MR-Elastography at the Microscopic Scale

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INTRODUCTION

Micromagnetic resonance elastography (μMRE) is a new technique for imaging low frequency acoustic shear waves (typically less than 1 kHz) in soft gels and biological tissues with very high spatial resolution (1). μMRE extends currently available MR-elastography to the microscopic scale using high field NMR systems. Magnetic resonance elastography (MRE) is a phase contrast-based MR imaging technique for observing acoustic strain waves propagating in soft materials (e.g., biological tissues: brain, liver, kidney, muscle, as well as gels, polymers and composites) (2). Mechanical shear waves, typically with amplitudes of less than 100 μm and frequencies of 100-500 Hz, are induced using either a piezoelectric or speaker coil oscillator directly coupled to the region of interest. By using multiple phase offsets and motion encoding gradients, MRE acquires data allowing the generation of images that depict shear wave motion and the calculation of local values of the tissue viscoelastic properties. Current MRE studies using 1.5 T MRI systems are directed at establishing techniques for quantifying changes in the mechanical properties of tissues associated with developing disease: malignant tumors appear to be stiffer than benign tumors; fibrosis and cirrhosis tend to increase liver stiffness; and articular cartilage softens in developing osteoarthritis. Work to date suggests that MRE may in fact be able to detect both early stage and diffuse disease well before it can be visualized by conventional MRI, ultrasound or X-ray/CT techniques. Recent MRE investigations are increasingly being conducted at higher spatial resolution to establish histological correlations between elasticity maps and tissue structures; such micro MR elastography (μMRE) studies require stronger static fields, higher performance RF coils and gradients, and more compact, higher frequency mechanical actuators. In this paper, we describe micromagnetic resonance elastography (μMRE), where the basic principles of MRE are extended to high resolution MR systems. The design for a new μMRE system at high magnetic field is presented where the 4-dimensional (4D) spatial-temporal shear wave vector is calculated with microscopic resolution. The presented technique is able to resolve the shear stiffness with microscopic resolution up to 30 μm^2 and to determine shear stiffness up to 64 kPa.

METHOD

Agarose gel phantoms with different stiffness mimicking biological tissues were constructed by mixing varying amounts of agarose gel (SeaKem® LE Agarose, Cambrex, East Rutherford, NJ) 0.25 - 1% w in 0.9% saline solution (Baxter, Deerfield, IL) at around 70 °C for 10 minutes, gelling temp around 35 °C. Two biological samples were tested. First, late-stage frog oocytes from *Xenopus laevis* with a typical diameter of 1 to 1.5 mm were isolated and tested within 3 days of harvesting. Second, engineered tissue constructs from adult mesenchymal stem cells were tested (3). Primary human MSCs were obtained from a healthy human donor via a commercial source (AllCell, Berkeley, CA). The tissue-engineered constructs were fabricated by seeding MSCs into gelatin sponges under different experimental conditions designed to stimulate osteogenic and adipogenic differentiations.

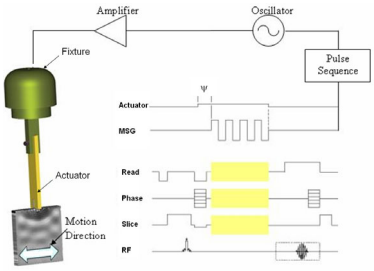

Figure 1. A schematic diagram for the μMRE system. The mechanical actuator is coupled to the sample via a thin needle. The modified pulse sequence controls a gated square wave oscillator tuned to the actuator frequency which is synchronized with the toggled bipolar pulses. Bipolar pulses can be added to the read, slice select, or phase encoding gradient.

Experiments were conducted using a standard 11.74 T (500 MHz for protons) vertical bore magnet (Oxford Instruments, Oxford, UK) using a Bruker DRX 500 MHz Avance spectrometer (Bruker Instruments, Billerica, MA). The acoustic signals were generated using a specially designed transducer (Piezo system, MA) and amplifier. The shear wave signal frequency ranged from 530 Hz to 585 Hz. Acoustic signals were applied with synchrony with the NMR pulse sequence. Saddle coils (D = 5 mm and 10 mm) were used to acquire phase difference maps. The field–of–view ranged from 4 to 14 mm. The μMRE system is shown in Fig.1.

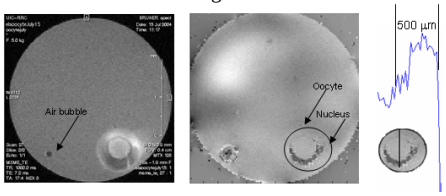

Figure 4. (a) MR image of a frog oocyte, **(b)** Corresponding shear wave image, **(c)** Line profile through the oocyte. In plane resolution 34 μm x 34 μm, slice thickness = 500 μm.

RESULTS

Fig. 2 shows 3-D shear wave images of a gel phantom. By superimposing the bipolar gradient along the slice select, phase encoding and read gradient the 3D shear wave vector can be fully visualized along any plane as shown in Fig. 3. Fig. 4 shows shear wave image through a frog oocyte embedded in agarose gel. A line profile along the oocyte nucleus is shown in Fig.4c where the shear wave amplitude through the oocyte can be distinguished from the surrounding gel. A half wave is visualized within the nucleus with an approximate shear modulus of 0.34 kPa. μMRE was used to examine tissue engineered constructs at different growth stages. After two weeks of incubation, adipogenic constructs were estimated to have a shear modulus of 3 kPa and approximately 64 kPa for the osteogenic construct.

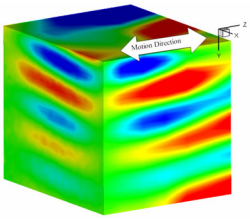

Figure 2. 3D shear wave propagating through a homogenous phantom. Imaging volume = 5 mm x 5 mm x 3 mm, in-plane resolution = 140 μm x 140 μm, slice thickness = 0.5 mm. For the XYZ orientations defined on the above figure: The imaging plane is the XY plane and 6 slices were taken along the Z-direction which corresponds to the slice select gradient. The motion sensitizing gradient is superimposed on the phase encoding gradient, parallel to the z-direction, and collinear with the actuator motion

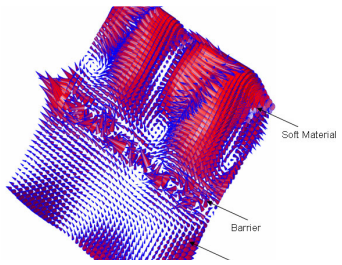

Figure 3. 3D shear wave vectors in a coronal view

CONCLUSIONS AND FUTURE WORK

A new technique called micromagnetic resonance elastography (μMRE) has been developed. This technique provides a very high spatial resolution, in plane resolution up to 32 μm x 32 μm with a 100 μm slice thickness. Further technological advances should include the design of higher frequency actuators that efficiently couple with microimaging solenoidal or surface coils.

REFERENCES: [1] Othman et al., 12th ISMRM, 2004. [2] Muthupillai et al., Science 1995;269:1854-1857. [3] Xu et al., 13th ISMRM, 2005