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Mechanical assessment of cervical remodelling in pregnancy: insight from a synthetic model

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ABSTRACT

During the gestation and the cervical remodelling, several changes occur progressively in the structure of the tissue. An increase in the hydration, disorganisation of collagen network and decrease in elasticity can be observed. The collagen structure disorganisation is particularly complex: collagen fibres turn thicker and more wavy as the gestation progresses in a transition from relatively straight fibres to wavy fibres, while pores between collagen fibres become larger and separated. Shear wave elastography is a promising but not yet fully understood tool to assess these structural changes and the cervix's ability to dilate. To this end, a numerical histo-mechanical model is proposed in the present study, which aims at linking variations in the microscopic histo-biomechanical processes with shear wave propagation characteristics. Parametric simulations are carried out for a broad range of mechanical and geometrical parameters. Results show a direct relationship between the histological and morphological changes during pregnancy and the viscoelastic behaviour of the tissue.

1. Introduction

The structural functionality of the cervix is currently believed to be a key determinant of pregnancy and delivery. The cervix undergoes important changes throughout the gestation period in a process called cervical remodelling. This cervical maturation involves catabolic processes leading to degradation of collagen, where the collagen network, its geometrical configuration and mechanical properties of cervical tissue concurrently change (Mahendroo, 2012; Timmons et al., 2010). Quantitative and objective information about the temporal evolution of the cervical remodelling may provide a complementary method to current techniques to identify cases at risk of preterm delivery and assess the likelihood of successful induction of labour (Mazza et al., 2014; Feltovich and Hall, 2013). Based on earlier experimental studies, high-frequency ultrasonic evaluation of the structure and mechanical properties of soft tissues may become a clinically relevant diagnostic tool (Barannik et al., 2002; Carlson et al., 2014a).

The composition of soft tissues like cervical tissue consists of a distribution of cells embedded in an extracellular matrix (ECM). The most important constituent of the cervical ECM is fibrillar collagen. These collagen fibres are responsible for the mechanical strength of the cervix. Other matrix molecules known to affect the collagen network include water, proteoglycans, hyaluronan, and elastin (House and Socrate, 2009). During the cervical remodelling several changes progressively occur in the structure of the tissue, such as an increase in hydration, a decrease in elasticity and disorganisation of the collagen network. Previous studies reported on the evolution of the collagen network in the cervix during the gestation. Collagen fibres appear thicker and more kinked as gestation progresses in a transition from relatively straight fibres to wavy fibres, while pores between collagen fibres become larger and father apart (Feltovich et al., 2010, 2012). Experimentally, these morphological characteristics are difficult to investigate individually, and this motivates the use of a numerical model.

Elasticity imaging has recently been introduced in obstetrics and gynaecology to evaluate the degree of cervical stiffness (Molina et al., 2012; Hernandez-Andrade et al., 2013; Carlson et al., 2014b). Although it has been successfully applied in the diagnosis and classification of tumours and/or cancer in other tissues as breast or liver (Booi et al., 2008; Muller et al., 2009), some assumptions are made that are inappropriate for the cervix. Indeed, the cervix is anisotropic, heterogeneous and small relative to the shear wavelengths that are characteristic in dynamic elastography. In addition, measurements made in this manner introduce artefacts that are difficult to correct given the fairly limited state of knowledge on the cervical-tissue mechanics. Thus, only a sound knowledge of the microstructure will allow a comprehensive assessment of the tissue mechanics and an appropriate interpretation of wave behaviour. As the long-term objective is to translate viscoelastic measurements

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into descriptions of ECM properties and pregnancy states, the relationships between stromal ECM features and viscoelastic measurements must be clearly understood.

Within this context, the main goal of this study is to link the variations of microscopic histological characteristics (both morphological and biochemical) with the macroscopic tissue-scale mechanical properties measurable by shear waves. To this end, we propose a multi-scale approach that combines three elements: collagen morphology, wave-tissue interactions and constitutive mixture theory. This approach allows us to rheologically link the micro-architectural changes during pregnancy with the viscoelastic gross behaviour of the cervical tissue.

2. Methodology

Cervical remodelling can be loosely divided into four distinct but overlapping phases termed softening, ripening, dilation and postpartum repair (Timmons et al., 2010). To study the mechanical and rheological behaviour of tissues mimicking the gestational states during this cervical remodelling, we propose a model that quantitatively describes the relationship between histological variables and ultrasonic mechanical properties. Such a model is based on three dimensions: a mesoscale morphology model, a constitutive mixture model and the finite difference time domain (FDTD) wave interactions.

The proposed methodology consists of 5 steps: (1) the shear wave propagation across cervical tissue at the micro-scale is simulated by a heterogeneous FDTD numerical model; (2) a parameterized morphology model, able to capture the collagen organisation, is proposed to feed the FDTD model; (3) a set of chemical variables that also change during gestation are incorporated in a mixture-theory-based model of mechanical properties of the constituents of the tissue, which feed the FDTD model and link the micro-scale to the mesoscale. To finally connect with the macro-scale, (4) the rheological properties are studied through the dispersion curves by a phase difference algorithm combined with a (5) model-based inverse problem (IP) to reconstruct the evolution of macroscopic viscoelastic properties in the tissue.

2.1. Finite difference time-domain model

The FDTD simulation technique is based on the linearized wave equations of continuity and motion written in the time-domain. Particular emphasis is posed in the ability to model heterogeneous tissue, where the properties are allowed to vary as a piece-wise constant function at each discretisation element. The equilibrium, constitutive and compatibility equations that govern the wave propagation,

$$\begin{aligned} \rho\dot{v}_i+\gamma\rho v_i &= b_i+\sigma_{ij,j} \\ \dot{\sigma}_{ij}+\gamma\sigma_{ij} &= \lambda(x,y)\delta_{ij}\dot{\varepsilon}_{kk}+2G(x,y)\dot{\varepsilon}_{ij} \\ \dot{\varepsilon}_{ij} &= \frac{1}{2}(v_{i,j}+v_{j,i}) \end{aligned} \quad (1)$$

are discretised directly in their differential notation. Where $i,j=x,y$ are the cartesian components of the particle velocity vector v_i and that of the stress tensor σ_{ij}, b_i are the volume force densities, $\gamma=\eta/\rho$ is the kinematic viscosity, which defines a damping scalar field related to dynamic viscosity η, ρ denotes the density of the medium, ε_{ij} is the strain tensor, δ_{ij} denotes the Kronecker symbol, and $\lambda(x,y)$ and $G(x,y)$ are the space-dependent Lamé constants.

A *staggered grid stencil* discretization is used, where velocity and strain/stress variables are defined at alternating positions and times shifted by a half-step in space and time (Fellinger et al., 1995). Since the problem considered involves an unbounded region, absorbing boundary condition (ABC) is implemented at the borders of the computational grid (Moore et al., 1988).

2.2. Mesoscale morphology model

The uterine cervix is a soft tissue formed mainly by fibrillar collagen (types I and III). At non-pregnant stage and at early pregnancy, the cervix has three preferred orientated collagen zones of collagen fibrils with gradual transition between them (Aspden, 1988; Weiss et al., 2005; Akins et al., 2010). The innermost and outermost zones of the stroma contain collagen fibrils preferentially aligned in the longitudinal direction, that is parallel to the cervical canal. In the middle zone the fibrils have a preferred orientation in the circumferential direction, i.e. surrounding the cervical inner canal. These preferentially aligned fibres are responsible for the typical anisotropic behaviour of the tissue, and they provide strength both longitudinally and circumferentially with respect to the cervical canal (Aspden, 1988; Weiss et al., 2005). In many connective tissue types, as the cervical one, when the collagen fibres are observed in between crossed polarisers in the optical microscope, they present an undulating appearance (Dale and Baer, 1974; Magnusson et al., 2002; Akins et al., 2010; Myers et al., 2009). This wavy configuration of the fibrils at the microscopic level imparts a high degree of elasticity to soft tissues, enabling them to be stretched repeatedly longitudinally without damaging the underlying structure at the nano and molecular levels (Wenger et al., 2007). Thus, both preferred alignment directions and the waviness of fibres play an important role, determining the general mechanical behaviour of the tissue. Experimentally, these geometrical and morphological characteristics are difficult to investigate individually, and thus a synthetic spatial medium, able to capture the morphological features, is developed here.

Three 2-D media are proposed, as a simplification of the tissue, to model these different zones that constitute the human cervix. We distinguish between longitudinal and transverse profiles, depending on how the collagen fibres are organised within the cervical tissue architecture. In the transverse profile collagen fibres are represented by its cross-section by non-overlapping and randomly distributed circular scatterers. While in the longitudinal profiles fibres are represented by its longitudinal section. Depending on how the fibres are aligned with respect to the shear wave propagation, we propose two longitudinal profiles: longitudinal profile with fibres parallel to the propagation ($\theta=0^\circ$), and longitudinal profile with fibres perpendicular to the shear wave propagation ($\theta=90^\circ$). The θ symbol represents the angle between fibres and wave propagation. Fig. 1 shows an example of the three synthetic spatial media. The dimensions of the spatial models were fixed on 250 $\times$ 250 μm. This size is large enough to capture the micro-scale architecture of collagen network and also, it allows us to keep the computational cost at an acceptable level.

Longitudinal profiles were generated with a randomised algorithm in Matlab®, where the crimped morphology of collagen fibres is described by a Beta distribution characterised by two shape parameters. The election of the distribution function was based on previous numerical tests performed by Elbischger et al. (Elbischger et al., 2004; Cacho et al., 2007), which suggest that the probability of the fibre waviness can be satisfactorily approximated by a Beta function. The input values for the algorithm include the size of the profile, collagen fibre thickness, desired values of fibre fraction and the standard deviation that characterises the waviness. Every fibre is randomly generated in an interval of defined length on the x-axis, such that at any point x within that interval, the associated coordinate y is an independent and normally distributed random variable with zero mean and a predefined standard deviation. It can be demonstrated (see the work of Cacho et al., 2007 for more details) that the crimped fibres generated in this way can be described by a Beta distribution.

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