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Anisotropic composite material phantom to improve skeletal muscle characterization using magnetic resonance elastography

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ABSTRACT

The presence and progression of neuromuscular pathology, including spasticity, Duchenne's muscular dystrophy and hyperthyroidism, has been correlated with changes in the intrinsic mechanical properties of skeletal muscle tissue. Tools for noninvasively measuring and monitoring these properties, such as Magnetic Resonance Elastography (MRE), could benefit basic research into understanding neuromuscular pathologies, as well as translational research to develop therapies, by providing a means of assessing and tracking their efficacy. Dynamic elastography methods for noninvasive measurement of tissue mechanical properties have been under development for nearly three decades. Much of the technological development to date, for both Ultrasound (US)-based and Magnetic Resonance Imaging (MRI)-based strategies, has been grounded in assumptions of local homogeneity and isotropy. Striated skeletal and cardiac muscle, as well as brain white matter and soft tissue in some other organ regions, exhibit a fibrous microstructure which entails heterogeneity and anisotropic response; as one seeks to improve the accuracy and resolution in mechanical property assessment, heterogeneity and anisotropy need to be accounted for in order to optimize both the dynamic elastography experimental protocol and the interpretation of the measurements. Advances in elastography methodology at every step have been aided by the use of tissue-mimicking phantoms. The aim of the present study was to develop and characterize a heterogeneous composite phantom design with uniform controllable anisotropic properties meant to be comparable to the frequency-dependent anisotropic properties of skeletal muscle. MRE experiments and computational finite element (FE) studies were conducted on a novel 3D-printed composite phantom design. The displacement maps obtained from simulation and experiment show the same elliptical shaped wavefronts elongated in the plane where the structure presents higher shear modulus. The model exhibits a degree of anisotropy in line with literature data from skeletal muscle tissue MRE experiments. FE simulations of the MRE experiments provide insight into proper interpretation of experimental measurements, and help to quantify the importance of heterogeneity in the anisotropic material at different scales.

1. Introduction

1.1. Background and motivation

Changes in mechanical properties of skeletal muscle tissue are associated with many diseases including spasticity, Duchenne's muscular dystrophy (Qin et al., 2014), hyperthyroidism (Bensamoun et al., 2007), atrophy (Ringleb et al., 2007), paraplegia (Basford et al., 2002), patellofemoral syndrome (Botanlioglu et al., 2013), and myositis (McCullough et al., 2011; Lieber and Friden, 2000; Sack et al., 2013). Electrical conduction in muscles is related to the degree of structural anisotropy (Garmirian et al., 2009); indeed, changes in muscle anisotropy may be a marker for the progression of neuromuscular disorders (Chin et al., 2008). Hence, a technique capable of noninvasively and quantitatively assessing muscular tissue viscoelasticity and anisotropy as it relates to the structural and functional properties of muscles, would potentially improve diagnosis and monitoring of the progression of diseases and their response to therapy.

Magnetic Resonance Elastography (MRE) is capable of noninvasively quantifying mechanical properties of muscular tissues in vivo (Bensamoun et al., 2007; Basford et al., 2002; Ringleb et al., 2007; Jenkyn et al., 2003). MRE is a dynamic elasticity imaging technique to generate quantitative maps depicting viscoelastic properties of biological tissues through the excitation and subsequent analysis of

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mechanical wave motion. MRE contrast is akin to the physician practice of palpation; yet, MRE is quantitative and potentially offers advantages in precision, operator-independence, and access to tissues not reachable by touch. Initial MRE studies focused on tissues or specimens that were assumed isotropic and locally homogeneous (Muthupillai et al., 1995). These simple models were used to characterize numerous organs and anatomical regions including brain (Atay et al., 2008; Clayton et al., 2013; Green et al., 2008; Johnson et al., 2013; Murphy et al., 2013; Sack et al., 2008), breast (Sinkus et al., 2005) and liver (Asbach et al., 2008; Klatt et al., 2010; Mariappan et al., 2009). In an MRE experiment, tissue mechanical properties are estimated from imaged displacement data using inversion algorithms: different approaches have been used including those based on the estimation of the wavelength at a location in the image, such as the Local Frequency Estimation (LFE) method, and those based on an inversion of the governing differential equations– the Helmholtz Inversion Method and the Algebraic Inversion of the Differential Equation (AIDE)– each with a multitude of variations based on assumptions, typically local homogeneity and isotropy (Manduca et al., 1996; Doyley, 2012; Papazoglou et al., 2008). Also, optimization algorithms based on the minimization of an error function have been used (Chatelin et al., 2016). For improved accuracy, directionally-dependent viscoelastic response (anisotropy) should be taken into account, which is significant in many biological tissues and at specific length scales (Lieber and Friden, 2000; Feng et al., 2013, 2017; Sack et al., 2008; Romano et al., 2012; Wuerfel et al., 2010; Schmidt et al., 2018; Green et al., 2008). In particular, muscle tissue typically exhibits a microstructure that is intrinsically heterogeneous, with hierarchical arrangements of constituents like fibers and fiber bundles surrounded by an intricate collagen network (Lieber and Friden, 2000). These characteristics make homogeneity and isotropy non-suitable assumptions. While various approaches have been proposed in the literature on the measurement of the anisotropy in brain tissue (Feng et al., 2013, 2017; Romano et al., 2012; Green et al., 2008; Wuerfel et al., 2010; Schmidt et al., 2018) and in skeletal muscle tissue (Gennisson et al., 2003; Garmirian et al., 2009; Papazoglou et al., 2006; Green et al., 2013; Wang et al., 2013; Guo et al., 2016; Qin et al., 2014; Aristizabal et al., 2014), there is not yet an accepted standard for the identification of the mechanical properties of anisotropic and viscoelastic tissues through MRE (Ryu and Jeong, 2017).

Inversion algorithms for anisotropic cases have been investigated including their suitability for incompressible or nearly incompressible transverse isotropic (NITI) materials (Romano et al., 2012; Rouze et al., 2013; Tweten et al., 2015, 2017; Qin et al., 2013; Royer et al., 2011; Schmidt et al., 2016; Clayton et al., 2013). But, due to the scattering phenomena introduced by inhomogeneities and the elongation of the wavefronts occurring in MRE experiments, the estimation of the material parameters for the anisotropic and heterogeneous media through a completely analytical inversion algorithm still needs to be developed.

The design of phantom materials exhibiting controlled anisotropic and rate-dependent responses is a useful tool to develop and evaluate new approaches for inversion in MRE (Chakouch et al., 2015). Phantoms have not only been used as a means of validation and standardization of MRE, but also to improve the performance and reliability of MRE inversion algorithms (Cao et al., 2017). Most studies with phantoms have focused on mimicking isotropic elastic material as in (Muthupillai et al., 1995). Anisotropic phantoms with different shear moduli in the planes parallel and perpendicular to the fiber direction have been built by Green et al. (2008) and Oudry et al. (2009). They implemented a cross-validation between Ultrasound-based Transient Elastography (UTE) and MRE for copolymer-in-oil phantoms formed from a mixture of styrene-ethylene/butylene-styrene (SEBS) copolymer and mineral oil. Viscoelastic and transverse isotropic phantoms have been fabricated using cryogel PVA in Wan et al. (2014), Chu and Rutt (1997) and Millon et al. (2006), where the oriented mechanical properties in cryo-hydrogels were induced by applying controlled strain to the PVA sample stretching the physical crosslinks of the polymeric chains during low temperature thermal cycles. In Chatelin et al. (2014) and Chatelin et al. (2016), physically crosslinked anisotropic PVA hydrogels, capable of replicating fibrous biological tissues, were created. Further examples of anisotropic phantoms are found in Namani et al. (2009), where magnetically aligned fibrin gels were built manually positioning the principal axis of the samples either parallel or perpendicular to the direction of the shear excitation, in Sakai et al. (2008), where a diffusion phantom was designed with micro water channels created on solid Silicon gels through chemical etching, in Qin et al. (2013), where agreement is found between MRE and direct measurements of the shear anisotropy combining MRE and Diffusion Tensor Imaging (DTI) on a composite materials phantom made of Spandex fibers in PVA matrix, and in Schmidt et al. (2016), where measurements of the fast and slow shear wave speeds in aligned fibrin gel phantoms were made.

1.2. Objectives

The aim of the present work is to develop and characterize a composite phantom for MRE experiments that has uniform controllable anisotropic properties meant to be comparable to the frequency-dependent anisotropic properties of skeletal muscle. The materials combination and structure is different from prior designs found in the literature (Qin et al., 2013; Chatelin et al., 2014, 2016; Namani et al., 2009; Sakai et al., 2008; Millon et al., 2006; Wan et al., 2014; Chu and Rutt, 1997). The novel anisotropic phantom was used in MRE experiments exploiting geometrically focused radially converging shear wave excitation as found in computational simulations in Clayton 2013 and in experimental studies by (Yasar et al., 2013). Finite element models were used to simulate the MRE experiments. To this purpose, homogenization analyses were performed to determine macroscopic material parameters and to save computational costs. Studies using such a phantom could clarify the influence of anisotropy, heterogeneity and viscoelasticity on shear wave motion, and help to optimize MRE protocols – experimental (pulse sequence and physical setup) and computational (measured signal analysis and inverse modeling) – to estimate mechanical properties in anisotropic tissues, such as skeletal muscle.

2. Materials and methods

2.1. Phantom manufacturing

Three different phantoms have been fabricated for the MRE experiments: a 3D printed anisotropic composite made of 15% w/v crosslinked gelatin solution for the fibers and of 5% w/v gelatin solution for the matrix, and two homogeneous and isotropic phantoms for the constituent materials of the anisotropic phantoms (5% w/v and 15% w/v crosslinked). The ideal geometry for a composite material mimicking the muscle tissue may be that of unidirectional fibers. However, this material arrangement is impracticable in terms of actual implementation through the 3D printing process employed in this study; so, an additional layer of fibers in a different direction is necessary to give support to the whole structure. (Alternate additive manufacturing strategies may be able to overcome this limitation in the future.) The solution strategy (Fig. 1) was to print a grid structure with two identical families of fibers aligned along two orthogonal directions and to embed it in a gelatin matrix. The fiber network is obtained through the printing of gelatin with higher percentage of crosslinker embedded in a softer matrix made of the same gelatin, with spacing between fibers of 0.8 mm in the horizontal direction and 1.8 mm in the vertical direction. The fiber volume fraction value for the composite phantoms is about 10%; the nozzle diameter of the fibers is 200 μm.

Gelatin powder is weighed and transferred to a 50 mL conical tube. In order to prevent clustering of undissolved gelatin powder, the tube is shaken and tilted to side so that the gelatin is scattered along the walls of the tube. An appropriate amount of sterile phosphate-buffered saline