Computer models to study uterine activation at labour

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ABSTRACT: Improving our understanding of the initiation of labour is a major aim of modern obstetric research, in order to better diagnose and treat pregnant women in which the process occurs abnormally. In particular, increased knowledge will help us identify the mechanisms responsible for preterm labour, the single biggest cause of neonatal morbidity and mortality. Attempts to improve our understanding of the initiation of labour have been restricted by the inaccessibility of gestational tissues to study during pregnancy and at labour, and by the lack of fully informative animal models. However, computer modelling provides an exciting new approach to overcome these restrictions and offers new insights into uterine activation during term and preterm labour. Such models could be used to test hypotheses about drugs to treat or prevent preterm labour. With further development, an effective computer model could be used by healthcare practitioners to develop personalized medicine for patients on a pregnancy-by-pregnancy basis. Very promising work is already underway to build computer models of the physiology of uterine activation and contraction. These models aim to predict changes and patterns in uterine electrical excitation during term labour. There have been far fewer attempts to build computer models of the molecular pathways driving uterine activation and there is certainly scope for further work in this area. The integration of computer models of the physiological and molecular mechanisms that initiate labour will be particularly useful.

Key words: computational modelling / parturition / systems biology / uterus

Introduction

The onset of regular painful uterine contractions is one of the main symptoms and signs of the initial stages of labour. Molecular events in the myometrium, the muscle layer of the uterus, stimulate it to contract in a phasic manner to expel the fetus from the uterus. However, the exact mechanisms that switch the myometrium from its quiescent state during pregnancy to a contractile state at labour are poorly understood. This is partly because labour is extremely complex and partly because it is a difficult system to study experimentally. Attempts to improve our understanding have been restricted by the inaccessibility of gestational tissues to study during pregnancy and at labour, and by the lack of fully informative animal models (Mitchell and Taggart, 2009). In sheep and cows, labour is an endocrine process that is reliably triggered by activation of the fetal hypothalamic pituitary axis and the subsequent decrease in the progesterone to estrogen ratio, but in humans no such major change in steroid synthesis occurs. Instead, labour probably results from a change in steroid receptor expression perhaps triggered by a change in inflammatory mediators (Fig. 1). The relative importance of each of these factors or their interactions in activating the uterus to contract is still unclear.

Improving our understanding of the initiation of labour is a major aim of modern obstetric research, in order to better diagnose and treat pregnant women in which the process occurs abnormally. In particular, it will help identify and perhaps prevent the mechanisms responsible for preterm labour (spontaneous labour occurring before 37 weeks’ gestation), which is a huge clinical problem contributing to 75% of all preterm births (Norman et al., 2009; Blencowe et al., 2012; Chang et al., 2013; Norman and Shennan, 2013). In Europe the incidence of preterm birth is around 6% of births per year (March of Dimes, 2009) and this is increasing (Norman et al., 2009). Globally, preterm birth accounts for 28% of neonatal deaths (Lawn et al., 2006) and is associated with longer term health problems in survivors such as physical, mental and developmental delays (Saigal and Doyle, 2008).

Preterm labour could occur following premature activation of the normal mechanisms that trigger term labour, or via alternative pathological mechanisms such as those associated with social stress or infection (Muglia and Katz, 2010). A better understanding of the normal mechanisms of labour at term is essential to developing effective methods to predict, prevent and treat preterm labour, and will require studying molecular and physiological events at subcellular, cellular, intercellular, tissue and organ levels. Although a worthy task, such an endeavour is not trivial and using traditional approaches could take many more decades of work before fruition.

However, computer modelling is a promising way to help focus this work and to generate novel hypotheses on pathophysiology and therapy. Despite the explosion in the use of bioinformatics in the past...
decade, computer models have been used relatively infrequently to study pregnancy (Gravett et al., 2010), and perhaps because of this there remains a critical gap in our understanding of the mechanisms controlling the onset of labour.

Models can be built at various levels. Lower level models describe protein and gene subcellular interactions, but higher level models might describe the functioning of tissues, organs, organisms or even the behaviour of populations (Wilkinson, 2006). They assemble complex experimentally derived data into concise mathematical representations of biological systems that reveal more about their operation and structure than wordy descriptions and/or diagrams ever could. They can consolidate the current state of knowledge of a system, test that it is correct, highlight gaps in our understanding and can inform design of biological experiments to bridge those gaps. Furthermore, a well-validated model that describes the system accurately can be used to predict how the system will react to different stimuli in ‘virtual’ experiments that might be time consuming and expensive in the lab (Smolen et al., 2004). Such models are particularly useful if they can reproduce or predict behaviours beyond those they were initially designed to describe (Smolen et al., 2004). They can then be used to generate and test hypotheses about how the biological system might be organized and regulated. These hypotheses can be tested using wet lab experiments, and models can be updated with new data and used to generate further hypotheses. It is important to note that the reliability of a model hinges on the availability and quality of the data obtained through such experiments. Models are also heavily dependent on decisions made regarding model design and which data to include or exclude. Wet lab validation helps to reduce this risk of bias.

**Computer models of labour**

Computer modelling of the events involved in initiating uterine contractions should help identify key pathways or mechanisms that might be altered in preterm labour. Such models have several potential applications. For example, they could be used to test, in silico, hypotheses about drugs to treat or prevent preterm labour. Models could also help identify a subgroup of women who are likely to respond best to certain treatments. In this way, they could provide a useful tool to help design expensive time-consuming clinical trials more efficiently. With further development, an effective in silico model could be used by healthcare practitioners to develop personalized medicine for patients on a pregnancy-by-pregnancy basis.

Some research groups are already developing computer models relevant to labour. These models fall into three categories: (i) models of uterine electrophysiology and propagation, (ii) models of the molecular mechanisms that initiate labour and (iii) models of the biomechanics of

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**Figure 1** Key endocrine and inflammatory factors associated with the initiation of human parturition. Green dotted lines denote activation pathways, and red dotted lines denote inhibitory pathways. ACTH, adrenocorticotropic hormone; COX2, cyclooxygenase; CRH, corticotrophin-releasing hormone; DHEAS, dehydroepiandrosterone; MMPs, matrix metalloproteinases; NF-κB, nuclear factor kappa B; PLA2, phospholipase A; PRA, progesterone receptor A; PRB, progesterone receptor B.
labour (the movement of the fetal head through the pelvic floor). Biomechanic models are not discussed here because they are less concerned with the onset of labour (for a comprehensive review of such models, see Li et al. (2008)). Here, we provide an overview of models of the electrophysiological and molecular mechanisms activating labour that have been published to date (see Fig. 2 for a diagrammatic summary).

Models of the physiology of uterine contraction

Models of the physiology of myometrial contraction aim to predict changes and patterns in uterine excitation during gestation and term labour. These predictions can help generate ideas about the possible mechanisms of disorders such as contractile dysfunction and early activation of uterine excitation in preterm labour (Aslanidi et al., 2011). Biological data to validate physiological computer models can be generated non-invasively from a variety of sources, including:

(i) Ultrasound measurement of the shape of the uterus.
(ii) Time series measurement of electrical signals generated by the uterus using electrodes on the surface of the abdomen (electrohystogram).
(iii) Measurement of contraction strength over time using an intrauterine pressure catheter during labour.
(iv) Magnetic resonance imaging (MRI) of the three-dimensional structure of the uterus.
(v) Diffusion Tensor MRI (DTMRI) to provide structural information about uterine smooth muscle.
(vi) Electrophysiological experiments using myometrial biopsies collected at Caesarean section in which:
   (a) Imaging calcium ions in myometrial tissue can provide spatio-temporal information on electrical excitation.
   (b) Single uterine smooth muscle cells can be obtained for voltage clamp studies investigating the role of different ion channels in contraction (Blanks et al., 2007; Shmygol et al., 2007).

Computer modelling of tissue electrophysiology is an established technique in cardiac research. Over the past 50 years, anatomical, cell excitation and tissue propagation models have been instrumental in advancing understanding of heart muscle physiology (Clayton et al., 2011). In an attempt to parallel this success, the same methodology is being applied to modelling the physiology of the labouring uterus. Reports of the development of such models have already appeared in the literature.

Anatomical models

Models that consider various aspects of uterine anatomy throughout gestation and labour are useful for characterizing changes in the uterus that might be important determinants and predictors of the timing and progress of labour. To our knowledge, the only attempt to build such a model was reported by Sokolowski et al. (2010). Sokolowski used a statistical modelling approach to model trajectories of uterine wall thickness, volume and tension throughout gestation. The model was based on intrauterine pressure catheter results from the literature and ultrasound measurements of the shape of the uterus collected from the first antenatal appointment until delivery in 320 pregnant women. By comparing trajectories between three groups (women with singleton pregnancies at term or preterm and women with twin pregnancies), they were able to assess whether or not uterine wall tension is an important determinant of the onset of labour. They saw no significant difference in tension in the preterm or twin gestation groups compared with the term group and therefore concluded that uterine wall tension is not a causal factor in preterm spontaneous labour in singleton or multiple pregnancies.

Cell excitation models

Cell excitation models tend to take a bottom-up approach by modelling the events in single cells with the assumption that the overall behaviour of the uterus can be explained either by the combined contributions of each cell, or by combining cell excitation models with tissue propagation models.

Figure 2 A diagrammatic overview of different modelling targets and uses for models of the initiation of labour.
Bursztyn et al. (2007) presented a mathematical model of uterine smooth muscle cell excitation with three elements: (i) intracellular calcium concentration (affected by three control mechanisms: voltage-operated calcium channels, calcium ion pumps and sodium–calcium exchangers), (ii) myosin light chain phosphorylation and (iii) stress produced by the cell in response to depolarization of the cell membrane. Model simulations were compared with the published results of voltage clamp experiments using pregnant rat uterine smooth muscle cells (Shmygol et al. 1998), and data on myosin light chain phosphorylation and force production in non-pregnant human uterine smooth muscle cells (Inoue et al. 1990; Young et al. 1991). The model successfully reproduced wet laboratory experimental results and highlighted the importance of cellular mechanisms of calcium control; however, it was very simple and did not include some of the other key mechanisms that regulate cell excitation.

Rihana et al. (2009) built a more detailed model that involved all the main ionic mechanisms behind uterine smooth muscle cell excitation. These were voltage-dependent sodium, calcium and potassium currents, calcium-dependent potassium currents, leakage currents, and pumps, exchangers and binding to regulate intracellular calcium dynamics. The model was based on data from published voltage clamp experiments on, predominantly, rat uterine smooth muscle cells. It reproduced spikes, spike trains and bursts of action potentials shown in these experiments and, as with Bursztyn et al.’s model, highlighted the importance of calcium control in regulating cell excitation.

The most detailed uterine smooth muscle cell excitation model to date was developed by Tong et al. (2011). The model included 105 differential equations, over 125 parameters and 13 ionic currents. These were a calcium current, a sodium current, a hyperpolarization-activated current, three voltage-gated potassium currents, two calcium-activated potassium currents, two myosin light chain phosphorylation, a sodium–calcium exchanger, a sodium–potassium pump and a background leakage current. The model also took cell size into account. Simulations were validated using published and unpublished results of voltage clamp experiments on pregnant rat uterine smooth muscle cells in the presence and absence of estradiol and experimental recordings of spontaneous action potential, calcium ion and phasic force in rat myometrial tissue strips. The model was very detailed and allowed investigation of the ionic mechanisms behind cell excitation at labour. It was also the first model to include a reconstruction of cellular changes in response to drugs (estriadiol).

Tissue propagation models

Tissue propagation models aim to predict the spread of smooth muscle excitation and contraction throughout the uterus at term gestation. They are often built using simplified geometries intended to mimic uterine anatomy.

Andersen and Barclay (Andersen and Barclay, 1995; Barclay et al., 2010) built a model to explain how contractions spread through the uterus. The uterus was represented as a hollow ovoid made up of discrete contracting cells that send electrical impulses to their neighbours, generate tension and have defined periods of contraction and refraction. The sum of the tension contributions from each cell was used to describe the contraction pressure in the whole organ. The authors found that the shape of contraction waveforms depended on the shape of the uterus and the position of a pacemaker, but not on the number of cells. They concluded that abnormal uterine contraction patterns may result from pacemaker activity in unusual locations (such as mid-uterus). The model assumed that intercellular communication occurs via action potential propagation only and neglects to include other mechanisms. Furthermore the model was not validated experimentally. Despite these limitations it was able to reproduce complex contraction patterns similar to published reports of those observed in human labour (Barclay et al., 2010).

Young (1997) built a model in which intercellular communication occurred via two mechanisms: action potential and calcium wave propagation. The model was based on five assumptions: (i) action potential propagation is a global, rapid, long distance method of intercellular communication, (ii) calcium waves are local and slow, (iii) the passage of an action potential initiates a calcium wave, (iv) myometrial bundles are ring shaped in cross section, with waves occurring radially from the centre and (v) myocytes communicate by direct contact only. The model program was validated against in vivo contraction recorded by an intramural pressure catheter in one labouring woman. The simulated change in force over time agreed strongly with the real contraction, suggesting that action potential propagation and calcium waves are both important factors in uterine contractility. Adjusting various model parameters highlighted myocyte bundle size and intercellular calcium wave speed as the primary determinants of contraction shape.

Vauge et al. (2003) argued that whereas Young used arbitrary mathematical interpolation to fit the experimental data, a model using more physiologically significant parameters would provide a more accurate representation of the changes in intrauterine pressure associated with a contraction during labour. Accordingly, they built a model using three differential equations to reproduce in vivo recordings of intrauterine pressure during human labour. The equations took into account the number of cells in each of three states (contracting, refractory and resting), the excitability of the cells in the resting state, the lifetime of the contraction state and the duration of the refractory state. The model was based on the hypothesis that uterine smooth muscle cells contract in an intermittent, unsynchronized manner throughout pregnancy, but greater synchronicity develops towards term under the influence of molecular factors. Although simple, the model was useful in highlighting the key physiological parameters involved in the normal progression of labour.

Taking a different approach, Bastos et al. (2010) developed a model to simulate intrauterine pressure in labouring women. The model was designed for use in a full-body labour and delivery simulator, thereby providing a risk free and controllable environment for training healthcare practitioners. The model consisted of a truncated Gaussian curve to mimic the bell shape of the uterine contraction waveform, with programmable parameters for amplitude, frequency, duration and resting tone. The model was based on analysis of 44 h of physiological data. To test the model, three healthcare practitioners were asked to attribute realism scores to model-simulated intrauterine pressure tracings. The experts were unable to distinguish simulated tracings from real tracings. Although not developed as a research tool, this work does show that models can be used to improve clinical management by providing healthcare practitioners with a realistic experience of changes in intrauterine pressure associated with complicated and normal labour. The model has since been extended to reflect specific clinical scenarios (Bastos et al., 2012) and to simulate the effect of oxytocin to augment labour (Lobo et al., 2013).
Multiscale physiological models

The ultimate aim of work in this area is to develop a model that can be used in a clinical setting to quantitatively relate measures of uterine activity to the electrodynamics of the uterus in order to predict onset of labour and labour dysfunctions (Taggart et al., 2007). Progress towards this stage requires the development of multiscale models that integrate knowledge of uterine anatomy with models of uterine smooth muscle cell excitation and propagation throughout the tissue (Aslanidi et al., 2011). Furthermore, it makes sense to validate these models using clinically acceptable techniques. For example, assessment of contraction strength using an intraterine pressure catheter is not recommended for routine clinical use (ACOG, 2011) because it shows no advantage in fetal or maternal outcomes over non-invasive methods (Bakker et al., 2012; Euliano et al., 2013). Therefore, models should be validated using non-invasive methods, such as the electrohystogram.

Laforet et al. (2011) developed a preliminary multiscale model using this approach. Their model combined a simplification of Rihana’s cell excitation model (Rihana et al., 2009) with a model of electrical activity conductance from the myometrium to the skin developed by Rabotti et al. (2010). They aimed to describe the pattern of uterine electrical activity from its onset at cell level to its propagation throughout the myometrium, to its conduction to the abdominal surface. The model was able to successfully simulate electrohystograms and although the authors stated that significant improvements would be required before the model could accurately represent the complex anatomy and physiologic-dynamical system of the uterus, it nevertheless showed an important proof of concept that such multiscale models can be useful.

Another multiscale model using non-invasively collected data was described by La Rosa et al. (2012). Their model considered the uterus as a sphere with one pacemaker located in the fundus, and they combined this anatomy with uterine electrical activity measured using abdominal surface electromyography and magnetomyography. The model was developed in two stages: first they used a cell excitation model and a tissue propagation model to simulate electrical activity in the myometrium, and then they computed the magnetic field and action potential at the abdominal surface. Their results agreed well with published data, which makes the model potentially useful for characterizing contractions and predicting labour using magnetomyography and electromyography.

In a recent review, Aslanidi et al. (2011) reported a current multi group effort to build a comprehensive multiscale model of the pregnant human uterus. At present this involves building a set of models of spatiotemporal patterns of uterine electrical activity including a reconstruction of the three-dimensional geometry of the pregnant uterus using in vivo MRI and ex vivo DTMRI, cell excitation models and tissue propagation models. The authors noted that modelling uterine activity is more complex than modelling cardiac activity because the uterus ordinally exists in a relaxed, non-labouring state but is transformed to contract physically through changes in gene expression. They asserted that comprehensive models of normal and preterm labour will therefore need to integrate information on electrophysiology with molecular data.

Models of the molecular mechanisms that trigger labour

Models of the molecular mechanisms that initiate labour aim to identify key molecular pathways that drive the onset of labour and predict the effects of pharmacologic agents that alter these pathways. The data required to build and validate such models can be gathered from diverse sources—from published literature in online protein pathway resources (such as KEGG (Kanehisa and Goto, 2000) or Reactome (Vastrik et al., 2007)) to proteomic or genomic analysis of in vitro time-course experiments on uterine smooth muscle cells. Despite the increased availability of published data and the common use of techniques to measure gene and protein expression, there are very few reports describing computer models of the molecular mechanisms that trigger labour.

Wanner and Pliska developed an early model that described an increase in uterine tension in response to an oxytocin stimulus. In their 1977 paper, they extended this model to include intracellular calcium concentration as a mediator of this response (Wanner et al., 1977). The model was built around three simple rate equations describing the change in calcium concentration in the extracellular space, the myoplasm and cell organelles (defined in the paper as the cell membrane and intracellular calcium stores). The equations were fed into an analogue computer, and the time course results were compared with experimental measurements of the isometric tension (assumed to be directly proportional to the concentration of calcium in the myoplasm) of an oxytocin-stimulated rat uterus. The model results agreed well with the experimental results, and the authors concluded that oxytocin must exert its effects on uterine tension by triggering the release of calcium bound to the cell membrane. This conclusion was reasonably accurate, but we now know that oxytocin signals via the inositol triphosphate pathway to release calcium ions from intracellular stores (Sanborn et al., 1998). However, it proves that simple models can describe complex behaviour in uterine smooth muscle and be used to generate hypotheses about the likely mechanisms driving this behaviour.

Current research into the molecular mechanisms of parturition tends to focus on proinflammatory pathways rather than endocrine or oxytocin mediated mechanisms. Bisits et al. (2005) used a directed acyclic graph (DAG) approach to model these alternative hypotheses and attempt to identify the most likely causal pathway leading to the initiation of labour. DAGs represent each element in the pathway as a node (for example, a labelled circle) connected to others by arrows indicating the direction of causal influence. The authors tested three alternative hypotheses about the main pathways initiating human labour, derived from the literature: functional progesterone withdrawal, inflammatory stimulation and oxytocin receptor activation. By incorporating data from previous qRT–PCR analysis of transcripts of key genes from labouring and non-labouring human myometrium, they statistically determined the likelihood of each of the three models using the computer programs LISREL and DGraph. Both programs identified inflammatory stimulation as the most plausible primary event in uterine activation (compared with the alternatives progesterone withdrawal and oxytocin receptor activation), with oxytocin receptor activation as the least plausible. Although we do not yet have a consensus on whether or not this prediction is true, research increasingly suggests that human labour is associated with a predominantly inflammatory event (Thomson, 1999; Young, 2002; Olson, 2003; Tribe et al., 2003). Regardless, this study presents the interesting approach of using of DAGs to assess the likelihood of causal events in biological systems that cannot be readily studied.

Equils et al. (2010) were the first to model the molecular mechanisms behind the initiation of labour at an intracellular level. They modelled the immune-endocrine interactions in a uterine smooth muscle cell with...
labour as the primary end-point, represented by an increase in the ratio of progesterone receptor A (PR-A) to progesterone receptor B (PR-B). Initial concentrations of reactants and the rates of their interactions were collected from the literature or estimated where data were not available. The reactions were based on a number of assumptions about the process of labour in humans regarding the roles of progesterone and estrogen in regulating labour, the role of nuclear factor kappa B (NF-κB) in regulating the PR-A:PR-B ratio, and the involvement of Cyclooxygenase 2 (COX2) and prostaglandins in labour. The model was run in Cellworks Group internal computational engine and found that NF-κB (assumed by the model to be a marker of infection) increased the PR-A:PR-B ratio. The ratio took less time to reach levels seen in labour with higher doses of NF-κB, possibly reflecting the association between preterm birth and infection. The authors also looked at the behaviour of the model in response to progesterone and COX2-inhibitor treatment and found that progesterone could reduce the PR-A:PR-B ratio at high doses, but COX2 inhibitors only began to prevent the increase in the ratio at levels high enough to also be associated with fetal toxicity. The model was not validated experimentally, so the accuracy of these predictions cannot yet be adequately assessed. Furthermore, the assumption that levels high enough to also be associated with fetal toxicity. The model was not validated experimentally, so the accuracy of these predictions cannot yet be adequately assessed. Furthermore, the assumption that labour is initiated by an increased PR-A:PR-B ratio is simplistic and not always supported in the literature (Wagner et al., 2012). This highlights the importance of choosing an appropriate model target in order to ensure that model predictions are useful. Nevertheless, the work provides important proof of concept that computer models can be used to make interesting, biologically plausible predictions about the molecular mechanisms of labour.

Conclusion

We are currently at the beginning of an exciting time in biomedical research when computer models are showing real potential in their ability to help us understand biological systems. Well-validated computer models of uterine activation at labour will improve our understanding of the mechanisms that initiate labour in women at term and preterm. The clinical applications of such models are also becoming increasingly apparent, with the potential to relate clinical physiological and molecular measurements to predict the onset of labour and labour dysfunctions. It is essential that computer models are validated using well-designed wet lab experiments, and model predictions are interpreted appropriately.

Promising work is already underway to model the electrophysiology of uterine contraction, but computational work on the molecular mechanisms underlying the initiation of these processes is lagging behind. There is certainly scope for the development of more models of uterine activation at labour. Given the complexity of parturition and given the challenges both of obtaining human tissue to understand pathophysiology and of testing therapies in pregnant women in vivo, the use of computer models is likely to be helpful in synthesizing knowledge, in identifying uncertainties which can be tested in wet lab experiments and in screening therapies to facilitate in vivo testing of only the most promising interventions.

Authors’ roles

G.C.S. wrote the review under guidance from J.E.N. and P.T.K.S. J.E.N. and P.T.K.S. commented on and contributed to revisions of the manuscript.

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