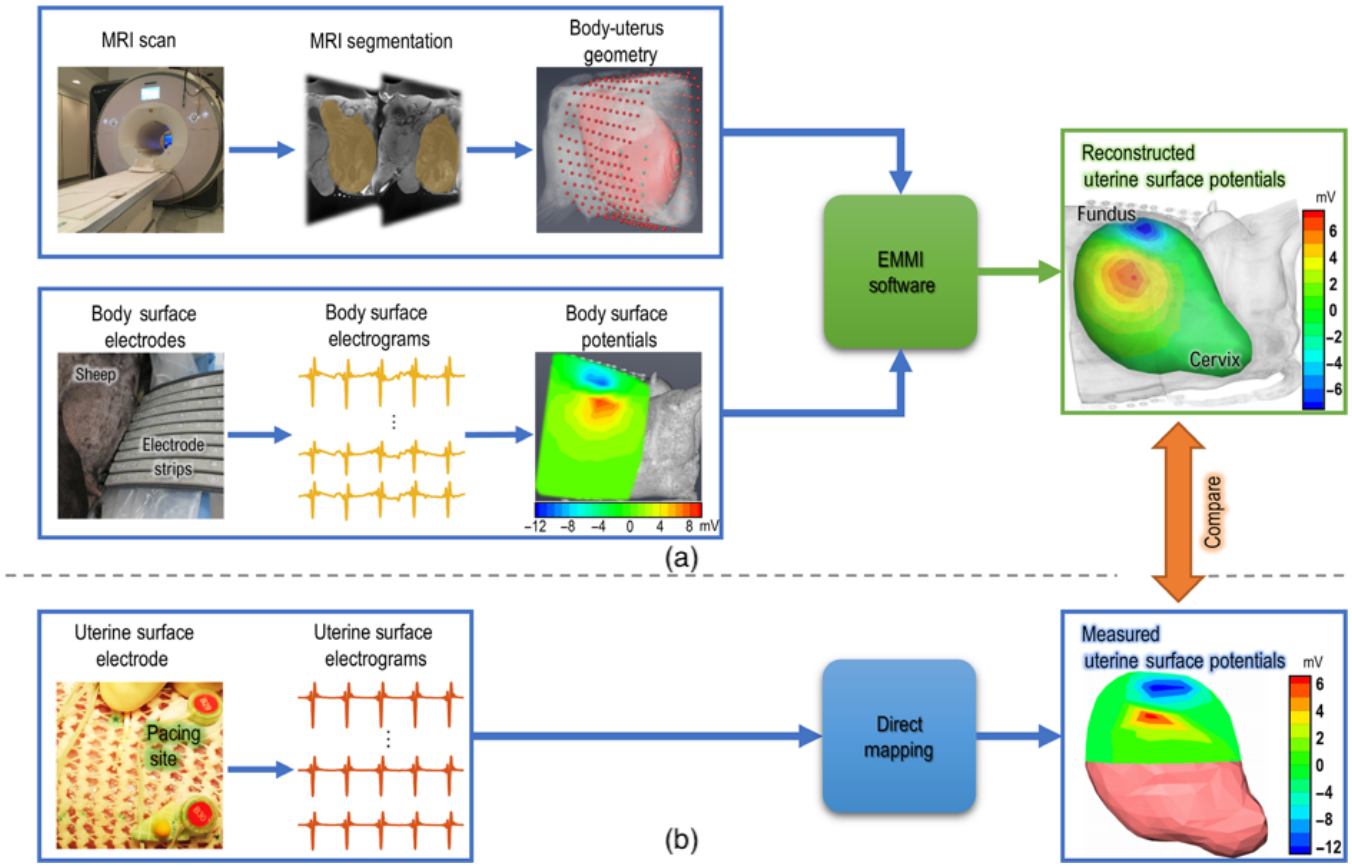


Fig. 4. Electromyometrial imaging (EMMI) for modeling uterine surface potentials and its validation [32]. (a) MRI scans were applied followed by MRI segmentation to produce body-uterus geometry. Body surface electrograms were recorded by the 256 electrodes placed on the body surface to generate body surface potentials. EMMI software combined the both to develop the model of reconstructed uterine surface potentials. (b) Surgery was made on the uterus and a sock with 64 electrodes was covered on the uterus to record uterine surface electrograms, which were then directly mapped onto the uterine surface derived from MRI to produce the measured uterine surface potentials. Body and uterine surface electrograms were recorded synchronously. Finally, the accuracy of EMMI model was assessed by comparing with the measured uterine surface potentials.

The fiber composite model at tissue level has been used for discovering the mechanical function of cervix, which aims to assist in predicting preterm delivery [62], [66]. Another application of modeling at tissue level, which is similar to the cellular-level modeling, is to improve the prediction of uterine contraction together with model at other levels [24]–[27], [29], [31], [33], [52], [54], [55], [60].

C. Model at Organ Level

Organ level models have been developed in order to provide a more macro view of uterus modeling. Not like the invasive data obtained for modeling and validating at cellular and tissue level, data from noninvasive measurements including EHG and magnetomyogram (MMG) which records the electric activity and magnetic fields, respectively, associated with the uterine activity, as well as imaging techniques such as magnetic resonance imaging (MRI) and ultrasound imaging have been widely available [37]–[46], [52], [55], [60], [67]–[80]. Such data can be used for generation and/or validation of the organ-level model. These models are in diverse aspects, to be specific, the electrical, mechanical, chemical, electromagnetic, and geometrical aspects. Although most models have been developed for contributing to the human beings, animal models were also taken into consideration with in vivo invasive recording which contains less noise and produces additional crucial information about uterine activity [32], [47]. Domino *et al*. considered porcine uterus as a reference model for preclinical study and indicated its high applicability [47], [48]. Wu *et al*. performed MRI scan and surgery on Karahdin sheep, whose abdomen size is similar as that of humans. They simultaneously recorded the noninvasive body surface electrogram and invasive uterine surface electrogram, respectively, for modeling and validation [32]. The processes of modeling and its validation at organ level are shown in Fig. 4. Most of the studies involving geometry of uterus consider it as a 3-dimension (3D) structure, but in variant shapes (*i.e.* spherical, ellipsoid or realistic). The examples of difference shapes of uterine volume geometry can be observed in Fig. 5.

Not a few studies involving organ-level uterus modeling have validated their model, most of which used either literature data [25], [27] or original experimental recording [11], [26], [32], [52], [55], [60], [77], [81], [82]. Kelsey *et al*. performed the validation using both the data recorded from 87 children and those extracted from other publications for the modeling of age-related uterine volume [83].

Uterine model at organ level has been applied to simulate

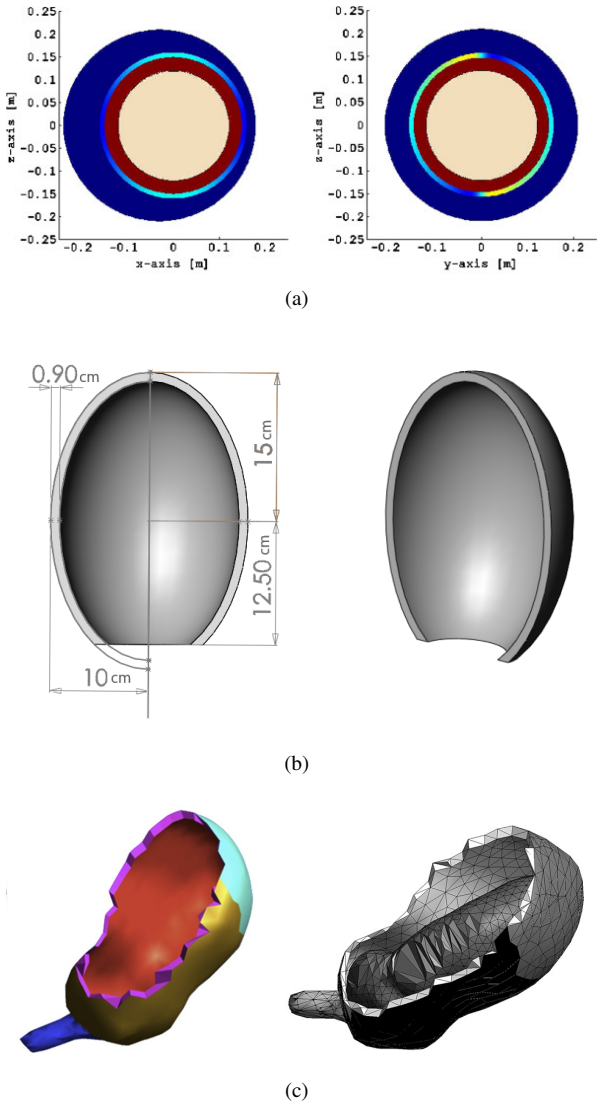


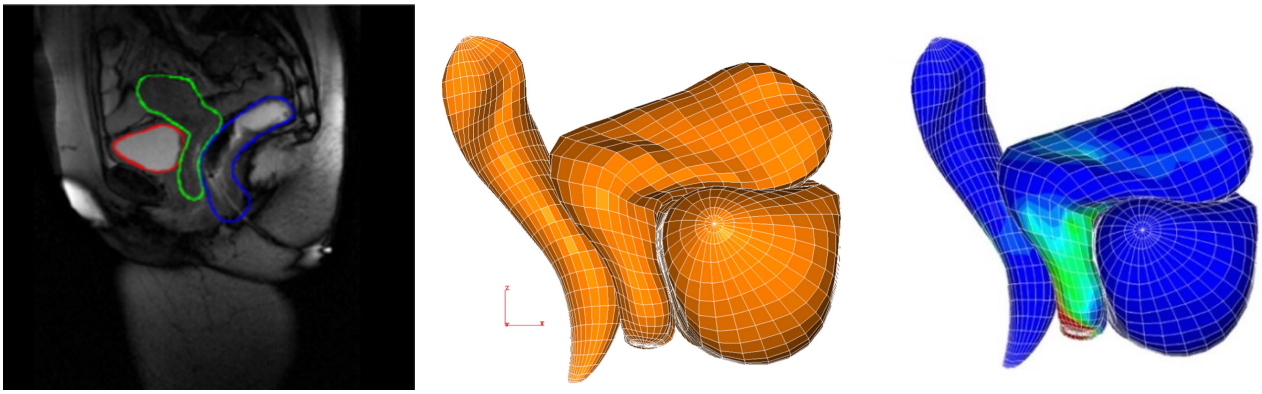
Fig. 5. Uterine geometry in three different shapes: (a) spherical [24]; (b) partial ellipsoid [27]; (c) realistic [1].

and monitor uterine contractions as well as discover the source and propagation of uterine electrical activity for assisting in prediction of problematic labors [1], [24]–[29], [31]–[33], [47], [48], [52], [54], [55], [66], [77], [84]. One of the models contains not only the uterus but also the foetus in order to study the uterine contractions during the expulsion of foetus [33]. Another model that involves the uterine environment with foetus was constructed for investigating the mechanical force that occurs during fetal movements, which can be used for exploring skeletal abnormalities [85]. It is the first model that describes the fetal membrane and uterine wall deformation quantitatively and able to serve clinicians with information useful for prenatal interventions. In addition, some geometric models were developed to aid the surgery [81], [82], [86]. An approach to construct geometric model for individual pelvic organs was proposed by Bay *et al.*, as the fist step to develop a patient-specific decision support software for the surgeon [81]. Aluwee *et al.* proposed a method of assisting the pre-surgical planning by the means of MRI analysis and 3D printing model of personalized uterus [82]. This model provides useful information of, for example, uterine anatomy and tumor location, and thus improving the efficiency and accuracy of surgical planning. Garofalo and Posner created a uterine towel model for adequately training the surgical skills of uterine compression sutures, which is able to control the postpartum hemorrhage [86]. Moreover, an age-related uterine volume model was generated to help for the assessment of disorders such as infertility, menstrual disorders and disorders of sex development [83]. Comparing to the previous researches on age-related uterus models, this model studies the changes in uterine volume rather than just uterine length and across a wider range of age.

It worth noting that more and more studies have taken account of the comprehensive multi-scale model rather than a single-scale model, which provides a global view for the investigation [24]–[27], [29], [31], [33], [52], [54], [55], [60], [66].

D. Model at System Level

There are studies considering uterus at organ scale but as part of a system, which is referred to as system level here to distinguish from the model of only uterus organ. System-level modeling in the review includes the model of uterus together with other neighboring organs, as well as the torso and whole body, where the uterus plays a vital role in their studies. The Finite Element Method (FEM) is one of the most common methods for biomechanical modeling at system level [87]–[101]. Finite element (FE) modeling integrates anatomical data obtained from imaging techniques such as MRI and ultrasound for the construction of a system-level uterus model. Models based on FEM subdivide a structure into smaller and simpler disjoint parts, each of which is associated with a simple but more accurate description, and thus allowing us to consider the differences of property regarding separated regions. An example is shown in Fig. 6 to illustrate the steps of FE modeling at system level. First, the MRI image is obtained and then segmented so that the organs of interest are separated visually (Fig. 6(a)). Next, a 3D mesh which contains thousands of elements is reconstructed for the organs (Fig. 6(b)). Finally, the stresses are estimated and visualized in Fig. 6(c). System-level modeling is necessary for the applications of clinical diagnosis concerning the system consists of other organs as well as uterus, such as the pelvic system, and even the whole body. Computational models regarding pelvic system have been proposed to understand the pathophysiology of pelvic floor dysfunction like pelvic organ prolapse (POP) and stress urinary incontinence [89]–[98]. Most of the pelvic system models were generated from in vivo MRI images [90], [90]–[92], [92], [93], [93], [94], [94], [95], [95], [96], [96], while some groups use ex vivo data from a cadaver [97] or involve both of them [89]. The analysis with these models can provide a powerful tool for clinical use such as clinical diagnosis and pre-surgery planning. Lew *et al*. proposed a torso model of a pregnant woman (see Fig. 7) for the evaluation of a scanner in terms of its ability to non-invasively monitor the electrophysiological activity of maternal and fetal organs [99].



(a) (b) (c)

Fig. 6. FE modeling for POP [90]. (a) Segmented MRI; (b) 3D pelvic organ mesh;(c) Stress distribution.

The body models of a pregnant woman (*e.g.* Fig. 8) were designed by Auriault *et al.* and Acar *et al.* to improve the prediction of adverse fetal outcome and investigate the impacts in car crash, respectively, for the improvement of the vehicle safety [100], [101]. The analysis in [100] is on the basis of the FE model developed in their previous work [88].

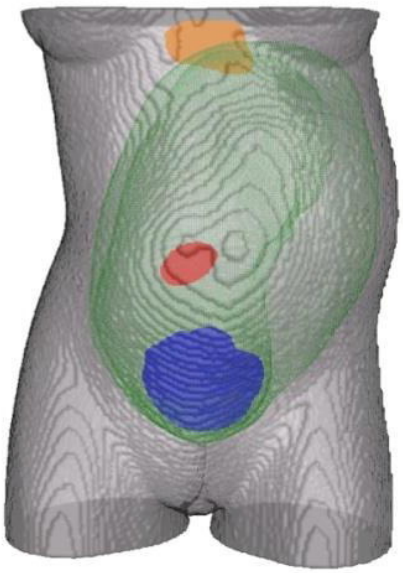


Fig. 7. Model of torso (gray) with uterus (green), fetus's brain (blue), fetus's heart (red) and mother's heart (orange) [99].

Only four of the publications mentioned above take model validation with experimental data into account [87], [91], [93], [94]. The validation process was excluded for the possible reason of minimizing the cost and simplifying the operation. In terms of the pregnant occupant models for vehicle safety study, it is impossible to record data from a pregnant women during car crash.

III. SUMMARY

The biomechanical role of uterus had been investigated by biologists, physiologists and clinicians without an engineering context until the value of combining it with advanced

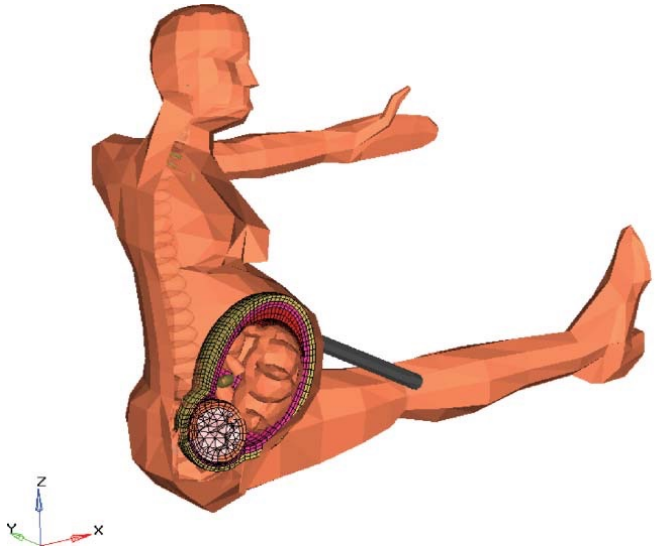


Fig. 8. A whole body model of pregnant occupant for vehicle safety study [101].

computational and experimental bioengineering analysis was recognized. With the development of computational tools and improvement of computational power, uterus can be efficiently modeled at different levels and then the mechanisms of various pathology can be discovered. In the review, we present some representative researches in the last decade that focus on the study of uterus-related modeling. It can be observed in Table I that, most publications include models at or beyond organ level. There could be two reasons: 1) experimental data from cell and tissue are difficult to obtain, and they are even impossible to record from a living person; 2) the ultimate goal is to understand the processes and mechanisms within the view of organ or whole system, which is necessary for exploring its clinical applications. Table I also shows the specific model involved in each study. We can observe that the majority of the models focus on the electrical and/or mechanical properties of the uterus.

Various mathematical tools have been used for uterus modeling. Calculus, for example, has been used as a tool for tensor analysis when building the human tissue material

model [62], [66]. The variables of electrical model were usually described by ordinary differential equations and partial differential equations. In addition, FEM has been proven to be a useful tool for 3D mechanical modeling and used widely in the studies. FE model has become more accurate since recently the technique of MRI was taken into use, other than using eye observations and other techniques of manual measurement, to generate organ geometries. In addition to MRI, EHG, which is low-cost, has also become a common used technique in the research of uterus in recent years [37]–[46], [52], [55], [60], [71]–[76], [78]–[80]. The technique of EHG makes it possible to record uterine electrical activity noninvasively with high temporal resolution, which is very suitable for monitoring the pregnant subjects. An example of 8-channel EHG and TOCO signals recorded from the surface of abdomen is shown in Fig. 9. Although the development of techniques for data recording allows us to obtain real clinical data more easily and accurately, many researches have been done without experimental data (see Table I). Even if the experimentation is involved in a research, the recorded data may not be enough or suitable for both developing model and its validation (see Table II). More details are discussed in Section III-A.

A. Limitations and Challenges

Despite the benefit that uterus model can be used for simulation as an alternative for in vivo experiments on animal and human subjects, the real data recorded from animals and human beings are essential for generating a uterus model that can produce accurate information for clinical use. That is the reason why the techniques which can record noninvasive data are of great importance. The researches in Table I which include experimental study are listed in Table II. Models in some of the researches without experimentation were constructed and/or validated using the literature data collected by other groups [25], [27]–[29], [31], [33], [95], [96], [98], [99]. These literature data were collected under different conditions many years ago so that they may not appropriate for the latter studies on modeling by other groups. Experimentation designed for a particular study can produce suitable data. Nonetheless, it is restricted by some ethical reasons. Invasive data has rarely been collected from the uterus of a living person because of the complications that may occur (*e.g.* intrauterine infection, injury to the fetus, rupture of membranes, etc). Animal subjects, cadavers and discarded specimens, as the substitution of a living person, have been used in the experiments for invasive data recording. Model based on such data, however, is not always applicable for clinical use on human patients. On one hand, animal uterine models are different from human uterus in terms of, for example, morphology and tissue organization. On the other hand, recording from the uterus in a cadaver or the discarded specimens can not provide information completely as same as the uterus in a living body provides. In the experiments on humans, noninvasive measurements including EHG, MRI, MMG, ultrasound imaging and so on have been used. Signals collected noninvasively always contain plenty of noise components which could hide the useful information. For instance, EHG signals are recorded for representing

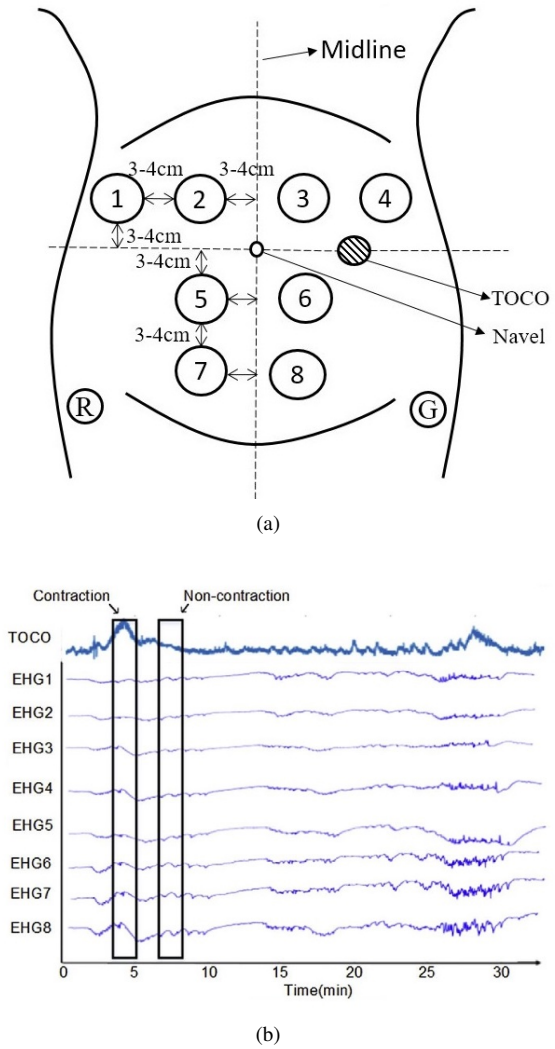


Fig. 9. (a) Configuration of EHG electrodes [78]. (b) TOCO and 8-channel EHG signals [46].

uterine electrical activity. Nevertheless, since EHG signals are recorded by electrodes placed on the surface of abdomen instead of directly on the uterus muscle, it is contaminated by various types of noise, such as motion artifact, electrical noise from external sources and cross-talk from other muscles. Advanced denoising algorithm regarding the particular signal, therefore, is necessary for the study of uterus modeling. In addition to the techniques shown in Table II regarding measuring uterine contractions, other measurement including intrauterine pressure (IUP) measurement and tocodynamometer (TOCO) transducer also suffers from the defects mentioned above [11], [75], [102]–[104]. Wu *et. al.* tried very recently to overcome the limitations existing in current techniques of measurement by an electromyometrial imaging (EMMI) method [32]. This method is on the basis of the principles of electrocardiographic imaging (ECGI) [105]–[110].

Another limitation that can be observed from Table II is the insufficient number of subjects used for experiment of uterus modeling. Most experiments in Table II recruit only one or two subjects, which can not represent the generality. Consid-

TABLE I
PUBLICATIONS ON UTERUS MODELING IN RECENT 10 YEARS SORTED BY DIFFERENT LEVELS. [a]

Level		Publication	Model	Experiment included
	Cell	[23]	Electrophysiological model of uterine smooth muscle cell	
		[58]	Electrophysiological model of uterine smooth muscle cell	
		[61]	Computational model of inhibition of voltage-gated Ca channels	
		[53]	Electrophysiological model for every individual potential oligomeric channel complex	√
		[30]	Model of electrical, electro-chemical and mechanical activities of single uterine cell	
	Tissue	[62]	Equilibrium material model for human cervical tissue	√
	Organ	[111]	Mathematical model of uterine wall tension trajectories at the onset of labor	√
		[81]	Geometric modeling of pelvic organs	√
		[83]	Mathematical model of uterine volume related to age	√
		[28]	Existing ECM model of uterine contraction and developed meta model [b]	
		[82]	3D physical model of uterus	√
		[1]	Biomechanical model of uterus	√
		[84]	Electro-mechanical model of uterus sources	
		[77]	Electromegnetic model of abdominal magnetic field of uterine contractile events	√
		[86]	Towel model of uterus	
		[47]	Probabilistic model of spontaneous myoelectrical activity of porcine uterus	√
		[48]	Probabilistic model of electrical activity of the porcine uterus	√
		[32]	Electrophysiological model of uterus	√
		[85]	Biomechanical model of fetal movements	√
Multi	Tissue & Organ	[25]	Electro-mechanical model of uterine contractions	
		[66]	Mechanical model of pregnant uterus, cervix, and fetal membrane	√
	Cell, Tissue & Organ	[60]	Electrophysiological model of uterine activity	√
		[24]	Electromagnetic model of uterine contractions	
		[52]	Electrophysiological model of EHG	√
		[27]	ECM model of uterine excitation, activation, and contraction [b]	
		[26]	Electrophysiological Model of MMG of uterine contractions	√
		[29]	Electro-mechanical model of uterine pregnancy contraction	
		[54]	Electro-mechanical model of uterine muscles	
		[55]	Electro-mechanical model of uterine muscles	√
		[31]	Electro-mechanical model of uterine smooth muscle with mechanotransduction	
		[33]	Biomechanical model of the uterus and the foetus	
	System	[87]	Anatomical model of whole-body pregnant woman	√
		[89]	Biomechanical model of pelvic system of pregnant women	√
		[90]	Biomechanical model of POP	√
		[92]	Biomechanical model of pelvic floor support systems of subjects with and without POP	√
		[91]	Biomechanical model of female pelvis	√
		[94]	Biomechanical model of female pelvis	√
		[93]	Biomechanical model of pelvic floor muscle contraction	√
		[95]	Biomechanical model of pelvic system	
		[96]	Biomechanical model of anterior and posterior POP	
		[97]	Biomechanical model of pelvic floor	√
		[98]	Biomechanical model of pelvic floor	
		[99]	Electrophysiological of pregnant woman's torso	
		[100]	Mechanical model of whole-body pregnant women	
		[101]	Mechanical model of whole-body pregnant women	

[a] It worth noting that this table does not contain all studies on uterus modeling in the last decade, but some ones that are representative in the authors' opinion;
[b] ECM model represents the electro-chemo-mechanical model.

ering the individual variation, data from sufficient number of subjects are required for constructing a general model. Patient-specific treatment can, then, be explored on the basis of the general model and specific clinical data. In spite of generality, some characteristics, such as fatness, may have influence on the quality of clinical data so that the model would be affected significantly.

Indeed, uterus modeling has the potential of providing a clinical tool useful for identifying risk probability of problematic labors and assisting clinical diagnosis of other uterus-relevant diseases, as well as helping planning the pre-surgery. It even has the potential to be used for evaluation of drug or hormone action. However, there are still many challenges on the way before the clinical applications based on uterus modeling can be put into use and future work is required.

B. Future Work Directions

Computational modeling of uterus has ability to serve as a quantitative and visualized tool for exploring the mechanisms and processes of the contractions. Nonetheless, the development of uterus modeling is far behind the cardiac model. As the model of another muscular organ in human and most other animals, cardiac model has been the most highly integrated and widely used model of virtual organ [113]. The cells and tissues of both uterine and cardiac muscles can be autorhythmic or excited. However, different from the underlying mechanisms of cardiac contraction, about which we have better understanding, the mechanisms of uterine contraction remain unclear. The advances of cardiac modeling root in reduplicative interaction between experimentation and modeling. Although some models and techniques used in the field of cardiology have been adopted in uterine modeling [23], [53], [63], [103], the experimental study is excluded in many

TABLE II
PUBLICATIONS THAT INVOLVE EXPERIMENTAL STUDY.

Publication	Subject	No. of Subjects[a]	Data for modeling	Data for validation	invasive or noninvasive
[53]	human, rat	not mention	in vitro voltage, Ca^{2+} time series	in vitro imaging and recordings	invasive
[111]	human	320	in vivo ultrasound imaging data	N/A	noninvasive
[81]	human	1	in vivo MRI	in vivo MRI	noninvasive
[62]	human	not mention	ex vivo data [e]	N/A	invasive
[83]	human	87	in vivo MRI, literature data	in vivo MRI, literature data	noninvasive
[82]	human	5	in vivo MRI	in vivo MRI	noninvasive
[1]	human	1	in vivo MRI	N/A	noninvasive
[77]	human	2	N/A	in vivo MMG, abdominal deflection	noninvasive
[47]	pig	8	in vivo EMG	N/A	invasive
[48]	pig	12	in vivo EMG	N/A	invasive
[32]	sheep	9	in vivo MRI, electrogram	electrogram	invasive, noninvasive
[85]	human	3	in vivo MRI	data from experimental setup text	noninvasive
[60]	human	1	N/A	in vivo EHG	noninvasive
[66]	human	2	in vivo MRI	N/A	noninvasive
[26]	human	1	in vivo MRI, MMG	in vivo MMG	noninvasive
[52]	human	1	in vivo EHG	in vivo EHG	noninvasive
[55]	human	1	N/A	in vivo EHG	noninvasive
[87]	human	16	in vivo MRI, ultrasound imaging data	routine image data [f]	noninvasive
[89]	human	2 [b]	in vivo MRI, ex vivo data	N/A	invasive, noninvasive
[90]	human	1	in vivo MRI	N/A	noninvasive
[92]	human	2 [c]	in vivo MRI	N/A	noninvasive
[91]	human	1	in vivo MRI	in vivo MRI	noninvasive
[94]	human	1	in vivo MRI	in vivo MRI	noninvasive
[93]	human	1	in vivo MRI	in vivo MRI	noninvasive
[97]	human	1 [d]	ex vivo data	N/A	invasive

[a] Note that the number of subjects corresponds to only the final subjects considered for modeling and/or validation;
[b] 1 living subject and 1 cadaver;
[c] 1 healthy subject and 1 patient;
[d] 1 cadaver;
[e] Data from their previous studies: Optical coherence tomopgraphy (OCT) data of cervix specimens from hysterectomy patients [64]; equilibrium compression and tension data of hysterectomy specimens from hysterectomy patients [65], [112];
[f] Validation were performed by visual inspection of clinical experts on representative images.

researches on uterus (see Table I). Since the study on uterus aims to make a contribution to the clinic, the experimental recording under particular conditions should be accounted as one of the very important elements in the studies. Uterine electrical signal is obviously a considerable signal that can provide desired information. EHG, as a noninvasive technique that records uterine electrical activity, has proved its ability and suitability for detecting uterine activity in pregnant women. In order to extract signal components relevant to the task of interest, advanced biological signal processing methods are needed for noise removal.

Advanced technique for recording uterine activity from a single cell and tissue in living body would be a strong demand for the future work on uterus modeling. Alternatively, experimental studies at cellular and tissue level with properer substitutes would be required to serve the modeling with sufficient and appropriate data. Meanwhile, investigations on the differences and similarities of cells and tissues between animal and human is worth doing, which would provide evidence of, for example, whether the data from animal studies could be suitable for a particular cell/tissue-level model of human. Future work is suggested to focus on incorporation of uterus modeling, signal processing and image processing. Specifically, first, the techniques of biological signal processing and image processing should be improved so as to obtain data and images of higher quality for better modeling in various aspects. The uterus is, then, modeled and simulated to obtain information that allows insight into the sources and paths of uterine activities during contractions for better understanding of the biological signals. Comparing to the electrocardiogram (ECG) signal used for cardiac modeling, whose physiological mechanisms have been comprehensively investigated, our knowledge in regard to the physiology of uterine signals is deficient. The better understanding of the signal, the more information that can be extracted for reflecting the uterine activity. Besides, revealing the pacemaker and path of uterine contraction by means of modeling the uterus makes it possible to predict the labor. Moreover, the relationship between uterine contraction pressures and electrical signals, *i.e.* whether there is piezoelectric effect and/or inverse piezoelectric effect or not, needs to be discovered. The model, in addition, can be used for the simulation of preterm delivery. Finally, the electrophysiological mechanisms of uterine contraction can be revealed by the uterus model and signal.

ACKNOWLEDGMENT

This work was supported by Bill & Melinda Gates Foundation [OPP1148910].

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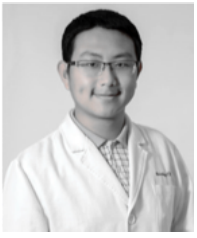

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