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Mathematical modelling of the female reproductive system: From oocyte to delivery.

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Abstract

From ovulation to delivery, and through the menstrual cycle, the female reproductive system undergoes many dynamic changes to provide an optimal environment for the embryo to implant, and to develop successfully. It is difficult ethically and practically to observe the system over the timescales involved in growth and development (often hours to days). Even in carefully monitored conditions clinicians and biologists can only see snapshots of the development process. Mathematical models are emerging as a key means to supplement our knowledge of the reproductive process, and to tease apart complexity in the reproductive system. These models have been used successfully to test existing hypotheses regarding the mechanisms of female infertility and pathological fetal development, and also to provide new experimentally testable hypotheses regarding the process of development. This new knowledge has allowed for improvements in assisted reproductive technologies and is moving toward translation to clinical practice via multi-scale assessments of the dynamics of ovulation, development in pregnancy, and the timing and mechanics of delivery.

Introduction

The female reproductive system is dynamically changing and many aspects of its function are not well understood. In the non-pregnant state, the system undergoes cyclical changes in its hormonal environment, as well as in the structure and function of the ovaries and the uterus. Once pregnant, the uterus and a specialised organ, the placenta, change and develop 'on demand' to accommodate the needs of the developing fetus and ultimately to deliver the child. As the system is so dynamic, we often observe only snapshots of its function clinically. This means that identification and treatment of pathology, as well as attempts to replicate the system in assisted reproductive technologies (ARTs), can be hampered by difficulties in bridging the gap between what is routinely measured and what we understand about the function of the system. This is particularly a problem in pregnancy, as access to the in vivo system becomes subject to increasing ethical constraints.

Mathematical models that describe components of female reproductive function are beginning to emerge as a valuable means to improve understanding of system function at all stages of the menstrual cycle and through pregnancy and delivery. Mathematical models provide a means manage complexity and to tease apart the primary contributors to reproductive function. Models also provide a robust framework that can be used to determine new experimentally testable hypotheses regarding biological function, and so can be used to guide experimental programs. Mathematical models have been used to investigate contributors to the timing of ovulation,[1-3] the optimal nutrient environment for oocyte (egg) or embryo development,[4-10] through understanding the physical changes in the reproductive system in pregnancy,[11-13] to the uterine environment that initiates the timing of delivery,[14-16] and the mechanics of delivery itself.[17-20] Here we summarise mathematical models that have contributed to our understanding the female reproductive system, and outline key open questions in the field that mathematical modelling may contribute to answering.

THE PATH TO FERTILISATION: OOCYTE DEVELOPMENT AND OVULATION

The female reproductive system comprises the ovaries, fallopian tubes, uterus, cervix and vagina. During the menstrual cycle (Figure 1), hormones that stimulate or regulate cell and organ behaviours fluctuate. Ovarian follicles containing oocytes (eggs) change in structure to allow oocytes to mature and to provide the optimum environment for dominant follicles to emerge prior to ovulation (in humans there is one dominant follicle but mammalian species can have several). At the same time, the structure of the uterine wall (the uterine endometrium) remodels to provide an environment for subsequent implantation. The control system that determines the selection of dominant follicles for ovulation and the subsequent atresia of non-selected oocytes, as well as the nutrient environment of the developing oocyte, are of significant interest to reproductive biologists and clinicians. Measuring or predicting the state of ovarian follicles through the menstrual cycle provides a means to understand the causes of female infertility (particularly anovulatory infertility) and 'aging' of the ovaries (the timing of menopause). Also, as ARTs typically require ovarian stimulation to produce numerous 'mature' oocytes, as well as handling and maturation of oocytes and embryos *in vitro*. Increased understanding of the *in vivo* conditions that lead to successful pregnancies has significant potential in improving ARTs.

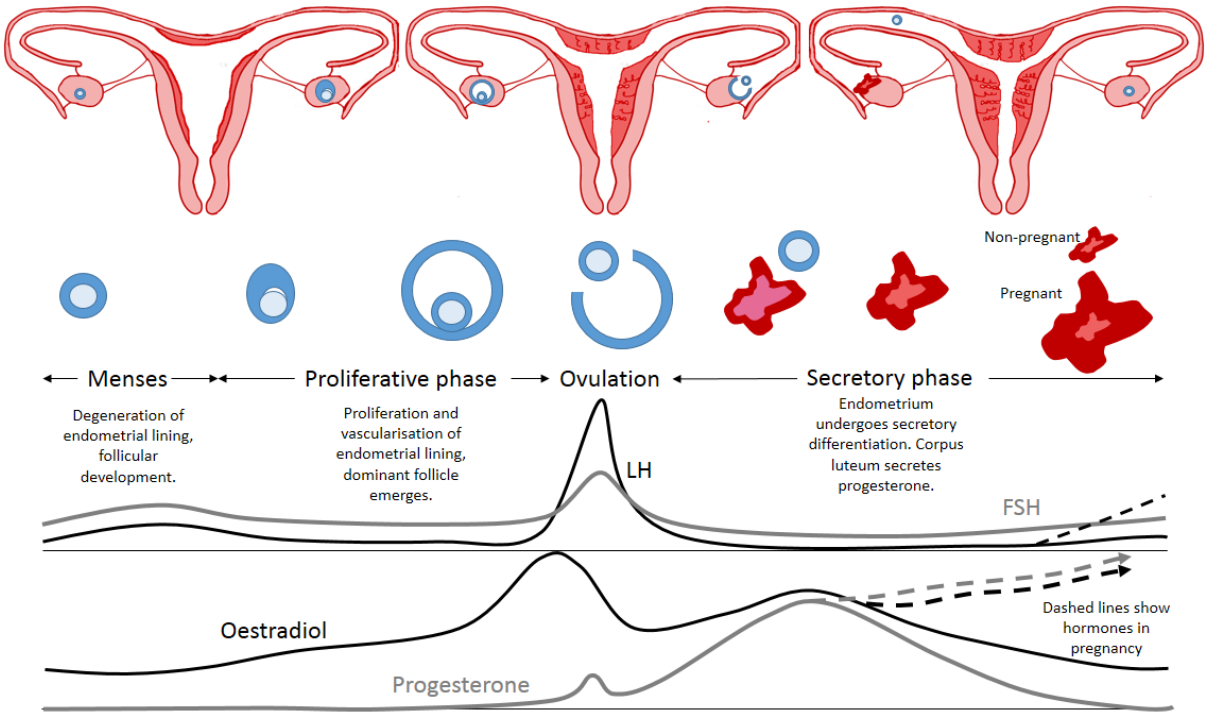

Figure 1: A schematic diagram of the structural, functional and hormonal changes that occur through the menstrual cycle. During menses the endometrial lining of the uterus is shed. Ovarian follicles develop from a stock of resting (primordial) follicles. The oocyte matures and companion cells (granulosa) proliferate to modulate the maturing oocyte's environment. During the proliferative phase the uterine endometrium proliferates and becomes increasingly vascularised, with enlarged glandular structures, ovarian follicles continue to mature and fluid filled antrums enlarge. During this phase a dominant follicle emerges. Following a hormonal surge, ovulation of the dominant follicle occurs approximately mid cycle, non-dominant follicles enter atresia. The oocyte and its surrounding cells are transported through the fallopian tubes to the primed uterus in the secretory phase. A corpus luteum that forms at the site of the ovulated follicle secretes hormones that signal the uterine endometrium to undergo secretory differentiation. If pregnancy occurs the corpus luteum is retained and hormone levels are elevated. If not it regresses, and the cycle begins again.

The optimal nutrient environment for oocyte maturation

Markers of 'oocyte quality' are often sought in fertility programs to indicate the likelihood of a successful pregnancy.[21, 22] Whether an oocyte is matured *in vivo* or *in vitro*, its intrinsic potential for embryonic development, and environmental factors, influence its maturation. *In vivo,* maternal age, the composition of follicular fluid, and the vascularity of the ovary are all factors that influence oocyte quality.[21] In *in-vitro* fertilisation (IVF) procedures, follicular fluid composition may be prognostic of outcome,[23] but accurately determining this composition hampers efforts to use follicular fluid samples as a predictor of outcome.[9, 24] Where oocytes are matured *in vitro* the aim of reproductive biologists is to both select oocytes from viable follicles and to replicate *in vivo* environments as closely as possible for *in-vitro* maturation of oocytes,[21, 22] but defining these *in vivo* environments is difficult.

The ovarian follicle is avascular, and early in development consists of the oocyte surrounded by companion cells (granulosa). Later in development a follicular fluid filled antrum forms around the oocyte (Figure 1). The oocyte is critically dependent upon nutrients such as oxygen and glucose which must diffuse through the follicle to the oocyte. Angiogenesis occurs in the tissue surrounding the follicle, with angiogenic factors known to be responsive to local oxygenation.[25] The development

and peripheral vascularisation of the ovarian follicle has been likened to that of a solid tumour,[26] for which several mathematical modelling studies have elucidated the role of oxygen in growth and function of tissue.[27, 28] However, although a solid tumour contains severely hypoxic regions, the existence of, or benefits of hypoxia or anoxia to the ovarian follicle are less clear.[25] Mathematical models of ovarian follicles have employed similar principals to early models of tumour oxygenation to predict local tissue oxygenation and its dependence on follicle structure through maturation.[5, 6, 9, 10] These models have suggested that the formation of the fluid filled antrum surrounding the oocyte could allow rapid follicle growth, and maximise granulosa cell proliferative capacity, while maintaining oxygenation at the oocyte. [5, 6, 9] The models do predict a low oxygen environment for the oocyte, but not the extremes of anoxia as predicted by early models.[8] By combining evidence from mathematical models with experimental data on haemoglobin and hypoxia-inducible factors it has been suggested that the interaction between follicle growth and local vascularisation must act to maintain a non-hypoxic environment prior to ovulation, transitioning to a hypoxic environment after ovulation to allow cellular differentiation.[25] The emergence mathematical modelling in this field has helped to support the modification of oocyte culture conditions to better match expected *in vivo* oxygenation, however it is clear from experimental and modelling studies that optimal conditions are species dependent, and changes in oxygen conditions in culture may need to be combined with changes in other metabolites to positively influence oocyte viability.[29, 30]

To improve understanding of species differences and to provide more complete understanding of follicular fluid composition, mathematical models have been extended to other key nutrients that are actively transported between cells (such as glucose),[31] and have been combined with experimental studies to allow species-specific estimation of the oocyte's micro-environment.[7, 32] This modelling therefore provides the potential to design optimal culture environments that are species- and cell-specific, which is preferable to using culture systems not designed specifically for oocyte maturation.[22]

Folliculogenesis and control of ovulation

The growth of the dominant (ovulated) ovarian follicle, and ultimately the viability of the oocyte within it, is governed by follicle secreted (e.g. oestradiol) and pituitary hormones (e.g. follicle stimulating hormone, FSH, and luteinising hormone, LH). Changes in these hormones through the menstrual cycle and in early pregnancy are shown schematically in Figure 1. Dynamic feedback occurs at several levels. For example, oestradiol secreted by the dominant follicle down-regulates FSH secretion and up-regulates LH secretion. However, observables are usually static, such as discrete assessments of blood or urine hormone levels, or ultrasonographic assessments of the ovaries. Predicting hormonal changes in the menstrual cycle and their relationship to follicle or oocyte maturity therefore has several benefits. These include, predicting ovulation for management of breeding in animals,[33] understanding aging of the follicular population and the onset of menopause,[34] understanding the causes of anovulatory infertility including in polycystic ovary syndrome,[35] and guiding oocyte retrieval in ARTs by using ultrasound measures of follicle maturity.[36]

Early models can be separated into population dynamics models (representing maturation as a probabilistic set of maturation states with no hormonal regulation), models that are regulated based on circulating hormones (endocrine regulated models) cell dynamics and locally regulated models (autocrine regulated models). Figure 2 compares the structure of these three classes of models.

Later models have combined these three approaches, to begin to take a multi-scale approach to understanding follicle development and ovulation.

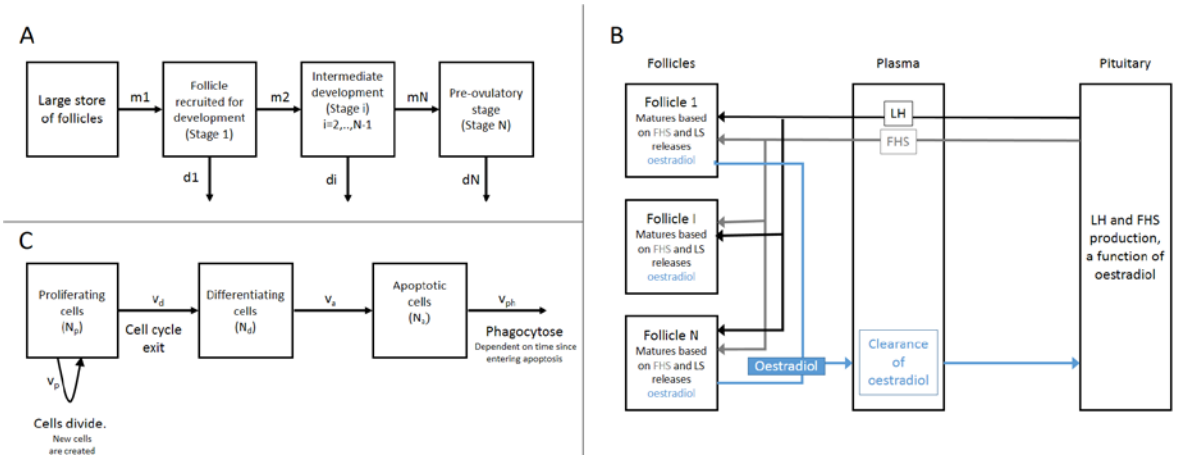

Figure 2: Typical model structure in three major classes of folliculogenesis model. (A) Modelling the population of follicles, where an initial large store of follicles is depleted by recruitment into maturation stages (at defined rates m1,..,mN), and subsequent follicle "death" (at rates d1,…,dN). (B) Models based on a population of models acting under hormonal control, with follicle maturation based on local levels of hormones (LH and FSH) which in turn depend of follicle excreted oestradiol. (C) Models of follicular cell populations, where cells proliferate, differentiate and enter apoptosis at defined rates. Each class of model was designed to answer specific questions regarding follicular population, but approaches are beginning to be merged as a drive toward multi-scale modelling emerges.

One of the earliest models of follicular dynamics, proposed by Faddy et al.,[34] considers a stock of ovarian follicles, grouped by maturation stage. Starting with an initial population of 'resting' or primordial follicles, a follicle can be recruited into maturation and then 'lost' from the population (via ovulation or atresia), shown in Figure 2a. This class of models can be both discrete (follicles migrate between maturation groups in a probabilistic manner),[37] and continuous (ordinary differential equations with variable rates of recruitment from the primordial state and of depletion).[34] The models do not consider hormonal control or cyclic changes in follicle dynamics. However, they have been used extensively in conjunction with clinical and experimental data to explain the mechanisms of ovarian 'aging' and variability in the onset of menopause.[34] Recently, this class of model has been applied with a concept of hormonal control, by allowing an age-dependent, semi-empirical relationship between the concentration levels of specific endocrine hormones and the loss of follicles.[38]

The second class of models, which focus on endocrine regulation (Figure 2b), began with the Lacker model, which was proposed in 1981.[1] This model has been well used, and has been adapted over time to improve its physiological relevance. This model assumes follicle secreted oestradiol as an indicator of maturity, and includes feedback between plasma levels of pituitary hormones LH and FSH, which control maturation, and secreted oestradiol which in turn controls production of LH and FSH. This class of model includes a pool of follicles in the model at various stages of maturity that influence one another via their oestradiol secretion into blood. The basic Lacker model has been modified to account for multiple ovulations,[2, 3] the effect of endogenous hormones (e.g. to stimulate the follicles for ARTs),[2, 39] and multiple waves of follicular growth.[3, 40] Attempts have been made to relate follicular structure observed in ultrasound to levels of LH, FSH and other hormones, via a Lacker-type model to allow inference of follicle maturity from ultrasound.[36] This type of technique may improve the use of ultrasonographic imaging to monitor follicle growth and regression over

time and to assess the impact of follicular stimulation, ovulation induction and/or to improve oocyte retrieval for ARTs, which aims to select follicles containing the most viable oocytes and is typically ultrasound guided.[36]

While the first two classes of models aim to describe follicle populations, the final class of models is based on cell population dynamics. This class of model predicts the maturation of individual follicles in response to local stimuli. The follicles are described as a collection of cells with the ability to change by proliferation or differentiation, with maturity of the follicle being assessed based on its cell number and cell maturity at any given time. .[41, 42] Initially these models focussed on the level of a single follicle,[41, 42] without hormonal feedback at the molecular level. More recent models have begun to take a more multiscale approach, simulating the cellular dynamics in multiple interacting follicles and adding a concept of controlled follicular release of oestradiol, which controls gonadotropin release, and so determines local FSH stimuli and progression through the cell cycle.[43] Control of follicle maturity was informed by a more complex mathematical model of biochemical reactions involved in follicle maturation at the late stages of development.[44] Research in this area has begun to focus on follicle maturation and selection as an optimal control problem.[45] The increase in complexity of these models to include physiological phenomena across scales has resulted in challenges in both computational tractability, and model calibration. However, this class of models and other emerging multiscale models that incorporate function across spatial and temporal scales[46, 47] are beginning to provide an integrated approach to understanding how pathophysiology in the ovulatory process emerges.

POST-FERTILISATION & EARLY EMBRYONIC STAGES

The days between ovulation and implantation are a critical time for determining whether a successful pregnancy will occur. The oocyte must be transported through the oviduct to the point of fertilisation and onwards to the uterus. After fertilisation, the preimplantation embryo must undergo a series of cell divisions and growth. Understanding the environment and development of preimplantation embryos is particularly important in development of ARTs, where success rates are generally relatively low and even embryos that appear healthy often fail to implant.[48] Computational modelling of the post-ovulation oocyte, the priming of the uterus for implantation, and the early embryonic stage is sparse. There is a large body of studies modelling spermatozoa transport through the reproductive tract and fertilisation of the oocyte both in the context of fluid dynamics,[49] and ART system development.[50] However, focus on the female reproductive system is lacking, despite a need to improve physiological knowledge in this area.

The transport of the oocyte/embryo through the oviduct to the uterus is important *in vivo* as if the timing of its transport is suboptimal it may prevent implantation. *In vitro* replication of the environment of the oviduct at fertilisation and early embryonic (blastocyst) development is desirable to improve the success of ARTs. The movement of the oocyte through the oviduct depends on flow of oviductal fluid that is driven by oviduct muscle contractions and the beating of cilia lining the oviduct. Both stochastic[51] and fluid dynamic[52] models of this transport have been proposed, with an aim to determine the balance between the 'to and fro' motion of the oocyte due to muscle contractions and a forward motion due to cilia propulsion. Both models highlighted the role of cilia in promoting pro-uterine transport, and helped to reconcile debate regarding whether cilia beating and/or oviduct muscle contraction are necessary for fertility.[53, 54]

Hardy et al.[55] used a combined mathematical and experimental approach to investigate embryo development arrest at the preimplantation stage. The model is probabilistic with each cell comprising the embryo dividing or dying at each generation. They showed that if an embryo has an 'innate' rate of cell death, that fitting their model to experimental data showed a large portion of embryos have high levels of cell death and so a high chance of arrest. Further, if an embryo with an intermediate level of cell death (innate) is subject to environmental factors that increase its rate of cell death there can be a rapid increase in embryo loss. This is consistent with rates of embryo arrest in simple salt solution compared with more optimised culture media,[55, 56] and highlights the need to develop optimal culture conditions for embryos as well as oocytes. To this end, Byatt-Smith et al.[4] modelled the uptake and diffusion of oxygen in a spherical preimplantation embryo. With the observation that generally static *in vitro* culture conditions may not provide enough oxygen to the embryo compared with dynamic *in vivo* conditions where the fluid in the oviduct is mixed during muscle contraction and cilia beating. The structure of this model was similar to a previous model of the immature ovarian follicle,[8] and to more recent models of nutrient availability of the oocyte.[6, 7, 9, 10] The model predicted that diffusion in static culture was sufficient to provide the embryo with the oxygen it requires for development. However, they noted that the model does predict potential problems with transient 'surges' in oxygenation, for example when embryos are moved between culture dishes, which may not be beneficial to the early embryo which has limited antioxidant activity. This type of modelling, potentially combined with cell proliferation models,[55] has potential to improve culture conditions but to date nutrients other than oxygen, which is transported by simple diffusion, have not been considered.

IMPLANTATION AND EARLY PREGNANCY: UTERINE STRUCTURE AND INTERACTIONS WITH THE PLACENTA

By the time the oocyte has been successfully fertilised and transported through the oviduct to the uterus, it is known as a blastocyst, and must now implant into the uterine wall to establish a successful pregnancy. Seventy-five percent of failed pregnancies are thought to occur as a result of a failure to implant.[57, 58] The days and weeks after implantation are also critical, as the placenta is formed from the implanting blastocyst.[59] It is estimated that only 50-60% of all pregnancies proceed beyond 20 weeks.[58] In humans it is particularly difficult to observe early pregnancy, for ethical reasons,[57, 59] because human pregnancy differs considerably to most animal models,[59] and because women simply do not know that they are pregnant at this stage. Mathematical models therefore provide a unique means to understand the mechanisms of implantation and early development of the embryo and placenta, and to test hypotheses regarding the factors that influence pregnancy success at this stage.

The blastocyst spends 3-4 days in the uterus before it reaches its implantation site, and during this time it is carried in uterine fluid. Uterine fluid movements, like that in the oviduct, occur because of a fluid flow driven by cilia beating and myometrial contractions. The blastocyst is very small compared with the size of the uterus, yet there are remarkable consistencies in implantation sites, implying a coordination of uterine shape, local nutritional supply, hormonal control of uterine contractions, all interacting with the influence of posture to control implantation.[60] Uterine contractions vary through the menstrual cycle. Ultrasound has shown that in the secretory phase, when implantation occurs, that there are spontaneous uterine contractions from the cervix to the fundus at a rate of 1-5 contractions per minute and that these contractions are asymmetric.[61, 62]

There is a hormonal control to these contractions, for example progesterone is utero-relaxing and so reduces the intensity of contractions.[63]

Assuming that myometrial contractions are a primary driver of blastocyst motion in the uterus, Eytan et al.[61] developed a computational model of the motion of uterine fluid under a prescribed wall motion. The model represents the uterus to be a 2D channel bounded by two walls, and makes use of lubrication theory to solve for Stoke's flow within this geometry. The study assessed how different phase shifts (asymmetry) between the two uterine walls on either side of the longitudinal axis of the uterus influence the direction of motion of the embryo, represented as a massless particle, and assessed the potential for embryo trapping near the uterine wall. Despite being unable to match the embryo's resident time in the uterus theoretically, they showed that the magnitude of uterine contractions may be key to determining the success and site of implantation. The model was later extended to investigate how hydrosalpinx (distally blocked fallopian tubes),[64] might influence implantation, and using a combination of experiment and modelling to provide advice regarding appropriate methodologies for embryo transfer in ARTs.[65, 66] In a similar model with a tapered channel, better reflecting the shape of the uterus, the authors showed that embryo trapping was favoured with relatively symmetric uterine contractions,[67] and that embryo transport phenomena are strongly influenced by the angle between uterine walls, implying that embryo transport in the uterus may vary between individuals. An individualised approach to modelling uterine fluid dynamics may be the key to improving the success of implantation in ARTs, and has been suggested as an important direction for future modelling.[60]

As well as the mechanisms determining the site of implantation, a key determinant of pregnancy success, particularly in humans, is the ability of placental cells to invade into the uterine tissue and establish an adequate maternal blood supply to the surface of the placenta.[59] In the early weeks of pregnancy, the placenta forms its complex structure from cells known as trophoblast. These cells form the chorionic villi, which support the placental circulation, and separate maternal and fetal blood at the placenta-uterine interface. Trophoblast also invade maternal uterine tissue and play a role in degrading the muscle lining of uterine arteries at this interface. Abnormal structure in chorionic villi, and inadequate trophoblast invasion are associated with pregnancy loss, intrauterine growth restriction and pre-eclampsia.[68] Rejniak et al.[13] developed a mechanical model of the formation of villous protrusions from a trophoblastic bilayer in which cells are able to divide, grow and fuse. They explained how different patterns of these mechanisms and different mechanical stiffness strengths result in villous structures seen *in vivo* and suggested that the relative rate of cytotrophoblast proliferation and incorporation into the outer syncytiotrophoblast layer may be a key factor in determining villous morphology. A continuum model of trophoblast invasion into maternal arteries has also been developed, which accounts for random diffusion of cells, chemoattractive mechanisms, and cell proliferation.[11, 12] Both models of early trophoblast dynamics draw heavily from similarities observed in tumour invasion processes and implantation,[69] and use techniques from the more well-developed field of modelling tumour dynamics. Like modelling of follicular development it is likely that future developments in understanding placenta-uterine development and interactions in early pregnancy will take inspiration from this field.

A final class of models that is relevant to changes in the uterus in early pregnancy, through to delivery consider blood flow and nutrient exchange at the utero-placental interface. The uterine vasculature changes dynamically during pregnancy to provide blood to the surface of the placenta

and to carry an increased maternal blood flow to the utero-placental interface through gestation. "Transmission-line" impedance models (Figure 3a) have been applied to understand uterine haemodynamics in the ewe,[70] and the human.[71] Simple, 1D steady models have predicted the implication of remodelling of uterine vessels that feed the placenta,[72] and more complex 3D fluid mechanics models have also been developed to understand uterine arterial flow (Figure 3b).[73] Although different in structural complexity both types of models have been used to describe how changes in uterine arterial (and placental bed) structure and compliance can explain uterine artery Doppler waveforms, including the conditions required for the emergence of pathological waveforms. At the opposite side of the utero-placental interface, 3D fluid mechanics models[74] and anatomically based branching models[75] have been used to describe how variability in the size and branching structure of the placental vasculature influences blood flow through the system. Recent studies have focused on the branching properties of the smallest branches of the placental villous tree,[76, 77] and the implications of placental structure on shear stress[78] and oxygen exchange[77] at the site of growth. A stochastic model of placental vascular development showed that the distribution of uterine arteries at the utero-placental interface is a key determinant of placental shape, which has been hypothesised as a marker of placental efficiency.[79] Finally, nutrient exchange at the interface between the uterus and placenta has been described via homogenised,[80] or geometrically simplified representations of this interface.[81, 82] The benefits of modelling the utero-placental interface are increasingly being recognised internationally,[83] and it is likely that modelling in this area will become more commonplace and more sophisticated as international teams combine to accelerate multi-scale model development. Models of utero-placental function have, to date been almost exclusively applied at term, which is understandable as the relative accessibility of data is greatest at the end of pregnancy. However, capturing the dynamic changes in uterine and placental structure in early pregnancy is likely to have greatest benefit in understanding the emergence of pathology, and ultimately to guiding treatment outcomes.

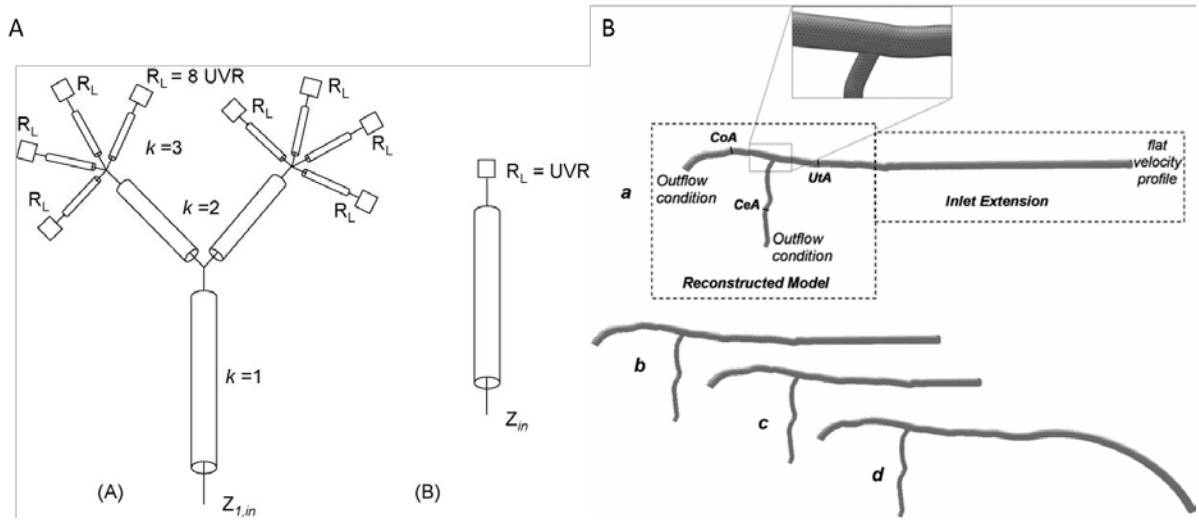

Figure 3: (A) Transmission line and (B) geometrically accurate representations of the uterine vasculature. Transmission line models represent a network of vessels as 1D tubes characterised by their resistance (R), inductance (I) and capacitance (C) and use these data to characterise the impedance (Z) of the system. 3D fluid dynamics models are able to capture more realistic flow profiles within an individual vessel but are typically restricted to study of a small number of vessels. Panel B shows the main uterine artery (Uta) and a single branch from that artery with observation points (CoA, CoE), with different inlet characteristics (labelled b, c, d). Panel A is reproduced from Zhu et al.[70] with permission. Panel B is reproduced from Pennati et al.[73] with permission.

BIOMECHANICS OF THE UTERUS AND TIMING OF DELIVERY

Toward the end of pregnancy, changes occur in uterine tissue to activate the uterine contractions required for delivery. The uterus transitions from a relaxed state to a contractile state, and this change has been associated with gene expression but involves coordinated activity across spatial scales from cell level calcium dynamics to uterine muscle fibre orientation.[14] Knowledge of the onset and mechanics of labour at the system level is sparse, and investigation of this period of pregnancy is hampered by difficulties in observing labour without invasive procedures. Early activation of uterine contractions (pre-term labour) and inadequate activation of contractions both have significant health impacts.[14, 84] Diagnostic tests that can identify pre-term labour early are desirable, before uterine and cervical progression to labour is irreversible. So, the key questions are what factors control the timing and onset of labour,[84] and how can ineffectual labour be detected early allowing more 'intelligent' decisions to be made regarding caesarean sections, for example[14]

At the cell level detailed computational models have been developed to understand contraction and relaxation of uterine smooth muscle cells as well as their electrophysiological behaviour.[85, 86] Tong et al.[85] aimed to provide a comprehensive description of this system in their ordinary differential equation based model of a single smooth muscle cell. The aim to provide a comprehensive model results in complexity with 105 coupled equations to be solved. This provides detailed information on cell behaviour but makes scaling of the model to multiple cells or ultimately the whole uterus computationally difficult. This complex mathematical model has been used, in conjunction with models of cardiac cells, to investigate the cell-specific effects of tocolytics (anti-contraction medication used to supress premature labour).[87] These drugs should target uterine smooth muscle cells and avoid influencing cardiac function, and the authors highlight the importance of computational models to test drug actions *in silico* prior to clinical trials. The model has recently been improved to account for long duration bursting action potentials characteristic of labour,[88] and extended to a network of cells.[89] Simplified models of cell-level activity have been incorporated into emerging multiscale models of uterine contractions and electrophysiology, allowing computational tractability of the problem.[15, 16]

At the other end of the spatial scale, several groups have attempted to model uterine electrophysiology at the organ scale. Diverse approaches have been taken, including representing the uterus as a network of discrete contracting cells sending electrical signals to their neighbouring cells in simple ellipsoidal geometries[90] and simple compartmental models of function.[91] Models of tissue excitation have also been applied in realistic uterine geometries (Figure 4),[14] with partial differential equations describing tissue excitation in a homogenous medium (reaction-diffusion coupled with a Fizhugh-Nagumo model for ionic currents), and the effect of geometry on wave propagation illustrated. Understanding the electrophysiology of the uterus lags behind studies in other organs, such as the heart,[14] and the contractile activity of the uterus is considered to be more complex than that of the heart.[14] It is clear then that a multiscale and multi-group effort is required to build a picture of uterine electrophysiology that is able to closely represent the *in vivo* situation and to predict emergent function responsible for normal and abnormal labour.[14, 92] The most complete multi-scale model to date includes a model of myocyte (cell-level) electrical activity, coupled to a meso-scale model of uterine muscle fibres to allow for different electrical conductivity along and across a fibre, and at the largest scale a simplified four compartment geometrical representation of the abdominal cavity, myometrium, amniotic fluid and fetus, through which an

electromagnetic field is defined by Maxwell's equations.[15] It should be noted uterine contractibility is not only important at the end of pregnancy, but also in early pregnancy where uterine contractions control the uterine fluid movement that determines implantation site.[86]

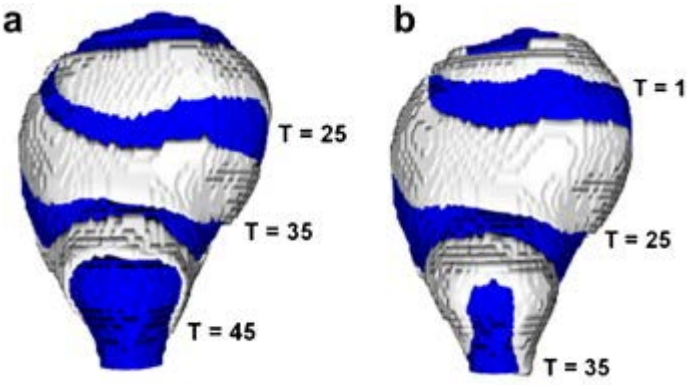

Figure 4: The propagation of a solitary wave initiated at the fundus in an anatomical model of the uterus. This model illustrates one of two classes of uterine electrophysiology models, with excitation modelled using the FitzHugh-Nagumu model. The same wave at three different time points are shown with white representing excited tissue and blue representing recovered tissue. This image is reproduced, with permission, from Aslanidi et al.[14]

THE MECHANICS OF DELIVERY

The final phase of pregnancy is delivery of the fetus and placenta. The clinically accepted mechanism for the second stage of labour, describes the change in attitude and position of the fetal head, relative to bony boundaries of the pelvis, as it negotiates its way through the birth canal.[93] The original mechanisms were based on descriptions from early pioneering work in the 18th Century by several obstetricians, when obstetrics started to become a science. Much of our understanding of the mechanism of labour, as we know it today can be attributed to these early pioneers.[94] In particular, William Smellie (1697-1763), who measured fetal skull and pelvic diameters and published these in a set of anatomical tables.[94] Most obstetric textbooks still describe the mechanism of second stage labour in relation to these bony diameters. Until recently, little cognisance has been paid to the contribution of the soft tissues to the mechanism of second stage. We still lack a fundamental understanding of the biomechanics of vaginal delivery.

The last decade has seen enormous improvements in imaging capabilities, allowing better visualisation of the anatomy and anatomical changes which occur following vaginal delivery. It is now widely accepted that the pelvic floor muscles are intimately involved in the birth process, contributing in particular to internal fetal head rotation during descent.[93] This group of muscles are also required to stretch substantially (up to three times their resting length),[95] to allow passage of the head through the birth canal. Improved resolution in imaging, both spatial and temporal, has revealed that in some cases this stretch is insufficient, and pelvic floor muscle damage occurs as a consequence of vaginal delivery.[96, 97] The damage typically manifests as a detachment of the muscle from its insertion site along the pubic ramus, occurring in 15 % to 30 % of primiparous women (first-time mothers).[98] This damage seems to be unequivocally linked to increased risk of conditions such as pelvic organ prolapse and urinary incontinence.[99]

Development of computational models of childbirth are beginning to provide some understanding of the biomechanics of delivery and how they might be used to develop new strategies for prevention and treatment. Recent reviews on modelling the second stage of labour[100] give a comprehensive overview on the current status of the models used, many of which are still constrained by lack of experimental data. Accurately defining boundary conditions for simulations (such as which aspects of fetal head movement to prescribe in a model), assigning realistic material properties, accounting for geometric variability between individuals and validating the model, are just some of the considerations which make implementation of childbirth modelling challenging. However, the number of research groups that are working in this area, has increased and many are directly confronting these issues. More anatomical structures have been incorporated into modelling frameworks, less prescription for fetal head descent, and in some cases, fetal head moulding has been taken into account.[17-20] Population based models have also recently been developed for both the 'passageway' and the 'passenger'.[101] These advances in the modelling frameworks, are beginning to enable quantitative analysis of the mechanics of vaginal birth in order to identify the contributions of various anatomical structures to birth outcomes. The prospect of these models becoming clinically useful is more tangible. The realisation that for some women, muscle trauma after delivery is more common than originally thought and a better understanding of the mechanisms of labour will inevitably assist with the development of new treatment paradigms for both prediction and prevention of childbirth trauma and the inevitable consequences.

THE FUTURE AND CHALLENGES

Mathematical modelling has proven useful in understanding normal and pathological reproduction, from the development of the pre-ovulatory oocyte to the mechanics of delivery. In each area of reproductive health discussed, models with simple geometric structures have first been developed to understand fundamental mechanisms of growth and development. These models are evolving to become more functionally accurate, more anatomically accurate, and to predict emergent function across spatial and temporal scales. Although modelling in most areas of reproductive biology can still be considered to be in its infancy compared to more established fields such as cardiac or tumour physiology, an increasing number of new and sophisticated models predicting the physiological system in health and disease have appeared in recent years, and as such, rapid development of models and progress in physiological understanding is to be expected in years to come.

Modelling the reproductive process has its own unique challenges. In particular, ethical constraints in collecting and assessing human tissue, and the short timescales in which the reproductive system can change structurally and functionally, mean that ascertaining suitable parameterisations for modelling is more difficult than in other organ systems. Access to human tissue, and imaging of the reproductive system, particularly in pregnancy, is limited.[57, 59, 102] This means that imaging data is typically lower resolution than can be acquired in other physiological systems; for example, imaging is normally limited to ultrasound and magnetic resonance imaging, rather than computed tomography or contrast enhanced imaging which is often the gold standard in medical imaging. Also, invasive measurements and access to *ex-vivo* tissue are limited. Animal models would typically provide significant information on physiological and pathophysiological function across organ systems. However, in several aspects of reproduction significant species differences result in difficulties in translating animal data to the human condition.[59, 103]

The basic mechanisms of the ovarian cycle are common among mammals, [103] but species differ in the number of ovulated oocytes as well as in the size (and nutrient environment) of the ovulated follicle. This means that although models can be developed to represent a generic mammalian follicle structure, their parameterisation and often their predictions are species specific.[6] The importance of managing cycles and fertilisation in farmed animals,[33] and ARTs,[22] however, means that data describing the nutrient environment and structure of the follicular population is perhaps more available in this early stage of the reproductive process than at subsequent developmental stages. By the time of implantation and early pregnancy, animal studies become less relevant to the human condition, postural differences in implantation sites, and differences in the structure and function of the utero-placental interface in early pregnancy become significant.[59, 103] The level of invasion of the human placenta into uterine tissue, and the structure of the placenta itself are strikingly different between mammals, with the level of invasion and placental structure not necessarily constraining fetal body size.[103] Throughout pregnancy there are significant species differences in physiology, including endocrine and paracrine metabolism,[102] the mechanisms that initiate pre-term birth.[102] Postural differences and differences in relative head size also mean that the mechanics of labour are not consistent between species.[104] These species differences make the role of mathematical modelling in elucidating function from limited experimental data critical, but care must be taken to validate models against appropriate data. For example, if animal data are used differences in physiology must be acknowledged when using the study to predict human function. Where human data are used, care must be taken in understanding whether data is directly acquired or inferred (i.e. oxygen uptake rate inferred from concentration differences between two anatomical locations) when assessing the predictions made by modelling. Throughout the reproductive process, mathematical models potentially offer significant benefits to reproductive biologists as they may enable researchers to better translate data from animal models to human, by providing predictions of whether species differences are simply structural (a function of the size or shape of the organ), or whether there are functional differences in cell or tissue behaviour, as has been observed in the metabolism of follicular cells.[6, 32]

The rapid evolution of structure and function over time in the reproductive organs, also results in difficulties when developing mathematical models in this field. This is unlike most other organs in the adult mammal, where there may be dynamic changes (for example in the beating heart and the breathing lung), but the overall anatomical structure of the organ does not change dramatically over time (outside of disease). Our knowledge of the reproductive system relies heavily on static snapshots of a dynamic system. Again, this means that care must be taken when parameterising and validating models, such that appropriate assumptions must be made about the evolution of the system over time where data is not available. However, the difficulty in assessing reproductive tissue provides an opportunity for computational models, as *in silico* testing of hypotheses is increasingly being recognised in reproductive biology as a critical tool for advancing knowledge.[83, 84] Mathematical modelling may prove most useful in suggesting appropriate timing for imaging of the ovarian cycle and pregnancy, or for suggesting optimised experimental design at cell, tissue and organ levels to further physiological knowledge.

Given the complexity of the reproductive system, and the move toward multi-scale and multi-physics approaches to modelling function, a collaborative effort is required to ensure reproducibility and scalability of models. Therefore, storage of published models in curated repositories should be a priority for modellers in the field. This would allow increased collaboration, avoid duplication of

modelling efforts and facilitate teams of researchers to build and test models that have components spanning multiple scales. The Physiome Model Repository (https://models.physiomeproject.org/welcome) serves to provide a database of models in computational biology, and is well-used across fields of computational biology.[105] The number of developmental biology models stored in this database are currently low with searches for placenta, oocyte, embryo, and uterus/uterine returning 0, 4, 4, and 4 unique models, respectively. These models are listed in Table 1, with links to their most recent exposures on the Physiome Model Repository. Most relate to cell level models, and several focus on the non-mammalian *xenopus* oocytes and embryos. Inclusion of models across spatial scales and species would be beneficial to the modelling community who should consider making model exposures available on this, or similar repositories, where possible.

Table 1: Developmental biology models available on the Physiome Repository, following searches for the terms "placenta", "oocyte", "embryo" and "uterus"/"uterine". Note that not all models cited are directly applied to developmental processes and some focus on non-mammalian species.

Search Term	Study Title	Latest Exposure on Physiome Model Repository
Embryo and Oocyte	Mathematical Model for Early Development of the Sea Urchin Embryo [106]	https://models.physiomeproject.org/exposure/d8a0d09ce5b7c5c11c133d30d66c80d7/ciliberto_tyson_2000.cellml/view
Embryo	Dynamical modeling of syncytial mitotic cycles in Drosophila embryos[107]	https://models.physiomeproject.org/exposure/1a3f36d015121d5596565fe7d9afb332/calzone_thieffry_tyson_novak_2007.cellml/view
	Sharp Developmental Thresholds Defined Through Bistability By Antagonistic Gradients of Retinoic Acid and FGF Signaling[108]	https://models.physiomeproject.org/e/50/goldbeter_2007.cellml/view
	A kinetic model of the cyclin E/Cdk2 developmental *Xenopus laevis* embryos[109]	https://models.physiomeproject.org/exposure/91e4ff7fd57b8187721183f2fe49f45f
Oocyte	Numerical analysis of a comprehensive model of M-phase control in Xenopus oocyte extracts and intact embryos.[110]	https://models.physiomeproject.org/exposure/1e1bee6ef3243503e7e1531cfd61bb3f/novak_tyson_1993_b.cellml/view
	On the Formation and Breakup of Spiral Waves of Calcium[111]	https://models.physiomeproject.org/exposure/d2ae260f34fea156204014df4f1b59b0/mckenzie_sneyd_1998.cellml/view
	Ultrasensitivity in the mitogen-activated protein kinase cascade[112]	https://models.physiomeproject.org/exposure/3227298fc9cc3afc14d058750142c69c/huang_ferrell_1996.cellml/view
Uterus/ uterine	Computational modeling reveals key contributions of KCNQ and hERG currents to the malleability of uterine action potentials underpinning labor [88]	https://models.physiomeproject.org/e/264/Tong_Tribe_Smith_Taggart_2014.cellml/view
	A computational model of the ionic currents, Ca2+ dynamics and action potentials underlying contraction of isolated uterine smooth muscle [85]	https://models.physiomeproject.org/e/263/Tong_Choi_Kharche_Holden_Zhang_Taggart_2011.cellml/view
	Computational modeling of inhibition of voltage-gated Ca channels: identification of different effects on uterine and cardiac action potentials[87, 113]	https://models.physiomeproject.org/e/260/faber_rudy_2000_with_corrected_ICaT.cellml/view
	Rhythmic secretion of prolactin in rats: action of oxytocin coordinated by vasoactive intestinal polypeptide of suprachiasmatic nucleus origin[114]	https://models.physiomeproject.org/exposure/677b58b6198476670f0f9e71424ee66f

Conclusion

Mathematical models provide a powerful tool to understand normal physiology and to guide treatment strategies in pathological conditions, across organ systems. The concept of *in silico* models to reconcile experimental and clinical data obtained in different species, at cell, tissue and organ scales is well-recognised and increasingly being used in reproductive biology. The use of *in silico* models has important applications in answering open questions in this field, as the female reproductive system in mammals is inaccessible to direct measurements, different between species, and changes dynamically with the menstrual cycle as well as in pregnancy. These questions include: What are the maternal and environmental factors that provide best oocyte quality? What differences are there in normal and pathological implantation and the first trimester of pregnancy? How can pre-term labour be detected earlier? And, how can we better manage risk of pelvic floor injury in childbirth?

Key areas of research in female reproductive health are summarised in this review. Although mathematical models of the reproductive process have proved useful in better understanding physiology and pathophysiology, they lag behind other areas in which *in silico* modelling is applied (e.g. adult physiology across organs or modelling of tumour dynamics). This provides an opportunity for modellers working in reproductive fields, particularly where appropriate analogies can be drawn between systems. Following well-developed strategies designed for other organ systems may provide a rapid pathway from translating current models that mainly focus on a single level of function (cell/tissue/organ), to truly multi-scale models that span spatial and temporal scales. Provided that care is taken in determining which aspects of function can be translated across organ systems, and how these models can be adequately validated against experimental or clinical data.

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