FDTD simulations for ultrasound propagation in a 2-D cervical tissue model

Laura Peralta, Guillermo Rus, Nicolas Bochud, Juan Melchor, Juan Chiachío, and Manuel Chiachío

Dpt. Structural Mechanics, University of Granada, 18071 Granada, Spain.
{lperalta,grus,nbochud,jmelchor,jchiachio,mchiachio}@ugr.es
http://www.ugr.es/~grus

Abstract. The cervix is a biochemically active tissue that changes its biomechanical properties in a remodeling process during pregnancy to be prepared for parturition. This maturation process is associated with changes of the mechanical properties of the cervical stroma. Preterm delivery is connected with undesired cervical changes bound to cervical ripening. Non-destructive evaluation using ultrasonic signals is a well-established method to obtain physically relevant mechanical parameters, and thus ultrasonic may be an useful tool to diagnostic preterm birth. A two-dimensional finite difference model for mechanical waves in the collagenous tissues has been developed, and used to understand how propagation of ultrasound is affected by the hierarchical structure of cervical tissue during pregnancy. The model simulates the wave propagation through two different soft tissues: a micrograph from human cervical tissue, and an artificially created profile with random generated fibers. Results show the ability of the proposed model to describe the mechanical behavior of the cervical tissue as a fiber-reinforced material, and that the ultrasonic wave propagation phenomena can be exploited to reconstruct the mechanical properties of soft tissues.

1 Introduction

The structural functionality of the cervix is currently believed to be a key determinant of pregnancy and delivery. The cervical maturation involves catabolic processes leading to degradation of collagen, where the collagen network, its geometrical configuration, and mechanical properties of cervical tissue change concurrently. In some patients, the spontaneous preterm birth is connected to undesired cervical changes which appear to be caused by impaired mechanical properties of the cervical tissue. Control of cervical ripening is hence considered one of the most pressing problems in obstetrics [1], and an early detection of premature maturation of cervix is a promising way to prevent the preterm birth [2].

A significantly earlier anticipation or preterm delivery is expected if the mechanical cervix effacement is quantitatively measured with sufficient precision. 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 [3, 4].

It is known that cervical mechanical properties arise from the ECM, which functions as a fiber-reinforced composite, and the collagen fibers are responsible for its mechanical strength. Cervical stroma has three preferred orientated collagen zones that will provide strength both along and around the tissue [5, 6]. These preferentially aligned fibers are responsible for the typical anisotropic behavior to the material. Furthermore, when the collagen fibers are observed in between crossed polarizers in the optical microscope, they present an undulating appearance. This waviness is found in many connective tissue types, such as tendon, ligament, cervix, cornea or intestine [7, 8]. 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. Experimentally, these characteristics are difficult to investigate individually, and thus a numerical model is needed.

In this study, a 2-D finite difference time-domain (FDTD) model to idealize ultrasonic measurements of cervical tissue in transmission configuration is developed. Surface profiles obtained from histological images of human cervix samples were inserted and performed in the model. Additionally, to evaluate the effect of the geometrical and mechanical properties of collagen fibers on the ultrasound propagation through the tissue, artificially created profiles with randomly generated fibers and different material parameters were implemented in the model. These synthetic profiles allow to analyze the influence of the collagen architecture, which represents over 70 % in the cervical tissue. Morphological features, as the waviness or the alignment of fibers, and the mechanics as well, were studied. Understanding the tissue-ultrasound interaction is the main objective of the present work.

2 Methodology

The proposed methodology consists of three elements: A (1) FDTD numerical model is used to idealize ultrasonic measurements of cervical tissue; (2) histological images of human cervix samples are performed in the model; and to study the geometrical features of collagenous fibers, (3) numerically developed spatial profiles are proposed to model soft-tissue.

2.1 Finite difference time-domain model (FDTD-model)

The FDTD simulation technique is based on the linearized wave equations of continuity and motion written in the time-domain. A numerical solution of the linear elastic wave propagation equations was computed in the simulation domain. The formulation of the equilibrium equations is obtained by applying the linear momentum theorem for each direction of the two dimensional orthonormal basis,

$$\rho \ddot{v}_i + \gamma \rho v_i = b_i + \sigma_{ij,j} \tag{1}$$

where $i, j = x, y$ are the cartesian components of the particle velocity vector v_i and of the stress tensor σ_{ij}, b_i are the volume force densities, $\gamma = \frac{\eta}{\rho}$ is the kinematic viscosity, that effectively defines a damping scalar field related to dynamic viscosity η, and ρ denotes the density of the medium in which the waves propagate.

The relation between the stress and the strain tensor is established with the constitutive equations. For a linear isotropic material with space dependency, they are described as follows,

$$\dot{\sigma}_{ij} + \gamma\sigma_{ij} = \lambda(x,y)\delta_{ij}\dot{\varepsilon}_{kk} + 2\mu(x,y)\dot{\varepsilon}_{ij} \tag{2}$$

where ε_{ij} is the strain tensor, δ_{ij} denotes the Kronecker symbol, and $\lambda(x,y)$ and $\mu(x,y)$ are the space-dependent Lamé constants.

Finally, the kinematic relations establish a relation between the displacement field u_i and the strain vector ε_{ij}. They are written in the index notation in the following compatibility equation,

$$\dot{\varepsilon}_{ij} = \frac{1}{2}(v_{i,j} + v_{j,i}) \tag{3}$$

These equations are discretized directly in their differential notation. A *staggered grid stencil* discretization was used, where velocity and strain/stress variables are defined at alternating positions and times shifted by a half-step in space and time [9]. Since the problem considered involves an unbounded region, absorbing boundary condition (ABC) are required at the borders of the computational grid. The purpose of the ABC is to avoid reflections at the boundaries so the grid appears to be unbounded [10]. The source is modeled by a broadband shear and compressional velocity pulse centered at 250 kHz, for S and P-waves respectively. The temporal resolution was taken following the stability criteria $\Delta t = \Delta x/\sqrt{2}c_{max}$, where Δt and Δx are the temporal and spatial resolution, respectively. The projections of the particle velocity, v_x and v_y, were recorded by the receiver. A simulation duration of 50 μs was chosen. It is enough time to guarantee most of the energy transmission and avoid possible reflections.

2.2 2-D collagenous tissue model

Spatial models are proposed for modeling and simulating the ultrasound propagation through the collagenous tissue, which is idealized as a fiber-reinforced material, that is collagenous fibers surrounded by a matrix. The geometry of the simulation domain is defined using a 2-D regular mapping of the mechanical properties of the considered media: (i) ground substance, and (ii) collagen fibers. The inhomogeneous soft tissue was represented by two-dimensional matrices of density and longitudinal and shear velocity values. These values were established for matrix and collagen materials, assuming that they have a constant values of density and Lamé parameters, and therefore a constant wave velocity. The material parameters used in the simulations were chosen according to the

Parameter	symbol	matrix	collagen
Density	ρ [kg/m^3]	1000	1200
Young modulus	E [MPa]	0.09	3000
Poisson's ratio	ν [-]	0.5	0.35
Kinematic viscosity	γ [s^{-1}]	$5 \cdot 10^4$	$5 \cdot 10^4$

Table 1. Mechanical parameter values used for the FDTD simulations.

bibliography [5, 11], and correspond to a realistic range of material properties for cervical tissue. Those properties are given in Table 1.

Two spatial mediums are used for modeling and simulating the ultrasound propagation through the connective tissue: a micrograph from human cervical tissue and artificially created profiles.

The micrograph was taken by an optical microscope in an human cervical tissue after a vaginal hysterectomy from a non-pregnant woman. Only a healthy part, far enough from the damaged areas, and with a single preferent direction in the collagen fibers was implemented in the FDTD model. The correspond spatial model is obtained by a segmentation of the micrograph. The image was segmented by defining a segmentation threshold, normalized into RGB interval and converted into a binary image, where fiber density is monotonically related to the segmentation threshold.

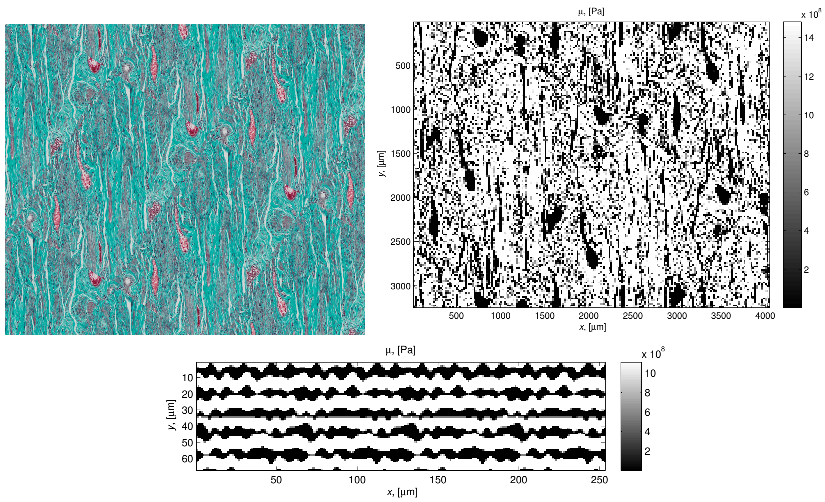

Figure 1. 2-D cervical tissue spatial models: Micrograph from human cervical tissue and its posterior segmentation used in simulations, and the artificial profile created ramdonly.

The wavy conformation of the fibrils at the microscopic level is known to impart 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 [8, 11]. Thus, the waviness takes an important role at the micro scale, determining the general mechanical behavior of the tissue. This characteristic is difficult to investigate in the micrograph images and thus an artificial model is needed to study the role that plays the waviness in the tissue. Thus, the effect of the waviness was evaluated by numerical simulations in synthetic profiles generated with a randomized algorithm in Matlab®, where the crimped morphology of collagen fibers is described by a Beta distribution characterized by two form parameters, α and β. The election of the distribution function was based on previous numerical tests performed by *Elbischger et al.* [12, 13], which suggests that the probability of the fiber waviness can be approximated satisfactorily by a Beta function.

The input values for the algorithm which generates the synthetic medium include the size of the profile, collagen fibers thickness, a minimum distance between fibers, desired values of fiber fraction and the number of fibers. Every fiber is randomly generated in an interval of defined length on the x-axis such that at any point x within that interval the associated coordinates y and z are independent and normally distributed random variables with zero mean and a predefined variance. Finally, the stretchability of every fiber is determined and described by a Beta distribution which is characterized by two form parameters, α and β, which in turn depend only on the variance [13]. Figure 1 shows the two different spatial medium performed in the numerical model: the micrograph taken from the cervical tissue and its posterior segmentation, and the artificial profile in a smaller scale in order to capture the role of the fibers waviness.

Finally, the dimensions of the spatial models were chosen after several simulations, where different values of spatial windowing have been applied. Thus, US propagations were performed in profiles with dimensions 250 x 65 μm and 4 x 3.2 mm in artificial created profiles and image taken from the micrograph, respectively. The spatial resolution step was adjusted to 1 μm, in the synthetic profiles, and 10 μm in the spatial medium taken from the microscope.

2.3 Parametric study

In a collagenous tissue, the velocity of plane waves varies depending on its propagation direction, the stretch and the preferred direction of fibers. In order to validate the FDTD code and to understand the wave propagation through cervical tissue, different cases were simulated. The modeling can be divided into three separate parametric studies as described next.

1. *Ultrasonic waves characteristics: incidence angle, wave type and excitation frequency.* Simulations with different values of incidence angle of the ultrasound beam, as well as different range of excitation frequency were made for compressional and shear waves.

2. *Mechanical properties of collagen fibers: Young modulus, E, and volume fraction, V_f.* A quantification of the mechanical parameters allows realistic simulations. To quantify how the fibers density and Young modulus affect the mechanical behavior of tissue, simulations were made for different fibers density (from 20 to 100 %) and Young modulus of fibers (from 3 to 7 GPa).
3. *Morphology of collagen fibers: waviness and stretch.* Wave velocity and amplitude were calculated from the modeled data obtained for five profiles with different waviness and fiber stretch, and fixed values of the material mechanical properties (see Table 1).

3 Results

Results show the evolution of velocity and attenuation waves, and they have a similar tendency in both considered spatial mediums. These tendencies can be explained by considering the microstructure of the tissue, i.e., the collagen fibers, and thus the wave velocity depends mostly on the collagenous stroma of the tissue, as it was expected.

The dependence of the velocity and attenuation on geometrical and mechanical properties of the collagen tissue was nearly similar for different material parameter combinations, for increasing values of velocity we got decreasing attenuations.

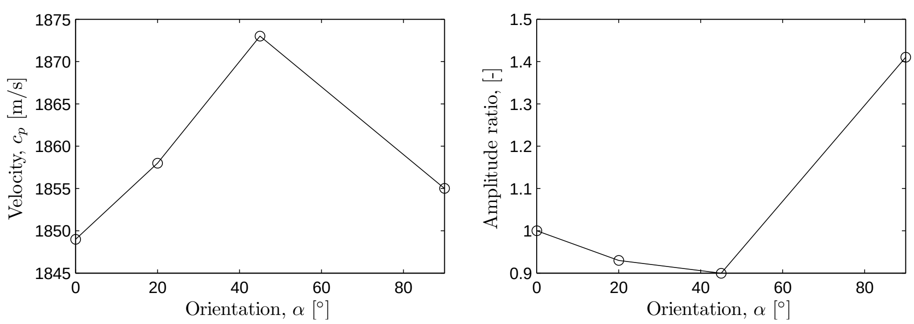

Figure 2. FDTD simulated dependency of P-wave velocity and amplitude ratio on the relative orientation between fibers and incoming ultrasonic wave using the micrograph as spatial medium.

The angular dependence of the velocity and attenuation is evident in Figure 2. The wave velocity is lower at 0 and 90 degrees, whereas it increases at intermediate angles, with a maximum around 45 degrees. The attenuation has the opposite trend, and it is stronger at intermediate angles, which can be explained by the increased scattering when the wave travels along misoriented interfaces.

Figure 3 shows how the proposed model is able to predict the influence of the frequency excitation on the ultrasound transmitted signals. The frequency

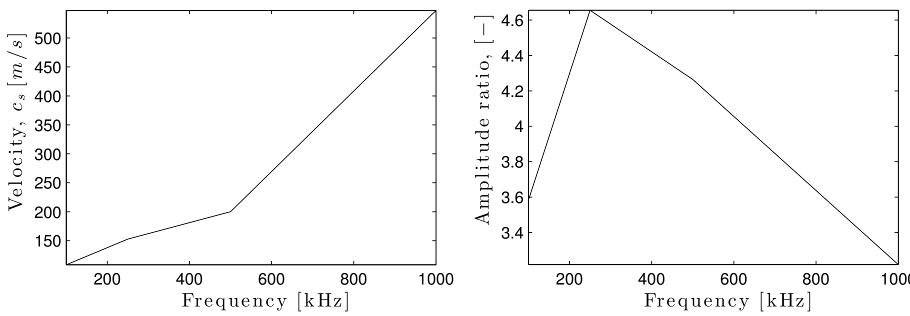

Figure 3. FDTD simulated dependency of S-wave velocity and amplitude ratio on the frequency excitation using the synthetic profile as spatial medium.

dependence of the phase velocity and attenuation of ultrasonic waves is a typical characteristic of viscoelastic materials as soft tissues.

To quantify how the fibers density affects the mechanical behavior of tissue, simulations were made for different segmentation thresholds in the micrograph spatial medium (fiber density is monotonically related to the segmentation threshold). In the synthetic profiles, to simulate the same, the volume fraction fibers was increasing. In both mediums, velocity and amplitude of waves are shown to increase with the density of fibers, due to the increase of the material stiffness, as it is depicted in Figures 4 and 5. The positive dependency of velocity of both P and S waves on the Young modulus of collagen is correctly predicted by the FDTD model. The dependency of the attenuation is also predicted.

Effect of the stretch of fibers or tissue elongation was computed in both considered spatial mediums.. In this case, opposite tendencies are observed. A negative dependency of the velocity is observed when the spatial medium corresponds to the microscopic image (Figure 6), while a positive tendency is shown when the simulations were made in the synthetic profiles (Figure 7). This result indicates the necessity of a more detailed spatial medium than the one got from the microscopic image, and justifies the synthetic profiles developed, which are able to capture the morphology of the collagen fibers at the micro-scale. As soon as the fibers are more straight, they guide the wave transmission, and consequently the velocity increases. Whereas the wave velocity is observed to increase with stretch, possibly due to alignment of fibers, the attenuation increases.

Finally, the waviness of the collagen fibers was analyzed in the synthetic profiles, evolution of velocity and attenuation were estimated in profile with different waviness of fibers. Figure 8 shows the influence of the morphology of collagen fibers in the ultrasound transmission. For any chosen combination of the values of the mechanical parameters, the same dependency of results on the morphological characteristics of collagen fibers was obtained. When the waviness of the collagen fibers increases, the wave velocity decreases, and the opposite tendency is observed in the attenuation. The higher sensitivity that shear waves have to the micro-architecture of soft tissues is depicted in Figure 8, where it

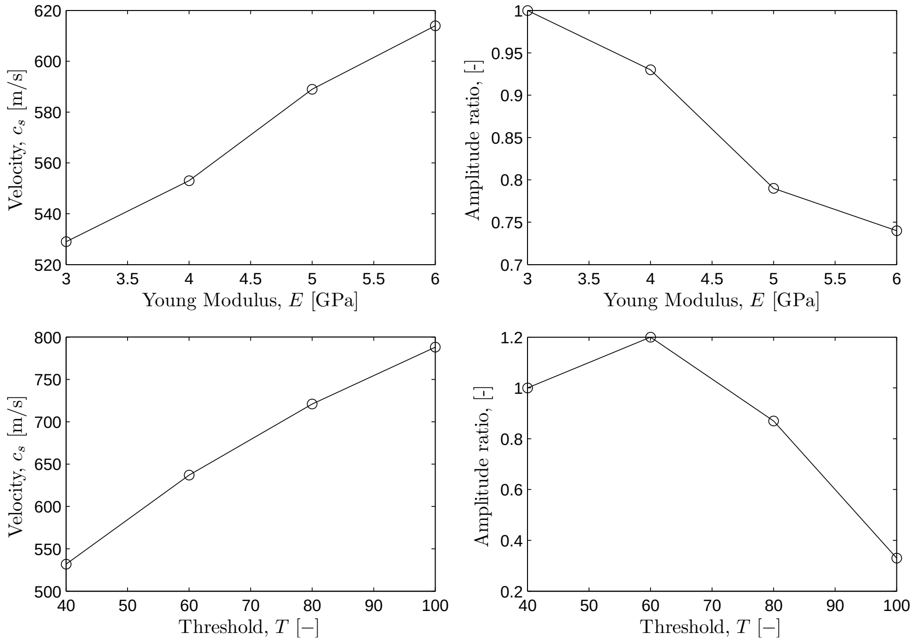

Figure 4. FDTD simulated dependency of S-wave velocity and amplitude ratio on Young modulus and quantity of collagen fibers using the micrograph as spatial medium.

is clearly shown how S-waves have stronger dependency on the waviness while none clear tendency is observed in the P-waves simulations.

Waviness of fiber is responsible for, in part, the mechanical behavior and creep of tissue. In the cervical micrographs analyzed, the middle zone of the cervix, where fibers are aligned in the circumferential direction, presents lower waviness than zones with longitudinal fibers. This is hypothesized to be due to the fact that the higher values of waviness that tissue cut in the longitudinal direction has a higher creep rate that tissue cut in the circumferential direction.

4 Conclusions

A Finite-Difference Time-Domain (FDTD) method was developed to simulate ultrasound propagation through a 2-D model of a cervical tissue. The FDTD simulations can be used both to show the interaction between ultrasonic waves and the hierarchical structure of connective tissues and to study the mechanical properties of soft tissues.

The results show the ability to describe mechanical behavior of the cervical tissue like as a fiber reinforced material. Ultrasound waves interact with collagen fibers (micro-scale), which determines macroscopic properties (centimeter scale) and are responsible for the mechanical behavior of connective tissue. Further-

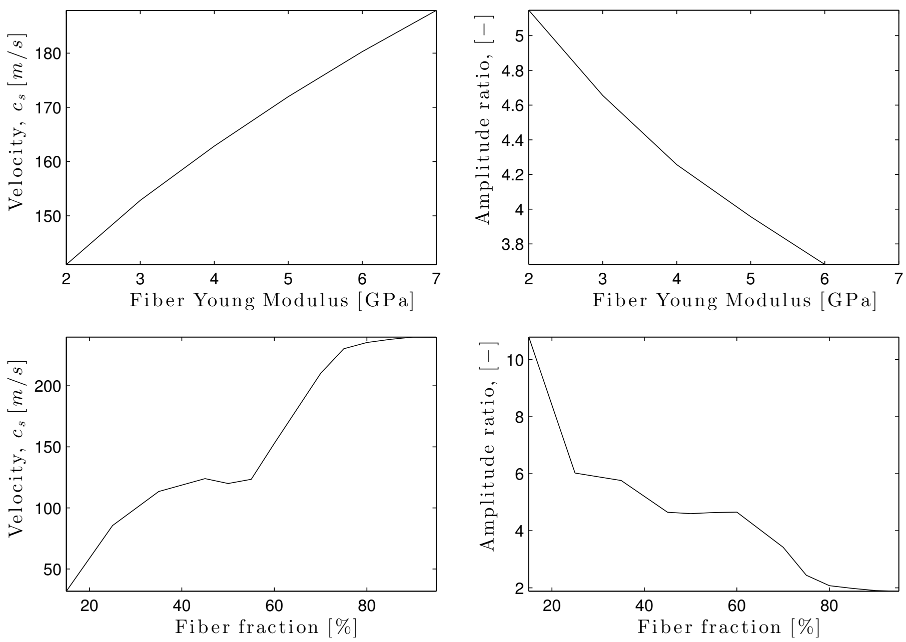

Figure 5. FDTD simulated dependency of S-wave velocity and amplitude ratio on Young modulus and volume fraction of collagen fibers using the synthetic profile as spatial medium.

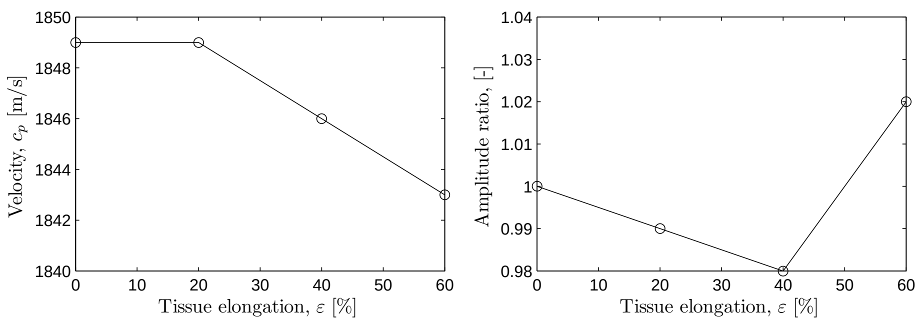

Figure 6. FDTD simulated dependency of P-wave velocity and amplitude ratio on tissue elongation using the micrograph as spatial medium.

more, this work manifests how shear-waves are more sensitive to collagenous tissues architecture than compressional waves.

This work highlights the role of collagen architecture in soft tissues mechanics, and in the cervical tissue particularly. Not only the main known mechanical parameters as the Young modulus are responsible for the tissue behavior, but

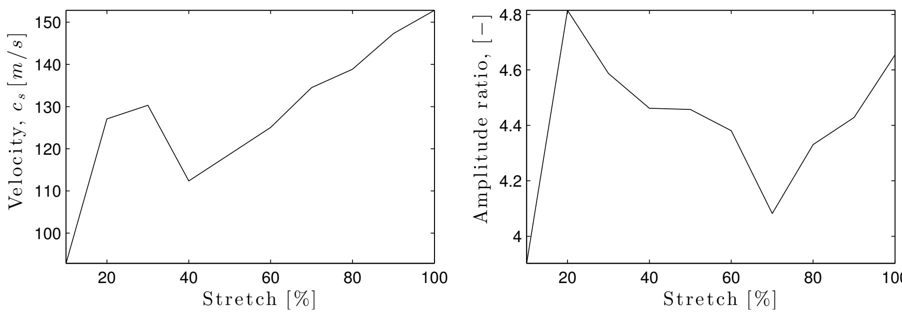

Figure 7. FDTD simulated dependency of S-wave velocity and amplitude ratio on tissue elongation using the synthetic profile as spatial medium.

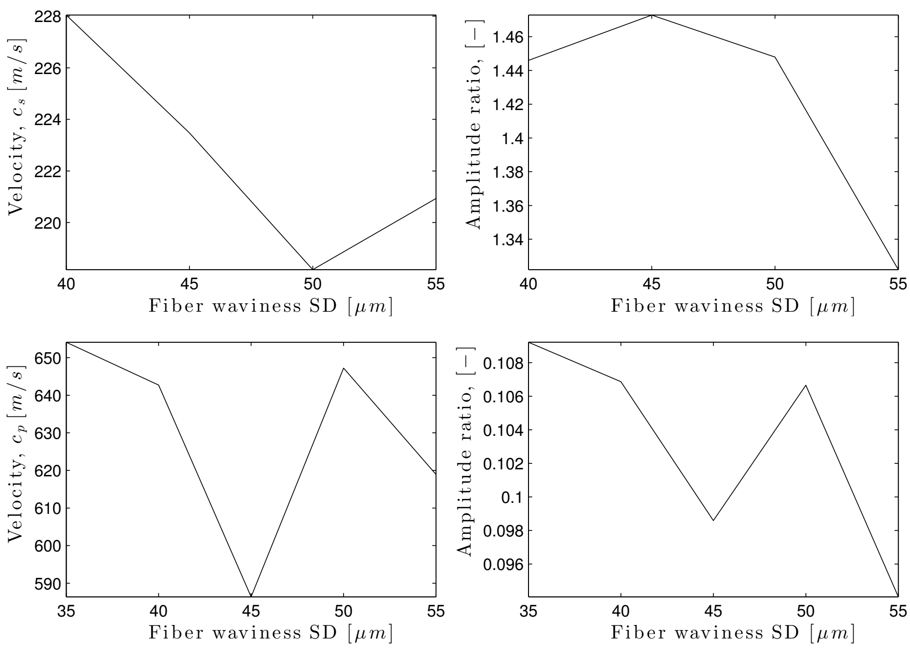

Figure 8. FDTD simulated dependency of S and P-wave velocity and amplitude ratio on waviness of collagen fibers using the synthetic profile as spatial medium.

also the geometry in the micro-scale. The distribution of fibrils as fibers or fibril bundles occurs as a common pattern in many tissues, with the fiber direction being aligned to provide the bespoke mechanical characteristics of the tissue. The response of the tissue to the applied stress strongly depends upon the strain rate, where high strain rates cause elongation of the collagen molecules and initiate shearing effects within fibrils. While at small strains there is a straightening of kinks in the collagen structure (first at the fibrillar and then at the molecular level).

The FDTD method can be used easily to simulate ultrasound propagation in more complex models of the cervix, which would lead to better understanding of the effect of cervix structure on an ultrasound signal. This understanding, in turn, would allow development of a new method to anticipate the preterm birth based on mechanical properties.

Acknowledgments. Spanish Ministerio de Economia for project DPI2010-17065, Spanish Junta de Andalucia for projects P11ŋCTS-8089 and GGI3000IDIB, and the European Union for program 'Programa Operativo FEDER de Andalucía 2007-2013'.

REFERENCES

1. N. Uldbjerg, G. Ekman, A. Malmström, B. Sporrong, U. Ulmsten, and L. Wingerup. Biochemical and morphological changes of human cervix after local application of prostaglandin e2 in pregnancy, *The Lancet*, Vol. **31**, pp. 267–268, (1981).
2. FS Molina, G Rus, LF Gómez, J. Florido, and KH Nicolaides. Reply letter, *Ultrasound in Obstetrics and Gynecology*, Vol. **40**, pp. 612–613, (2012).
3. T. Matsumura, T. Umemoto, Y. Fujihara, E. Ueno, M. Yamakawa, T. Shiina, and T. Mitake. Measurement of elastic property of breast tissue for elasticity imaging, *In Ultrasonics Symposium (IUS), 2009 IEEE International*, pp 1451–1454. IEEE, (2009).
4. E.A. Barannik, A. Girnyk, V. Tovstiak, A.I. Marusenko, S.Y. Emelianov, and A.P. Sarvazyan. Doppler ultrasound detection of shear waves remotely induced in tissue phantoms and tissue in vitro. *Ultrasonics*, Vol. **40**, pp. 849–852, (2002).
5. R.M. Aspden. Collagen organisation in the cervix and its relation to mechanical function. *Collagen and related research*, **8**(2), pp. 103–112, (1988).
6. S.Weiss, T. Jaermann, P. Schmid, P. Staempfli, P. Boesiger, P. Niederer, R. Caduff, and M. Bajka. Three-dimensional fiber architecture of the nonpregnant human uterus determined ex vivo using magnetic resonance diffusion tensor imaging. *The Anatomical Record Part A: Discoveries in Molecular, Cellular, and Evolutionary Biology*, **288**(1), pp.84–90, (2005).
7. W. C. Dale and E. Baer. Fibre-buckling in composite systems: a model for the ultrastructure of uncalcified collagen tissues. *Journal of Material Science*, **9**(3), pp. 369–382, (1974).
8. SP Magnusson, K. Qvortrup, JO Larsen, S. Rosager, P. Hanson, P. Aagaard, M. Krogsgaard, and M. Kjaer. Collagen fibril size and crimp morphology in ruptured and intact achilles tendons. *Matrix biology*, **21**(4), pp. 369–377, (2002).
9. P. Fellinger, R. Marklein, KJ Langenberg, and S. Klaholz. Numerical modeling of elastic wave propagation and scattering with efitUelastodynamic finite integration technique. *Wave motion*, **21**(1), pp. 47–66, (1995).
10. T.G. Moore, J.G Blaschak, A. Taflove, and G.A. Kriegsmann. Theory and application of radiation boundary operators. *Antennas and Propagation, IEEE Transactions on*, **36**(12), pp. 1797–1812, (1988).
11. M.P.E. Wenger, L. Bozec, M.A. Horton, and P. Mesquida. Mechanical properties of collagen fibrils. *Biophysical journal*, **93**(4), pp. 1255–1263, (2007).

12. PJ Elbischger, H. Bischof, P. Regitnig, and GA Holzapfel. Automatic analysis of collagen fiber orientation in the outermost layer of human arteries. *Pattern Analysis & Applications*, **7**(3), pp. 269–284, (2004).
13. F. Cacho, PJ Elbischger, JF Rodriguez, M. Doblare, and G.A. Holzapfel. A constitutive model for fibrous tissues considering collagen fiber crimp. *International Journal of Non-Linear Mechanics*, **42**(2), pp. 391–402, (2007).