

Appendix 1 : brief introduction to history of MRE technology development and clinical application

History of technology development

Parker (13), as the elastography pioneer, firstly imaged the biomechanical properties of tissue using ultrasound elastography. From then, the field of “imaging the elastic properties of tissues” has been expanding rapidly in imaging modalities including MRE over the last 30 years.

Actuator

- ❖ In 1995, the electromagnetic vibration device was designed by Muthupillai *et al.* to generate waves in agar gel (61).
- ❖ In 1999, Rossman *et al.* (107) developed an electromagnetic vibration device for mechanical excitation of the human.
- ❖ In 2003, Braun *et al.* (108) designed an electromagnetic actuator for generating variably oriented shear waves.
- ❖ In 2003, Doyley *et al.* (63) developed a piezoelectric actuator applied inside the diameter spherical imaging volume.
- ❖ In 2006, Chan *et al.* (109) developed a needle-based shear wave generator with piezoelectric bending elements to instead of a long piezoelectric stack. The wave propagation in a target region has a well-defined shape with longitudinal motion of around 200mm, reducing orientation-related error in the wavelength estimation in application of surface drivers.
- ❖ In 2006, Sinkus *et al.* (110) used aortic valve closure as internal driver to generate shear wave for measuring the shear modulus of the interventricular septum.
- ❖ In 2008, Talwalkar *et al.* (111) developed a system for MRE examination of the liver, in which a loudspeaker and a passive driver was connected by a pneumatic tube.
- ❖ In 2011, a design concept with piezoelectric stack was developed by Claton *et al.* (64) to generate high-frequency vibrations for small-animal brain MRE studies over a broad range of driving frequencies, from 600-1800Hz.
- ❖ In 2011, Murphy MC *et al.* (94) used the soft pillow driver for 3D brain MRE and verified the soft vibration source was reliable and comfortable.
- ❖ In 2018, Guertler *et al.* (65) designed a custom multi-directional jaw actuator to transmit vibrations from a pneumatic driver into the mini-pig brain for direct estimates of brain mechanical properties.
- ❖ In 2019, Huang X *et al.* (112) designed an ergonomic

pillow-like passive driver for brain MRE.

MR sequence and imaging strategies

- ❖ In 1989, the first MR elasticity experiment was conducted using 1.5T MR system (General Electric, Milwaukee) with a standard spin echo sequence by R. Buxton and A. Sarvazyan at the University of California at San Diego (113).
- ❖ In 1992, MR elastography studies with static loading of tissue mimicking phantoms were conducted at the University of Michigan-Ann Arbor (114).
- ❖ In 1995, propagation of the shear wave in the homogeneous phantom was recorded by MR imaging in the University of Michigan and Artann Laboratories (115).
- ❖ In 1996, Muthupillai R (116) developed a modified phase contrast gradient echo sequence for motion-sensitizing cyclic gradient waveforms. In 2006, Maderwald S *et al.* (83) designed a multiecho phase-contrast gradient echo sequence to accelerate MRE acquisitions.
- ❖ In 2002-2003, Braun J *et al.* (68) and Weaver JB *et al.* (117) respectively used a single shot echo planar imaging (EPI) with spin-echo sequence and gradient-echo sequence to accelerate the scan time. In 2006, Kruse SA *et al.* (69) studied the mechanical properties of the brain using fast EPI based 3D MRE.
- ❖ In 2006, Klatt D *et al.* (70) combined steady-state free precession sequence with fractional MRE for rapid measurement of liver stiffness in vivo.
- ❖ In 2007 Rump J *et al.* (84) introduced fractional MRE, in which the motion encoding gradient with duration shorter than the vibration period was utilized for fractional encoding of harmonic motions. Soon after, Klatt D *et al.* (85) developed a multifrequency MRE for the simultaneous acquisition of multifrequency vibrations along one spatial dimension within one temporally resolved MRE experiment.
- ❖ In 2013, Klatt *et al.* (86) developed sample interval modulation-MRE to improve MRE efficiency and shorten the acquisition time. MEG along 3 encoding directions with different starting time was performed to simultaneously encode 3-directional tissue displacement into the phase of MR signal. Then displacement information at each encoding direction can be fully recovered from harmonics to calculate stiffness using Fourier transform on the phase offset.
- ❖ In 2014, Yin *et al.* (87) proposed a diffusion-MRE technique in which MRE and diffusion-weighted

imaging images were simultaneously acquired to provide complementary information about tissue mechanical properties and structural characteristics. In 2017, Yin *et al.* (88) expended this technique to perform DTI and MRE simultaneously.

- ❖ In order to accelerate the acquisition time, Ahmad *et al.* (89) in 2016 proposed a compressed sensing MRE, in which utilized composite regularization with a constant magnitude to recover phase images for estimating the stiffness, and in 2017, Guenther *et al.* (90) developed a simultaneous multislice MRE technique, largely relies on the total number of receiver coils available and their complex sensitivity profiles.
- ❖ In 2021, Xi *et al.* (71) used spiral staircase for 3D brain MRE.
- ❖ Multifrequency MRE (tomoelastography) (k-MDEV algorithm), a milestone within the MRE community, was invented by Tzschätzsch *et al.* (91). This method results in compound maps of wave speed, which reveal variations in tissue elasticity in a tomographic fashion. Three models including Voigt, Maxwell and spring-pot models are commonly used, especially the spring-pot model with better representing soft-tissue behavior in the frequency range of MRE (118).

Inversion algorithm

- ❖ Local frequency estimation invented by Knutsson *et al.* (119) in 1994 is the basis of the commercial MRE from Resoundant. This inversion algorithm calculates only local wavelength or wave speed.
- ❖ Linear inversion solves a linear minimization problem by assuming that stiffness variables as the unknowns are linearly dependent. This method results overdetermined matrix system, which is solved by least-squares matrix inversion. Manduca A *et al.* (120) in 1996 presented a local frequency estimation, which utilizes the local spatial frequency of shear waves to estimate the shear modulus via a wave velocity equation under assumptions of local homogeneity and incompressibility. This method is suitable for regions where the elastic properties do not vary significantly. In 2007, Rouviere O *et al.* (49) introduced a local direct inversion, which utilizes the curl operator to eliminate the compressional component and the unknown shear modulus is estimated directly from measurement data via direct inversion of a Helmholtz-like equation with a local homogeneity assumption.
- ❖ Nonlinear inversion was initially developed by Van

Houten *et al.* (121) in 1999 to improve the estimations for elastography maps of viscoelastic or poroelastic parameters via solving a nonlinear constrained minimization problem. This method only considers displacement fields that satisfy the governing equations. Therefore, it is strongly dependent on model assumptions such as initial stiffness values and boundary conditions.

- ❖ In 2018, Murphy MC *et al.* (122) used artificial neural networks to inversion of MRE data to estimate stiffness.

History of clinical application

Liver

- ❖ MRE was originally developed for liver imaging (49). In 2006, Huwart *et al.* (123) initially studied the feasibility of MRE for determining the stage of liver fibrosis. In 2007, Yin M *et al.* (124) obtained preliminary estimates of the sensitivity and specificity of the MRE in diagnosing liver fibrosis. Their results provided continued motivation for further evaluation of hepatic MRE in patients with suspected hepatic fibrosis. In 2016, Meissner *et al.* (125) used MRE to assess the treatment response in HIV and HCV patients with simtuzumab.
- ❖ In 2009, Talwalkar *et al.* (126) performed a preliminary study on measuring spleen stiffness in patients with chronic liver disease and found that portal hypertension increased the stiffness of liver and spleen. They concluded that MRE could be used as a quantitative method for predicting the presence of esophageal varices in patients with advanced hepatic fibrosis.
- ❖ In 2008, Venkatesh *et al.* (127) performed a study including 44 patients with benign or malignant tumors. The preliminary results showed that malignant tumors were stiffer than healthy liver and benign tumors similar with the healthy liver. In 2017, Thompson *et al.* (128) assessed tumor aggressiveness with MRE and found the stiffness of poorly differentiated hepatocellular carcinomas was significantly lower than well/moderately differentiated hepatocellular carcinomas. In 2019, Shahryari *et al.* (129) applied tomoelastography to map quantitatively the solid-fluid tissue properties of soft tissues and found that tomoelastography could distinguish between benign and malignant liver lesions with high sensitivity based on stiffness.
- ❖ In 2014, Chen *et al.* (130) used MRE to assess treatment response with laser ablation. In 2017, Gordic *et al.* (131)

evaluated the efficacy of yttrium radioembolization in patients with hepatocellular carcinomas. In 2021, Marticorena Garcia *et al.* (132) used tomoelastography to longitudinally evaluate viscoelasticity changes in the liver and in renal allografts after direct-acting antiviral treatment in kidney transplant recipients with chronic hepatitis C virus infection and suggested that tomoelastography can be used to monitor the therapeutic results of HCV treatment based on hepatic and renal viscoelastic parameters.

Breast

- ❖ In 1998, Lawrence *et al.* (133) initially reported the MRE technique for the breast in healthy volunteers and demonstrated that the shear modulus of glandular tissue was 4- to 7-fold higher than the fat.
- ❖ In 2003, Lorenzen *et al.* (134) studied the changes of shear modulus in fibroglandular tissue based on menstrual cycle with MRE and revealed significantly periodic changes.
- ❖ In 2002, Lorenzen *et al.* (135) performed a preliminary study with MRE in patients with neoplasms and demonstrated that malignant lesions had a mean elasticity much higher than benign lesions. In 2007, Sinkus *et al.* (136) found that malignant lesions with more aggressive features may exhibit more liquid-like behavior. In 2018, Balleyguier *et al.* (137) found that the phase angle was an important parameter in predicting malignancy.

Kidney

- ❖ In 2011, Rouviere *et al.* (138) evaluated the feasibility and the reproducibility of renal MRE in healthy volunteers. In 2012, Lee *et al.* (139) demonstrated the feasibility of MRE on renal transplant and supported known multifactorial influences on renal stiffness. In 2016, Marticorena Garcia *et al.* (140) confirmed that renal stiffness was significantly lower in recipients with nonfunctioning transplant using multifrequency magnetic resonance elastography.
- ❖ In 2018, Prezzi *et al.* (141) explored the feasibility of MRE for characterizing indeterminate small renal tumors and found that the viscoelastic parameters had diagnostic potential for distinguishing renal oncocytoma from clear-cell renal cell carcinomas.
- ❖ In 2018, Marticorena Garcia *et al.* (142) applied tomoelastography to measure normal renal stiffness in adults and found that this modality could provide

full field of view maps of renal stiffness with highly detailed resolution. In 2019, Marticorena Garcia *et al.* (143) first performed renal subregional analysis for the medulla, inner cortex, and outer cortex in patients with lupus nephritis using tomoelastography and compared with other MR modalities. They summarized that tomoelastography can be used to detect the nephropathy in patients with lupus nephritis and had a better diagnostic performance than BOLD and DWI. In the same year, Lang *et al.* (144) evaluated renal stiffness changes in patients with IgA nephropathy using tomoelastography and further confirmed that this modality had high diagnostic accuracy for IgA nephropathy and positively correlated with estimated glomerular filtration rate.

Pancreas

- ❖ In 2015, Shi *et al.* (145) evaluated the feasibility of 3D MRE to determine the stiffness of the pancreas in healthy volunteers. The results showed that 3D pancreatic MRE provided promising and stable stiffness measurements throughout the pancreas. In 2018, Wang *et al.* (146) certified some predictive accuracy of MRE in detecting and classifying chronic pancreatitis.
- ❖ In 2019, Serai *et al.* (147) studied the feasibility of MRE in pediatric patients and found that stiffness in patients with acute recurrent pancreatitis or chronic pancreatitis decreased comparing to healthy controls.
- ❖ In 2020, Marticorena Garcia *et al.* (148) performed subregional analysis of pancreatic head, body and tail with tomoelastography in patients with pancreatic ductal adenocarcinoma and found that tomoelastography provided a quantitative imaging marker for tissue stiffness depicting pancreatic ductal adenocarcinoma boundaries. In 2021, Zhu *et al.* (149) investigated the stiffness and fluidity of pancreatic ductal adenocarcinoma and autoimmune pancreatitis with tomoelastography and made a conclusion that both pancreatic stiffness and fluidity can be used to differentiate between pancreatic ductal adenocarcinoma and autoimmune pancreatitis with high accuracy. Gültekin *et al.* (150) used tomoelastography to assess the prediction of tumor aggressiveness in patients with pancreatic neuroendocrine tumor and confirmed that tomoelastography could predict the greater tumor aggressiveness by increased stiffness and was positively correlated with PET derived asphericity.

Brain

- ❖ In 2008, Kruse SA *et al.* (151) used MRE to obtain estimates of the shear modulus of human cerebral tissue in healthy adult volunteers. In 2013, Murphy *et al.* (152) measured the characteristic topography of brain stiffness with MRE and found that test-retest repeatability with errors of 1% for global stiffness and 2% for stiffness in the lobes of the brain. In 2016, Johnson *et al.* (99) reported that the repeatability error in measuring stiffness in subcortical gray matter was 3-7%. In 2019, Yeung J *et al.* (153) performed study with multifrequency MRE to characterize the brain tissue stiffness in children compared with adults.
- ❖ In 2010, Wuerfel *et al.* (58) first applied MRE to measure the brain stiffness in a disease state and showed brain stiffness was decreased in patients with MS compared with age-matched controls. In 2011, Murphy *et al.* (154) performed MRE studies focused on neurodegenerative disease and reported the similar results in subjects with Alzheimer disease. In 2017, Elsheikh *et al.* (155) compared brain stiffness changes in 4 classes of dementia with MRE and demonstrated stiffness changes in different regions.
- ❖ In 2007, Xu *et al.* (156) first introduced MRE to assess intracranial tumor's stiffness and showed large variability in viscoelasticity. In order to explore the adherence of the tumor to the surrounding tissue, Yin *et al.* (157) developed a MRE-based slip interface imaging for evaluation of vestibular schwannomas in 2015, based on the assumption that a discontinuity will be created when a shear wave propagate across the boundary.

Prostate

- ❖ In 2004, Kemper *et al.* (158) initially assessed the technical feasibility of *in vivo* MRE of the prostate gland and acquired a successful MR data.
- ❖ In 2011, Li *et al.* (159) investigated the feasibility of MRE in the diagnosis of prostate cancer at 3.0T and found that the significant differences in stiffness exist between prostate malignant and benign tissues.

Lung

- ❖ In 2006, Goss *et al.* (160) performed lung MRE study and provided preliminary evidence that MRE can be used for assessing the regional mechanical properties of the lung. In 2014, Mariappan *et al.* (161) developed a rapid MRE technique to quantify the respiration-dependent shear stiffness of lung parenchyma. The

preliminary data demonstrated clinically feasibility.

- ❖ In 2017, Marinelli *et al.* (162) quantitatively assessed the stiffness of pulmonary fibrosis in patients with fibrotic interstitial lung disease and showed that parenchymal shear stiffness was increased compared to healthy volunteers at both residual volume and total lung capacity.

Heart

- ❖ In 2008, Elgeti *et al.* (163) investigated the feasibility of MRE for measuring pressure-related left ventricular function parameters and reported similar results with invasively determined left ventricular pressures. In 2014, Elgeti *et al.* (164) used MRE to diagnose myocardial relaxation abnormalities in patients with diastolic dysfunction and found that the decrease in shear-wave amplitudes within the left ventricular region correlated with the severity of diastolic dysfunction.
- ❖ In 2017, Sui *et al.* (33) developed a MRE technique with reduced field of view in healthy volunteers. The results showed reducing ghosting artifacts and improving image quality significantly compared to the conventional full field of view acquisition.

Vessel

- ❖ In 2013, Xu *et al.* (165) performed gated cine MRE to assess the mechanical properties of the abdominal aorta wall. The images at different phases of the cardiac cycle were reconstructed from acquired data throughout the cardiac cycle and the differences in aortic wall stiffness between diastole and systole were calculated.

Muscle

- ❖ In 2001, Dresner *et al.* (166) used MRE to quantify the changes in stiffness of skeletal muscle with loading *in vivo* and provided a useful method for studying muscle biomechanics.
- ❖ In 2010, Klatt *et al.* (167) developed a multifrequency MRE to investigate the viscoelastic properties of human skeletal muscle in different states of contraction.
- ❖ In 2019, Zonnino *et al.* (168) introduced a multi-muscle MRE to quantify force for each muscle in the forearm during application of isometric wrist torques and laid a foundation for investigating the neuromuscular control of coordinated motor action.
- ❖ In 2019, Schrank *et al.* (103) introduced a real-time MRE to measure the changes of viscoelastic parameters induced in different groups of skeletal muscles of the

lower extremity during dynamic exercises.

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