

Magnetic Resonance Elastography: An Emerging Tool for Cellular Mechanobiology

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Introduction

Malignancies and other pathological processes are often characterized by marked changes in *tissue mechanical properties*. This accounts for the efficacy of palpation as a clinical tool for detecting cancer in accessible regions of the body. Indeed, many tumors of the thyroid, breast, and prostate are still first detected by this centuries-old diagnostic technique. Unfortunately, small or inaccessible lesions cannot be detected by touch, and conventional diagnostic imaging methods do not provide information that is in any way analogous.

In engineering terms, palpation assesses the tendency of tissue to resist deformation, a physical property called *elastic modulus*. The elastic moduli of various human tissues are known to vary over a wide range. Most of the physical properties depicted by conventional medical imaging modalities are distributed over a much smaller range. For instance, the x-ray attenuation coefficients of various soft tissues assessed in CT imaging vary by only by a factor of about 2. In contrast, the elastic moduli of soft tissues vary by factors of as much as 10,000. In addition, the elastic modulus of tumors may differ from surrounding tissues by a factor of 20.

While the potential for detecting and characterizing abnormal tissue provided the original motivation for seeking practical methodologies for imaging the elastic properties of tissues, additional impetus has come from the growing awareness of the importance of tissue *matrix mechanics* on cellular function in natural and engineered tissues. Cells are known to sense their mechanical environment through myosin-based contractility of the *cytoskeleton* in conjunction with *adhesion molecules* such as integrins and cadherins. Cells react to the dynamic and static properties of their matrix environment through *mechanotransduction* and cytoskeletal remodeling. There is increasing interest in assessing the mechanical properties of the matrix environment, given its profound influence on the behavior of cells in diverse areas such as *morphogen-mediated cell programming* and differentiation in developing embryos, growth of tumors, *activation of hepatic stellate cells* to initiate liver fibrosis, regulation of ovarian follicular function, and cell behavior in engineered tissue constructs.

Magnetic resonance elastography (MRE) has emerged over the last decade as a practical and powerful technique for quantitatively assessing the mechanical properties of organs, tissues, cells, and biomaterials. This presentation provides an overview of the basic methodology and a survey of results obtained by investigators who have been working in the field.

Methods

In general, estimating elasticity involves the following steps: (1) causing a known static or cyclic mechanical stress within the medium, (2) measuring the deformation of the medium in response to this stress, and (3) computing the elastic modulus of the medium from the measurements. MRE uses harmonic low frequency transverse acoustic waves (10 Hz - 1.1 kHz) as the source of external mechanical stress. The acoustic waves cause tiny cyclic displacements (on the order of tenths of microns) as they propagate. With mechanical waves, the calculation of regional elastic modulus is simplified, because it can be computed directly from the local wavelength, rather than requiring estimation of the regional static stress distribution.

The MRE method consists of three major elements: (1) a system for generating mechanical waves within the object to be imaged, (2) a sensitive NMR-based method for imaging mechanical waves in tissue, and (3) an analysis algorithm for converting images depicting propagating waves into qualitative or quantitative maps of elasticity. Acoustic shear waves are generated within the object by a surface-mounted electromechanical driver, a piezoelectric device, or radiation pressure from a modulated ultrasound beam. Mechanical waves are imaged using a modified phase-contrast MRI technique. An oscillating, motion-sensitizing field gradient is applied synchronously with acoustic mechanical waves that are generated inside the imaged object. The cyclic motion of the spins in the presence of these motion-sensitizing gradients causes a measurable phase shift in the received NMR signal. The phase shift is proportional to the displacement amplitude and the number of the cyclic motion-sensitizing gradients. Thus, extreme sensitivity to small amplitude synchronous motion can be achieved by accumulating phase shifts over multiple cycles of mechanical excitation and the motion-sensitizing gradient waveform. From the measured phase shift in each

voxel, it is possible to estimate the amplitude of displacement of each voxel in the reconstructed image. This displacement map yields a snapshot of the mechanical waves propagating within the object. The cyclic motion-sensitizing gradients can be superimposed along any desired axis, and therefore it is possible to estimate all components of the strain dyadic non-invasively. The wave images are then processed to generate shear modulus images, using spatial filtering to calculate local wavelength or other methods direct solution of the wave equation.

Applications

MRE has been implemented by multiple investigators on large and small bore MR imagers, at field strengths from 0.5 – 7.0 T. The technique has been applied successfully to generate quantitative images of mechanical properties of biomaterials, engineered tissue constructs, tissue specimens, as well as tissues and organs *in vivo*, from mice to humans.

The MRE technique can image acoustic shear waves with displacement amplitudes of less than 100 nanometers in tissues. MRE-derived measurements of the shear modulus of tissue-simulating gel specimens correlated well with independent mechanical testing results.

Investigators have shown that MRE can be used to quantitatively assess the matrix mechanical properties of engineered constructs and to non-invasively follow the behavior and development of cells within engineered tissues.

Studies of organ and tissue specimens have provided quantitative elastograms depicting the shear modulus of kidney, liver, muscle, breast, eye, aortic wall, and adipose tissue. Measurements have demonstrated that the viscoelastic properties of some tissues are isotropic, while other tissues such as muscle is highly anisotropic. Studies of human pathologic specimens have demonstrated the feasibility of delineating breast and prostate tumors with the technique.

In human studies, MRE has been applied by multiple investigators to quantitatively depict the mechanical properties of brain, skeletal muscle, breast, thyroid, heart, lung, liver, spleen, pancreas, and other tissues. MRE studies of the brain in human volunteers have provided quantitative images of brain elasticity, demonstrating for instance, that white matter has a higher shear modulus than gray matter. In applications to brain imaging, human studies have demonstrated that it is feasible to apply MRE to quantitatively image the mechanical properties of gray and white matter, providing a new tool for tissue characterization, diagnosis, and mechanical modeling in brain pathologies such as hydrocephalus. A variation of the technique, using impulse mechanical waveforms, allows dynamic visualization of micron level strains as mechanical transients propagate through the brain, providing a direct way to study the biomechanics of traumatic brain injury. In recent years, investigators have begun to report applications of MRE to study abnormal tissues in humans, including brain tumors and skeletal muscle in myopathy. Studies of volunteers and patients have demonstrated the feasibility of imaging normal breast anatomy with MRE and delineating breast cancer. These results provide motivation for exploring the capacity of MRE to detect and characterize breast tumors, particularly in premenopausal women.

However, the first well-established clinical application of MRE is to evaluate liver disease. Chronic liver disease is serious worldwide problem, and hepatic fibrosis is the most important consequence, which if not detected and treated, eventually leads to cirrhosis which is irreversible and associated with high mortality. Currently, needle biopsy is the accepted method for detecting and quantifying hepatic fibrosis. This procedure is invasive, expensive, and is affected by sampling error.

Clinical studies by multiple investigators have recently established that MRE is an accurate method for diagnosing hepatic fibrosis. In this application, the liver is illuminated with shear waves, typically in the range of 40-90 Hz. MRE-derived hepatic stiffness increases systematically with fibrosis stage. In a recent published study, encompassing 50 patients with biopsy-proven liver disease and 35 normal volunteers, ROC analysis showed that, with a shear stiffness cut-off value of 2.93 kPa, the predicted sensitivity and specificity for detecting liver fibrosis is 98% and 99%, respectively. ROC analysis also provided evidence that MR elastography can discriminate between patients with moderate and severe fibrosis (grades 2–4) and those with mild fibrosis (sensitivity, 86%; specificity, 85%). Importantly, hepatic stiffness is not systematically influenced by the presence of steatosis.

Recent research has also suggested that MRE has promise for characterizing focal liver lesions. Benign focal liver masses, including cavernous hemangioma, hepatic adenoma, and focal nodular hyperplasia have typical stiffness values in the 3 kPa range, slightly stiffer than normal liver parenchyma. Malignant focal masses of the liver, including hepatocellular carcinoma, metastases, and cholangiocarcinoma are much stiffer than normal liver tissue. In a series of 48 liver masses (36 malignant and 12 benign), a threshold of 5 kPa correctly differentiated 100% of malignant from benign masses.

Conclusions

MR Elastography is emerging as a practical and versatile quantitative tool for mapping the viscoelastic properties of tissue *in vivo*. The technique allows measurement of *shear modulus*, *shear viscosity*, and the *anisotropy* of these properties, as new tissue characterization parameters. Studies of MRE as a clinical diagnostic method, have shown that it can be used to non-invasively “palpate” regions of the body that are beyond the reach of the physician’s hand. Multiple studies have now established that MRE is a reliable method for diagnosing hepatic fibrosis and that it is intrinsically safer, less expensive, and probably more accurate than biopsy in this regard.

In addition, MRE seems to offer unique opportunities to explore tissue matrix mechanics and to address unique questions in cellular mechanobiology, as well new experimental options in fields of acoustics and materials science.

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