NON-GAUSSIAN SIGNAL NOISE IN
MAGNETIC RESONANCE ELASTOGRAPHY

by

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ABSTRACT

Introduction

Magnetic resonance elastography (MRE) is a phase-contrast MRI technology that creates mechanical property maps of the brain in vivo through induced vibration. Signal noise often degrades the quality of reconstructed images and is a limiting factor in developing higher resolution images. While gaussian noise can be filtered during processing, MRE data also contains non-gaussian random noise which is more difficult to correct. Thus far, signal noise has not been thoroughly investigated in MRE. Several different factors have been proposed to contribute to signal noise in MRE including head motion, cardiac cycle, respiration, and table motion. The purpose of this thesis is to quantify different sources of signal noise that degrade the quality of images in MRE. The ability to understand and evaluate sources of noise will allow for the improvement of MRE as a tool for brain health.

Methods

To analyze head motion effects, each subject received three separate MRE scans: (1) both motion encoding gradient (MEG) and vibration off, (2) MEG on and vibration off, (3) both MEG and vibration on. A subject received this protocol twice – one scan with the head restricted with foam pillows (Head Restricted MRE) and the second set without the pillows (Traditional MRE) to compare motion noise. To analyze effects of the cardiac cycle, scans were acquired with 8 slices and 250 repetitions. The subject’s head was secured with foam pillows to limit bulk movement and individual wore a pulse oximeter device to record the cardiac cycle while the motion encoding gradient was recorded through an Arduino device. After scanning, the pulse oximeter data was aligned with the motion encoding gradient and noise data
to assess the differences in volume of noise depending on where a person was in the cardiac cycle when the MEG was played. Lastly, in order to understand how non-gaussian noise impacts the mechanical property estimation procedure, the correlation coefficient was computed for a voxel in relation to the entire image. Plotting the correlation coefficients in-plane and out-of-plane, a line of best fit was found in order to compute the correlation length. This process was performed for the three subject’s data in the head motion MRE experiments where (1) MEG was turned on and Vibration off and (2) when the MEG was turned on and the Vibration was on. Thus, the average correlation length in-plane and out-of-plane could be a metric to determine the extent non-gaussian noise corrupts MRE images.

**Results**

Overall noise was seen to be reduced when a human subject’s head was packed within the head coil during the MRE scan. During the vibrational scan, a larger amount of noise was observed in the y-direction, likely due to the restriction of movement in the x and z directions. Packing reduces the amount of non-gaussian signal noise present and thus decreases the spread of the signal noise, which can likely improve the capabilities of filtering techniques. In the cardiac cycle assessments, the standard deviation and average noise was greatest in the first cardiac bin. These images likely correspond to systole, meaning motion encoding at the peak of systole leads to the most inaccurate image.

In the correlation experiments, noise was observed to be more correlated in-plane than out-of-plane. Upwards of 8 pixels was computed as the average correlation length in plane. These differences are likely due to the way the images are acquired, such that adjacent voxels in the plane of the image most likely experience similar non-
gaussian sources of signal noise, and thus are very related to one-another. Because
NLI uses a 10x10 block of pixels to estimate mechanical properties, noise that is
highly correlated in-plane may cause errors that current gaussian filtering techniques
do not account for.

**Conclusion**

This is the first report to characterize sources of signal noise in MRE. By
individually assessing image, physiological, and vibrational noise, it can be seen how
non-gaussian sources of noise lead to errors in mechanical property calculations. The
use of foam pillows to restrict left-right head movement may be a physical technique
to reduce the volume of signal noise and improve the signal-to-noise ratio of data.
Identifying that physiological noise closely follows the cardiac cycle demonstrates
how harmonic movement outside of induced mechanical vibration can alter the wave-
propagation of MRE and thus alter the data used to calculate mechanical properties.
Recognizing this is an error that occurs periodically can lead to techniques to filter or
remove cardiac pulsation noise. Lastly, calculating correlation length in-plane and out-
of-plane of noise can assist in researchers developing better techniques to optimize
NLI. The ability to identify and characterize the nature of signal noise in MRE will
allow for the translation of MRE to be utilized clinically in the brain.
Chapter 1

INTRODUCTION

1.1 Overview & Motivations

1.1.1 Magnetic Resonance Elastography

Elastography is the general application of palpitation to measure tissue mechanical properties. Harmonic mechanical motion is induced in a region of interest, which causes incremental tissue motion, which relates to intrinsic mechanical properties that are used to quantify tissue integrity. [1]–[4] Magnetic resonance elastography (MRE) is an MRI technique to noninvasively visualize mechanical properties of tissue. It generally involves imaging the propagation of acoustic waves using an adapted MRI pulse sequence.[2], [3], [5]

MRE is currently clinically used to assess liver fibrosis, which is the stiffening of the tissue and is associated with diseased organ states. Fibrosis occurs due to increased collagen deposition which stiffens the tissue.[6] Liver biopsy, an invasive procedure, is traditionally used to determine the extent of liver fibrosis. Instead, MRE is a noninvasive way to diagnose liver fibrosis as it can measure tissue stiffness.[6] In research, MRE has also been extensively explored in other organ systems, including the heart, breast, skeletal muscle, and lungs. [5]

Because of the difficulty to physically assess mechanical properties of brain tissue, MRE has been utilized to non-invasively measure these physical properties. Traditional MRI scans of the brain evaluate the degree of physical changes in the brain
while mechanical properties of the tissue typically can only be assessed in neurosurgery.[5] Thus, MRE is proposed as an easier, noninvasive alternative to better understand measures of both healthy and diseased states.

1.1.1.1 MRE of the In Vivo Brain

Brain tissue is viscoelastic, meaning it exhibits both elastic and viscous behaviors. Viscous materials resist shear flow and strain while elastic materials will resume original shape after a strain is removed. Brain tissue experiences both behaviors when it is deformed. Viscoelastic properties assessed in the brain include shear stiffness and the damping ratio, which can vary across species, populations, ages, and regions within a brain.[7] Stiffness is defined as the measure of degree of rigidity and ability to deform. Meanwhile, the damping ratio is the level of energy dissipated after a deformation. [8] Mechanical property assessments can be completed on an entire brain scale as well as in different regions including white matter tracks, gray matter structures, and brain lobes.[9] Different changes in the brain such as inflammation, myelination, and demyelination are associated with these mechanical properties.[5] Myelin sheaths coat nerve fibers and are important in signal propagation in neurons. Myelination is the creation of these protective sheaths, which align with childhood development.[10] Meanwhile, demyelination is associated with the loss of myelin sheaths and is associated with neurological disorders such as multiple sclerosis and Alzheimer’s disease. Tissue stiffness is hypothesized to be associated with the amount of myelin present, with higher stiffness associated with greater myelin content.[7] Because of the important role myelin plays as a biological marker of brain health, MRE can indirectly assess brain integrity.
1.1.1.2 MRE Acquisition

The first step to acquire MRE data is to generate a source of motion, known as actuation. Examples of actuators include electromagnetic, acousto-mechanical, pneumatic, and piezoelectric sources. Each of these methods transmit the vibration to the head via a passive driver. Different types of passive drivers utilized include a bite-bar, head cradle, and soft pillow. In the pneumatic actuator design, a pillow-like device is placed under a subject’s head in the head coil (Figure 1). The pillow is connected to tubing going to the passive driver, which is in the control room. Compressed air is transmitted to the passive driver pillow. The compressed air is delivered at a set frequency typically between 10-100 hertz (Hz), causing the head to move in a nodding motion.[5] The lower frequency waves weaken less rapidly than higher frequency range, thus the ability to see deeper regions but at a lower signal. Higher frequencies have a shorter wavelength and can provide higher spatial
resolution. The appropriate frequency which maximizes these trends typically ranges between 50-60 Hz. The tissue displacement induced in brain tissue is then normally around 5-50 µm. [5]

Unlike traditional MRI, MRE employs an additional motion encoding gradient (MEG) to encode the spatial position of spins in voxels within a tissue. The MEG spatially maps and measures the displacement that is caused by the wave propagation through encoding the trajectory of the spins into the accumulated phase. It is necessary for the motion to be synchronized with the MEG such that protons are synchronized with vibrational movement. This event causes the polarity to change and accumulate phase. This synchronization is changed to image how waves propagate through a series of phase offsets. A typical sequence normally has four or eight phase offsets. This process of inducing phase then needs to be scaled to encode an entire 3D wave field in order to map the wave propagation. Therefore, MEG encoding occurs in three directions: readout (x), phase-encode (y), and slice (z). [5], [9]

Various pulse sequences have been developed to capture the tissue displacements. These sequences record changes in phase while maximizing SNR through sampling k-space in different ways. Single-shot spin-echo echo planar (EPI) is one sequence that is implemented.[11]–[13] In an EPI sequence, the readout MEG samples k-space in a zig-zag pattern along the horizontal axis while phase encoding occurs vertically. EPI is very common because it acquires data in a relatively short amount of time. However, the sequence is prone to distortion because it has a longer read-out time and thus does not maximize the SNR. To counteract this problem, 3D multi-shot multi-slab spiral EPI has been developed. [9] This novel technique requires shorter scan time by incorporating multiple 3D volumes (slabs) that cover the entire
brain. Furthermore, k-space is sampled in a spiral in this sequence rather than horizontally, so read out time is reduced. The technique also incorporates navigators to correct for phase shifts and motion-induced errors.

1.1.1.3 Mechanical Property Calculations

After an MRE scan is complete, the raw phase images undergo pre-processing to reduce noise. The phase images are then Fourier transformed to acquire the frequency domain complex displacement field and isolate the vibrational harmonic motion. High-pass filtering is also incorporated to further remove low-frequency bulk waves, so only high-frequency shear waves remain. [9]

After pre-processing, the raw images are then entered into the algorithm. Multiple equations are implemented to model the wave motion and be able to translate it into mechanical properties, such as shear stiffness. When developing a model for viscoelastic tissue, both elastic energy storage and viscous energy dissipation must be included. Navier’s equation is utilized to incorporate this phenomenon:

Equation 1. \( G^* \nabla^2 \mathbf{u}(f) + (\lambda + G^*) \nabla (\nabla \cdot \mathbf{u}(f)) = -\rho \omega^2 \mathbf{u}(f) \)

In Equation 1, \( \mathbf{u} \) is the vector displacement field, \( \rho \) is the tissue density, \( \nabla^2 \) is the Laplace operator, \( G^* \) is the complex shear modulus, and \( \omega \) is the angular frequency. This equation can be simplified to the Helmholtz equation when it is assumed that the tissue is incompressible:

Equation 2. \( G^* \nabla^2 \mathbf{u}(f) = -\rho \omega^2 \mathbf{u}(f) \)

The tissue displacement is related to the elastic complex shear modulus \( G \). This complex shear modulus takes into account both elastic and viscous tissue properties. The complex shear modulus can be decomposed in real and imaginary components which are:
Equation 3. $G^* = G' + iG''$

$G'$ is the real part of the shear modulus which equates to the mechanical energy in the system. The imaginary component $G''$ provides a measure of dissipated energy.[5]

The complex shear modulus is related to the shear stiffness, which describes the resistance of a material to harmonic shear stress[5]. The relationship between shear stiffness and the complex modulus is described in the following equation:

$$G_s = \rho v^2 = \frac{2(G'^2 + G''^2)}{G' + \sqrt{(G'^2 + G''^2)}}$$

Several different algorithms utilize these equations to calculate shear stiffness. One technique to calculate mechanical properties is by completing a single frequency direct inversion. Direct inversion (DI) inserts measured displacements into the appropriate wave equation for a material. The technique prefilters and differentiates data to produce a linear system of equations in terms of the shear modulus, which is unknown. Viscous, anisotropic and geometric effects are all variables in the input. The inversion algorithm utilizes assumptions to develop a mathematical model of the tissue system and relates an applied stress to a resulting strain for a homogenous, linear, viscoelastic material. [1] Equation 2 relates measured displacements directly to the complex shear modulus, $G^*$. [5] There are several limitations to using DI. DI is highly susceptible to noise because it uses 2nd order Laplacian derivatives. It also assumes that the tissue mechanical properties are locally constant, which is not entirely accurate in brain tissue because different regions, tissues, and microstructures possess different anisotropic and viscoelastic properties.

Nonlinear inversion (NLI) using finite-element models is an alternative technique to solve for mechanical property parameters (Figure 2).[14] The elastogram
is generated by iteratively updating a model of tissue. Each iteration attempts to minimize the difference between the experimental measure and the prediction. The entire system is divided into overlapping subzones to reduce computation time. Different finite elements and meshes are used to support the displacement and mechanical properties. One mesh utilized is the displacement mesh, which is a 27-node quadratic which reduces the computational load of the forward problem. Another mesh utilized is the property mesh which represents heterogeneous material properties with 8 nodes.[14] These nodes are arranged in a rectangular grid. The property mesh provides values for displacement so property estimates are subsequently made. [14]

To solve the forward problem, property meshes are sized to overlap the complete displacement mesh. The approximation for the entire system is calculated when the calculated displacements that are predicted from the forward problem agree with the measured displacements.[5] The NLI algorithm allows calculation to be completed beyond the assumption of linear elasticity and viscoelasticity. However, NLI can take several hours to compute mechanical properties while a DI algorithm would take a couple of seconds.

Figure 2. Diagram of NLI Process. Mechanical shear wave maps are entered into the algorithm which then iteratively estimates the stiffness of the tissue.
1.1.1.4 Applications

MRE has been a useful tool for assessing various aspects of human health, aging, and disease. Results from MRE have been standardized in order to represent the same mechanical properties. Standardized values of shear stiffness exist for the global brain as well as grey and white matter (GM and WM). Values for shear stiffness across varying levels of vibration of the global brain range between 0.62 kPa – 2.99 kPa.[5] For studies using 50 Hz vibration, the mean shear stiffness was found to be 2.07 kPa ±- 0.42 kPa. The relationship between stiffness and vibration frequency is a regression. WM is typically stiffer than GM, with the modulus of WM to be 1.877 kPa and GM modulus reported to be 1.216 kPa.[15] Mechanical properties have also been assessed regionally. WM has been shown to be softer than the corpus callosum and the corona radiata.[16] The corticospinal tract (CST) was observed to be twice as stiff as WM.[17] Furthermore higher values of the storage modulus have been reported within the brainstem relative to cerebral or cerebellar tissue.[9] The putamen was demined to be the stiffest structure out of the seven subcortical GM structures. Additionally, viscoelasticity of subcortical gray matter structures also differ from global viscoelastic properties.[18]

MRE has also been utilized to study trends in various healthy and diseased populations, helping characterize the effects of aging as well as disease on the brain. MRE has been used to determine the malignancy of tumors as an alternative to biopsy during surgery. Thus the technique can serve as an assessment tool for surgeons to utilize the correct equipment during removal surgery.[19] MRE is also utilized to study diseased states in older populations. MRE has been utilized to study changes in elastic properties of brain tissue due to Alzheimer’s disease. MRE can become an invaluable tool to providing insight on the mechanisms of memory loss of Alzheimer’s
disease. Specifically in the brain parenchyma, a decrease in stiffness was observed in Alzheimer’s patients relative to healthy population of the same age (Figure 3A).[20] Stiffness decline in Alzheimer’s disease has been observed across the cerebral cortex, specifically reported in the middle and superior temporal gyri and precuneus.[21] Furthermore, MRE has been used to study changes in the adolescent brain. In a study focusing on adolescents 12-14 years old, the temporal and parietal cerebral lobes were softer in adolescents relative to adults (Figure 3B). Meanwhile, subcortical gray matter structures and the putamen were stiffer in adolescents while the hippocampus and amygdala were less stiff.[22] These stiffness trends can be used to evaluate development of brain structure throughout adolescence.[22]

Figure 3. (A) Comparison of younger and older adult stiffness.[23] (B)(C) Comparison of Adolescent and Adult stiffness in brain regions.[22] Significant between populations indicated with star.
MRE has a wide variety of applications in assessing brain health. It is a tool for studying development and aging in addition to various pathological states. As a noninvasive technique to assess brain mechanical properties, MRE can help assess aging and predict the onset of diseased states in the brain. Because of its potential, it is necessary to develop the technique such that it can be translated into a clinical population. Further understanding what causes lower-quality images, can help the development of MRE for evaluating brain health.

1.1.2 Signal Noise in MRI

Signal noise can be defined as deviations from the true signal that are captured during the transmission and acquisition processes of MRI. In an MRI, the manipulation and motion of hydrogen atoms (spins) in a region of interests is recorded in k-space. In post-processing, these frequencies are translated in physical spatial value. During the acquisition, low-frequency phase shifts cause signal noise to occur, due to field inhomogeneity, susceptibility, and flow.\[24\] \[25\] The output images contain both real and imaginary components of signal. The real and imaginary aspects of MR raw data not only contain desirable signal but are corrupted by additive noise that are recorded in the scanning process.\[26\], \[27\] Because the noise is baked into the image it is very challenging to identify what is the true signal and what is noise.

Instead of calculating the volume of noise present in an image, noise is often expressed as a ratio relative to the signal of an image. To compare the signal to the noise present in an image, the signal-to-noise ratio (SNR) is utilized. A higher SNR is associated with a better-quality image. While it is common to utilize this ratio, some work reverses the comparison in order to better conceptualize the volume of noise in
an image. In this alternative ratio, the inverse is true, as a higher value ratio is associated with a lower quality image.

The unwanted aspects of the acquired signal can be conceptualized in multiple ways. Background noise, which is predominately found outside of the region of interest, is commonly identified. This type of noise occurs due to the thermal agitation of subject and the electronics of the MR system. The background noise contains radiofrequency (RF) noise due to contact between metal components and RF noise from the external environment.[28] Engineering efforts to optimize sequences and implement band pass filters have been implemented to minimize the effects of background noise.[29] Filtering in post-processing removes the frequencies outside the spatial frequency of interest and thus reduces the level of background noise.[30]

Gaussian noise is an assumption that has been widely incorporated in MRI post-processing techniques (Figure 4). Many filters falsely assume that all noise present is gaussian.[31]–[33] Gaussian noise means the distribution of noise fits a Gaussian probability distribution function.[31] Gaussian noise specifically arises from receiver electronics and are viewed as factors that are additive to the signal. During image reconstruction, noise can also be fitted with other distributions such as Rician or non-central Chi distributions. Rician noise is noise fitted with a Rayleigh distribution in the background and approximated by Gaussian noise in the foreground where signal is present.[34] Each model can be adjusted for stronger fit by applying various filtering techniques.[34] More complex imaging techniques, such as parallel imaging and multichannel acquisition, can model the noise by noncentral x-distribution, Rician, or 𝜒-distribution. [34]. Although noise can be represented by other statistical distributions, it is most common to assume a gaussian distribution, which does not
accurately model the signal noise in the image. Any noise that does not follow this random distribution is considered to be “non-gaussian”.

Gaussian White Noise

Figure 4. Comparison of a brain slice with minimal signal noise (left) and added simulated gaussian noise. Simulated noise added at various levels of standard deviation.

Motion induced noise is another significant factor influencing the quality of MRI images. In regions of low signal, MR technology is extremely sensitive towards motion induced noise. In scans that are based on a time series of images, movement can cause errors in the images. When the subject moves in the scanner, the signal of interest changes from its initial state, thus motion-related artifacts occur. Therefore, longer acquisition and repetition times result in greater potential for subject movement. Movement artifacts will then typically appear as ghosting or blurring. [35] The phase of an image is more susceptible to motion changes because it observe the changes in the spins over time. Any changes due to bulk motion will lead to inaccuracies in observing desired changes. In structural scans, these artifacts do not cause as many errors, as the scans are not dependent on observing the change of phase in an image. The images are also often very high resolution, so a higher SNR is achieved. However, head motion can still compromise volumetric measurements. [35]
It has been well documented the effects of head motion in techniques that observe changes in the brain over time, such as fMRI. [28], [36] Head motion can lead to signal changes, potentially causing errors in interpreting which regions of the brain are active during task-based fMRI scans. [35] Similar motion-induced errors also occur in diffusion-weighted MRI imaging (DWI), which observes the directional variation of molecular diffusion. Because the technique also has a long acquisition, with repetition time (TR) up to 10s, the technique is extremely sensitive to motion. Diffusion tensor imaging (DTI) has greater acquisition times than DWI so it suffers an even greater sensitivity to motion. [35]

Other MRI noise is present in images as well. However, post-processing tools and sequences have been developed to mitigate the effects of these sources of signal noise. For these secondary sources of signal noise, their effect on the outcome of MRI are minimal or filtered out and thus are not necessary to isolate and study.

1.1.3 Physiological Noise in MRI

Several MRI techniques utilize a time series of images, including fMRI, diffusion MRI, and MRE, the topic of the thesis, in order to observe and measure change. In these scans, the change in phase of a series of spins is observed. The desired effect is that when a gradient is applied, all spins phase identically. However, physiological influences can impact the velocity of spins in a space, causing the observed phase to change.[37] For MRI techniques which record in a time series and utilize motion encoding through the phase image, physiological noise is another factor that affects the quality of images. Relevant literature has identified the biological influences of physiological noise as well as proposed techniques to circumvent its affects. Subject motion, cardiac pulsation, and respiratory activity to alter the tissue
composition of each voxel due to a change in positioning and thus magnetic field fluctuations occur.[28]

The cardiac cycle is a predominant aspect of physiological noise as cardiac pulsation leads to brain motion. The process can be divided into two parts: diastole and systole. In diastole, the blood vessels return blood to the heart in preparation for the next ventricular contraction. Diastole begins with the closing of the aortic or pulmonic valve and ends with closing of the mitral or tricuspid valve. Meanwhile, during systole the mitral or tricuspid valve closes and it concludes with the ventricular contraction that forces blood in to the arteries. [38] The energy propelling blood into the ventricle during diastole comes from the potential energy stored in the elasticity of the blood vessels. In systole the heart forces this blood into the system or pulmonic systems. [38] This rhythmic process of changing pressure and volume of the heart are represented graphically in a Wiggers diagram (Figure 5C).[38]

Figure 5. (A) One interval for ECG signal.[39] (B) Comparison of ECG and pulse-oximeter signals.[40] (C) ECG signal with changes in atrial and ventricular pressure over two cycles.[41]
Measurement of heart contraction and relaxation can be measured using medical devices (Figure 5A). An electrocardiogram (ECG) records the spread of electricity through the heart during each cardiac cycle. Electrodes are placed on the patient’s skin and are connected with cables in order to record electrical activity. Each information from a cable allows the ability to have a unique view of the electrical waveform of the heart. The pattern of activity produces a signal corresponding to electrical activity of the heart and thus heart rhythm. [42] Meanwhile, pulse-oximetry is an indirect measure of cardiac pulsation (Figure 5B). Pulse oximetry utilizes the concept that oxyhemoglobin and deoxyhemoglobin absorb red and near-infrared (IR) light differently. [43] The device has a sensor placed over the fingernail that reads red and near-IR light. The levels of red and IR light absorbed fluctuate with the cardiac cycle because arterial blood volume increases during systole and decreases during diastole. [43] The ratio of absorbance in red to IR correspond to oxygen saturation in the blood and can be plotted. Peak oxygen saturation occurs when the blood volume peaks during systole. [43] Both technologies measure the cardiac cycle, but utilizing different aspects of the cardiac cycle. Delays between the two measurements are due to technical and physiological delays as pulse-oximetry is from the hand while ECG is directly around the heart.

Cardiac pulsation causes noise due to resultant cyclical brain motion.[44] When the heart beats, the brain is displaced to the scale of hundreds of microns.[45] The pulsatile motion has been observed to originate in the brain stem and then propagate towards the periphery of the brain.[46] Displacement of brain structures varies regionally, with peak displacement experienced by the brain stem and the smallest intracranial displacement in the occipital lobe. [46] Pulse-oximetry can be
implemented to record the oxygen content in blood as a measure cardiac cycle. ECG can also be utilized to measure heart activity at 1.5T MRI; however, the leads are susceptible to noise interference from the gradients.[47]

Cardiac pulsation has been observed in various MRI techniques. The cardiac cycle influences the quality of MRI techniques that require a time series of images, which have greater sensitivity to pulsation. For example, fMRI measures levels of deoxyhemoglobin in the blood, referred to as the Blood Oxygenation Level Dependent (BOLD) signal, as an indirect measure of brain activity.[48] Blood oxygenation changes due to the cardiac cycle would interfere with the BOLD signal. Some regions of the brain are more susceptible to this cardiac noise, such as large vessels, white matter, and ventricles. [28] In diffusion weighted MRI and diffusion-tensor imaging (DTI) the cardiac cycle causes phase errors. [37] The pulsatile motion during systole causes larger displacements of water molecules which can alter diffusion measures.[49] White matter tract directions observed in DTI can be altered by induced pulsatile motion. Cardiac gating can be implemented as a method to mitigate these effects. [49]

Respiration is another smaller source of error in MRI. Respiration, like cardiac pulsation, displaces the brain an incremental amount and thus contributes to bulk motion effects.[28], [36] In fMRI, the expansion and contraction of the chest cavity causes bulk changes in magnetic susceptibility which give rise to changes in the phase of the image.[28] Breath holding has been utilized in fMRI studies in order to reduce motion artifacts effects, but some studies have observed indiscernible changes between having a test subject breathe normally and control breathing. [50]
Several sources of physiological noise influence MRI data that is acquired as a time series. Repeated images of the same slice are dependent upon measured changes and thus are more susceptible to physiological influences, which include bulk motion and the cardiac cycle. Other physiological influences exist, such as breathing, but have smaller affects than more dominant sources of noise, which would be of primary interest.

### 1.1.4 Signal Noise in MRE

Signal noise arises from several different sources. Additional noise in MRE arises because the scan is a time series rather than a singular image of a slice captured in a moment. MRE is also particularly susceptible to bulk motion artifacts because any changes in the wave propagation will lead to inaccuracies in NLI. Additional challenges of MRE in the brain include the structural limitations of the skull, meninges, and cerebro-spinal fluid, which shield the ability for waves to propagate.[51], [52] This shielding can affect wave propagation, thus leading to lower SNR images. Achieving high SNR is important to accurately generate stiffness maps.

Signal noise in MRE can be assessed through three primary divisions: image noise, physiological noise and vibrational noise. Image noise is the largely gaussian noise present in all images, often due to the mechanical and electronic imperfections.[53] Physiological noise is also present as well. Because MRE utilizes the MEG, the scans are susceptible to physiological causes of motion, such as from the cardiac cycle and respiration. MRE captures a time series of images in order to observe changes in wave displacement from the vibration. Multiple images captured can observe the change in motion through the change in the phase image over time. Thus, non-gaussian sources of noise are present and are not from simply basic
hardware and software errors. These different sources include bulk motion, cardiac cycle, and respiration. Lastly, vibrational noise is signal noise that occurs due to induced mechanical vibration. This signal noise is unique to MRE. Vibrational noise compounds the effect of subject movement as the subject movement alters the nature of the shear wave propagation. It occurs due to imperfect actuation of the vibration during the scan.[9]

The most common factor that disrupts wave propagation is unwanted motion. Bulk motion can be attributed to non-physiological factors that cause additional unwanted brain movement during a scan. Patient movement and table shaking disrupt the propagation of shear waves through the brain, thus causing the input data of the nonlinear inversion algorithm to be incorrect [54]. The MEG specifically records the changes of phase in the images due to wave propagation so any subject motion will change the resulting phase images, which are then utilized to calculate mechanical properties. Meanwhile, physiological influences, which are internal factors that cause brain movement, also contribute to signal noise in MRE. Cardiac cycle and breathing inadvertently move the brain, thus altering the captured images during MRE. Typical MRE vibration displaces the brain a couple of microns while the heart beating can cause movement of up to hundreds of microns. [9], [45] This change in displacement will change the pattern of the wave propagation and thus alter the phase images of the brain. Furthermore, breathing not only causes involuntary movement, but alters blood flow and oxygenation, which could on a larger scale disrupt tissue mechanical properties. However, for MRE, breathing contributes most to motion artifacts as inhalation and exhalation move the body. [50]
In MRE processing techniques, the signal noise that is corrected is assumed to be gaussian in nature, which ignores the complexity of additional sources of noise present. [55] Methods to mitigate noise involve sampling more data, which would increase the scan time. The octahedral shear strain-based measure for SNR (OSS-SNR) is used to measure the quality of images for MRE.[51] The SNR measure takes into account motion, serving as a measurement for the quality of elastograms. However, OSS-SNR measures assume Gaussian noise and miss non-Gaussian which may be more damaging.[51]

Furthermore, non-gaussian sources of signal noise, which include bulk motion and the cardiac cycle, cannot be corrected through traditional methods in MRE. Other techniques have developed methods to mitigate signal noise effects. For example, in DTI, non-single shot EPI sequences can have added navigator echoes to remove patient head motion. [56] In multi shot diffusion sequences, cardiac gating is implemented. During cardiac gating, the diffusion encoding is triggered after a cardiac cycle peak, so that data is collected only off-peak. However, because the MEG is aligned with the induced mechanical vibration, gating the MEG with the cardiac cycle causes fluctuations in the frequency of the vibration. Because the mechanical vibration is no longer a constant frequency, the subsequent shear wave propagation is inconsistent. Therefore, the data that would be entered into NLI would be incorrect. Thus, resultant mechanical property maps would have errors as they were calculated from inaccurate data.

1.1.5 MRE Noise Previous Literature

While SNR is generally used to assess signal noise in MRI, a specific measurement of SNR was developed based on the octahedral shear strain (OSS-SNR).
McGarry et al., 2011 describes the theory that was utilized to develop the measurement. Octahedral shear strain is the maximum shear strain that is in any plane for 3D vector of strain, which is appropriate to incorporate into an MRE SNR measure as the scan is motion based. The shear strain is related to the shear modulus, so noise in the strain can be used to determine the quality of the motion data. Thus, the strain can be a stronger assessment of the reconstruction accuracy than a typical SNR measurement. [51] OSS-SNR can be utilized as a measure to indicate the quality of MRE images. The measure can be taken to determine the quality of the data sets to be utilized in assessing signal noise in the study.

Several preliminary experiments focusing on MRE signal noise have been completed previously. Some work has investigated isolating image noise, physiological noise, and vibrational noise in MRE. [55] Three sequences were utilized: (1) MEG and vibration was off to observe image noise, (2) MEG turned on and vibration remained off in order to observe physiological noise, and (3) both the MEG and the vibration was turned on to assess vibrational noise. [55] The study demonstrated how physiological and vibrational noise are present in images, using quantile-quantile plots. This work was very preliminary but the methods from this study can provide the foundation for adjusting sequences to study image, physiological, and vibrational noise individually. Only two subjects were scanned as a part of this study, so a greater number of subjects can demonstrate the variability of physiological noise subject to subject. Additionally, no mechanisms were used to secure a subject’s head to prevent left-right motion during the scan, which could be tested in the future. However, none of this work has been extensive in assessing or analyzing signal noise.
Signal noise has been studied regionally in the brain, specifically in the cerebral cortex, which has complex geometries in the microstructures present. An analysis confirmed the ability of MRE to calculate mechanical properties of these microstructures through implementing simulations of the regions with adding incremental levels of gaussian noise.[57] The experiment demonstrated the limitations of NLI as it sometimes overestimated or underestimated the stiffness of different structures. The work is limited to only modelling the effects of gaussian signal noise. It is therefore necessary to develop models that contain realistic MRE noise in order to more accurately understand how noise influences NLI calculations. Thus, this work provides considerations when developing MRE simulations.

Additionally, preliminary developments have been done to improve post-processing. To improve SNR, low-rank denoising was proposed as a method to denoise MRE data. [58] The model was uses singular value decomposition to be able to salvage low SNR data to reconstruct in vivo data sets as well as MRE simulations with added gaussian noise. Low-rank denoising improved the OSS-SNR of data sets. However, as noise increased, DI reconstruction of stiffness failed while in NLI, a threshold of noise could be achieved before the data became corrupted. This study offers a technique of minimizing noise. [58] The study only focused on the addition of gaussian noise in simulations and then a subject MRE scan. Differences between these two models are due to the addition of physiological and vibrational noise, which are not represented in the gaussian noise assumption. Developing simulations with these additional non-gaussian sources of noise can help model realistic MRE conditions and thus provide realistic feedback on applying low-rank denoising.
Few extensive assessments of signal noise in relation to MRE have been completed. Conceptualizing noise in three primary categories can be implemented to isolate different sources of noise and test methods to mitigate the effects of noise. Other work on developing simulations to observe noise effects is essential to understanding the accuracy of NLI. However, there is a need understand how non-gaussian signal noise affects NLI calculations, as NLI only accounts for gaussian noise. Because MRE is dependent on the propagation of shear waves, the technique is more susceptible to physiological noise, including the cardiac cycle, than other techniques. Thus, gaussian noise is an inadequate assumption for MRE noise.

From this preliminary work, there is a demonstrated need to better define, characterize, and measure signal noise in MRE and stiffness calculations in NLI. It is the objective of my research to identify the influences of non-gaussian noise in NLI calculations. Further investigating physiological noise can help develop methods to correct and limit the amount of signal noise in MRE scans. Creating new techniques to measure as well as correct for signal noise is pertinent to implementing MRE in a future clinical setting.

1.2 Previous Literature

1.2.1 Cardiac Pulsation Effects on Diffusion Imaging

Previous diffusion studies have extensively developed methodology for isolating, measuring, and correcting for errors due to cardiac pulsation. Diffusion is a similar technique to MRE because it uses motion encoding gradients and thus has similar phase effects from physiological motion. Multishot diffusion suffers problems due to inconsistencies in phase due to various physiological noise. In the study, the
divided noise into two primary categories: (1) rigid body noise when a person shifts, and (2) non-rigid body noise which was assumed to entirely consists of cardiac cycle effects for the scope of this study. Diffusion-weighted GRE MRI was performed on three subjects in three different directions (S/I, L/R, A/P) while the subjects wore a pulse-oximeter device to record the cardiac cycle. In post-processing, non-rigid body noise was isolated from the signal and other noise. The raw pulse-oximeter signal was normalized by subtracting the local minimum and dividing by the local maximum. The location of peaks was found and then the timing of the signal was corrected for MR electronic and physiological delays. The signal peak-to-peak was then segmented into 10 individual cardiac bins. The image at each associated time point was sorted into a bin as well. The results from the study demonstrated how the non-rigid body phase was greatest when encoding motion in the S/I direction, greatest in the midbrain, brainstem, and pons, correlated to the pulse-oximeter signal, and reproducible beat-to-beat.

This study demonstrated the ability to associate a time-series of images with the cardiac cycle. Because MRE is also a technique dependent upon a time series of images, the configuration for the scanning can be transferred to MRE. Taking multiple repetitions of the same slice allows the ability to observe changes in noise over time, likely corresponding to the cardiac cycle. The methods from this journal article can serve as a baseline for developing methods to quantify physiological signal noise in MRE.

1.2.2 Tracking Cardiac Cycle Effects on Brain Motion

Zhong, 2009 developed a spiral cine displacement-encoding stimulation echo (DENSE) MRI technique to measure brain motion during the cardiac cycle. [59] The
technique has the ability to measure brain motion for an individual tissue pixel. The study demonstrated the change in pulsatile motion from the brain stem to the peripheral brain, thus mapping the motion trajectory in the brain. Displacements maps further showed the motion of the brain at multiple places in the cardiac cycle as a greater intracranial motion is observed in the brain stem and smaller displacements occurring in the occipital lobe and cerebellum. Zhong argued that these displacements were relatively small so were less likely to affect diffusion MRI, focusing on the application of the technique to improve the treatment of brain disorders. Because the technique measures intracranial motion, it can observe whether significant changes have occurred post-surgery. [59]

A follow up study was published by Pahlavian, 2018. This assessment focused on assessing the ability for using DENSE MRI to quantify 2D brain tissue strain through measuring the displacement of the brain from the cardiac cycle. [46] The brain stem had larger motion, which was observed previously in Zhong, 2009. The cerebellum and corpus callosum had larger motion and strain relative to periphery structures. The study demonstrated that cardiac pulsation in the brain is quantifiable through measuring tissue displacement and strain and that larger displacements were associated with a greater strain in brain regions. [46]

This work provides invaluable insight into cardiac motion in the brain. Zhong, 2009 and Pahlavian, 2018 demonstrate how the brain changes over time due to the cardiac cycle. It is necessary to take into account that different regions of the brain experience various changes in the cardiac cycle. Thus, it is important to take into account slice placement when understanding cardiac cycle effects in MRE. Slices located closer to the brainstem may experience a greater volume of noise relative to
those slices of the cerebellum. Pahlavian, 2018 was able to demonstrate how DENSE MRI not only measures cardiac displacements but can be utilized to estimate strains, which is similar to MRE acquisition. The motion described in both of these articles may impact the propagation of shear waves of MRE, so it is necessary to consider the findings of this work in regard to the outcome of our study.

1.2.3 Regional Patterns of Physiological Noise Artifacts in Diffusion Imaging

Walker, 2010 characterizes artifacts in diffusion imaging that are due to physiological noise. [60] Methodology utilized in the study demonstrated consistency in regions of the brain which experienced greater error. Because of unique regions experience difference levels of non-gaussian signal noise, the assumption that all brain tissue follows similar statistical tissue properties is inaccurate. Clusters of artifacts typically occur in similar regions. The presence of these artifacts can influence the statistical outcomes of diffusion imaging. Instead, the study proposes the use of robust fitting, which is known as RESTORE. [60]

Walker, 2010 reaffirms the findings of Zhong, 2009 and Pahlavian, 2018 [59] Walker also demonstrates how the patterns of noise do not only occur in similar regions of the brain but also have similar patterns across subjects. This noise that Walker, 2010 observes may be tied to cardiac pulsation and other physiological influences. Understanding that cardiac pulsation noise is similar across subjects is a transferrable concept to MRE. It allows the ability to review and average statistical trends across subjects. Furthermore, diffusion imaging is similar to MRE in that is a time-series based scan, thus it is necessary to evaluate noise in different regions of the brain in MRE too.
1.2.4 Estimating Effect of Noise Covariance

Constantinides, 1997 provides a method to measure SNR based on magnitude-reconstructed images. They analyze the probability distribution of the measured signal intensity is measured both in conditions with signal and without to determine the effects noise. The standard deviation of noise is assessed as well as the root mean square error around the average signal of a region of interest. Most notably, the work discusses the existence of noise correlations in phased array systems. The degree of correlation of noise results in spatial variation of the total noise in the resultant image. The noise correlations do not affect signal estimates from the background of an image, but rather noise pixel to pixel can influence produced images. Noise correlation was grouped into extrinsic and intrinsic. In the extrinsic condition, noise correlations are caused by voltage differences in coils. Meanwhile, intrinsic correlations refer to changes due to eddy currents caused in a sample that shares common paths. To account for these errors Constantinides developed correction plots to improve the SNR of noisier regions of an image.

This work is notable in its discussion of pixel-pixel noise variation. The degree that noise in an adjacent voxel is correlated to the previous can determine the type of noise present in the image. In NLI, which utilizes 10x10 matrixes to estimate mechanical properties, highly correlated noise can cause miscalculations of mechanical properties if the correlation extends over several pixels. Evaluating this relationship between a singular pixel and surrounding ones can provide a trend to how correlated noise changes spatially. Measuring the correlation coefficient serves as a metric to evaluate the degree of correlation between noise at adjacent pixels. Associating the correlation between noise with subsequent NLI mechanical property calculations can evaluate the degree in which correlated noise influences.
1.3 Objectives

The goal of this study is to better assess, quantify, and limit the effects of various types of signal noise that degrade the quality of acquired images in MRE. Increasing our understanding of the causes of signal noise effects on mechanical property calculations can lead to better sequences and methodologies.

Three objectives are associated with subsequent aims. The first primary objective is focused on characterizing bulk motion noise in both human and phantom models. Because MRE is specifically measuring displacements in brain tissue from mechanical vibration, minimizing extra motion noise is essential to having high SNR images. Different methodologies of restricting head motion will be completed as well as the extent of bulk motion noise present in MRE images.

The second objective is characterizing physiological noise present in MRE images. Specifically, noise due to cyclical cardiac cycle effects will be analyzed to quantify the repeatability and extent that cardiac cycle noise influences MRE raw images.

The third objective is focused on assessing the 3-dimensional spatial extent of singular noise events that can occur in NLI to determine how non-gaussian noise affects calculations. Pixel-to-pixel correlations will be performed to assess the nature of noise on a voxel scale. The correlation length will be determined in all three motion encoding directions both in-plane and out-of-plane.

These objectives will allow the ability to further understand the causes and effects of signal noise present in MRE. Further understanding the nature of signal noise will lead to the improvement of MRE as a tool for assessing brain health.
1.4 Aims

This study aims to:

1. Characterize bulk motion noise in the in vivo brain and in phantom models.
2. Isolate and quantitatively assess cardiac cycle signal noise in the in vivo brain.
3. Quantify noise effects on NLI Stiffness Calculations
All images were collected using Siemens 3T Prisma MRI scanner (Erlangen, Germany). The 20-channel head coil was used to collect data. MRE data was acquired using echoplanar (EPI) sequence. When vibration was required for MRE scans, it was delivered at 50 Hz. The vibration was delivered to a subject via a resoundant-actuator system with passive driver (Figure 6).

![Figure 6. MRE process (A) Traditional MRE configuration. Passive driver is connected to pneumatic actuator which prorogates vibrations at the posterior head. (B) EPI MRE pulse sequence.[6] (C) During scanning images are taken of individual slices with multiple repetitions of each slice. These inputs are entered into the nonlinear inversion algorithm, in which the output is mechanical property maps.](image_url)

All images followed a traditional MRE post-processing pipeline. All raw dicom images were changed to nifti images through the FSL eyes package. The phase images were then masked such that the background phase was removed. The resultant image file would then only contain signal in the brain.
To isolate signal noise from MRE scans, all repetition images taken of an identical slice were averaged. This average phase was then subtracted from individual repetitions of images. Thus, as these values are complex exponentials, the noise is the angle of the division of an individual repetition by the overall average of the slice (Figure 7).

![Diagram](image)

Figure 7. Visual of process to isolate signal noise from raw MRE images. Multiple repetitions of the identical slice are averaged and the difference between the average and the individual repetition was considered the noise.

2.1 **Aim 1: Characterize bulk motion noise in the in vivo brain and in phantom models**

Bulk motion was assessed in both human and phantom subjects in order to observe the influence of motion in imaging outputs. In human subjects, bulk motion includes person movement and physiological influences while the phantom only has noise due object movement, which might come from imperfect actuation or scanner table vibration.[62], [63] Therefore, this analysis would only monitor changes in motion rather than biological noise.
2.1.1 Brain MRE

2.1.1.1 Imaging Methods for Brain MRE

Three subjects were scanned to assess head motion noise. The subjects included 2 females and 1 male, who were on average 24 +/- 1 years old. Each subject received 6 total MRE scans under two separate conditions. The first time the subject was scanned, cushions surrounded the person’s head in the head coil to limit movement. This condition was considered a “Head Restricted” MRE scan as the cushions prevented patient movement (Figure 8). In the second series of scans, the subject had the pillows removed. All sequences were EPI and had 48 slices, 20 repetitions, and 3 motion encoding directions which include the Phase (y), Read (x), Slice (z). Interleaved slices settings were used, and data collected was 3 mm³ resolution. Each subject received three different MRE sequences twice. In the first sequence, the MEG was set to 0.1 mT/m and the vibration as turned off. This condition was essentially designed to have both the MEG and vibration considered off, thus allowing only image noise to be assessed. In the second scan, the MEG was set to 70 mT/m and the vibration was turned off. This sequence was designed to have the motion encoding set for a typical MRE scan, while the vibration continued to not be used, thus the ability to observe only physiological sources of noise. For the third scan, the MEG remained on at 70 mT/m and vibration was set to 50 Hz to assess motion noise due to vibration. Further imaging details include TR = 6720 ms, TE = 65.0 ms, FoV read 240 mm. The total scan time for a subject was approximately 48 minutes without standard imaging and shimming.
2.1.1.2 Statistical Methods for Head Motion

After post-processing, the raw signal noise was averaged for an individual image. This average value was computed for an individual repetition of a slice in each imaging directions. This process was iterated through for all scans including both the traditional MRE configuration and head restricted MRE. These resultant matrixes were then averaged across all subjects to have a global mean of noise for individual images.

In addition, the distribution of noise was evaluated. The histogram for the matrix of the net average noise in all three directions for individual images was computed using the histfit MATLAB function. These were fitted with a normal distribution curve in order to compare the fit and full width half maximum (FWHM), which is an indicator of the spread of noise. The FWHM was computed using the MATLAB function, fwhm. In addition, the distribution of noise for individual directions, x, y, and z were plotted and FWHM was calculated. Subsequently, the global mean and standard deviation of noise across all three subjects for individual
scans was computed. These values helped characterize the variation and average noise to serve as a comparison between different scan conditions.

Additionally, statistical values were computed to further characterize the distribution of noise present. Kurtosis, the sharpness of a peak for a distribution curve, was calculated for the net noise across all subjects in all directions as well as in x, y, and z individually. The kurtosis is an indicator to evaluate the distribution of noise relative to a gaussian distribution, which has a kurtosis of 3.

2.1.2 Phantom Motion

The purpose of the phantom motion experiments was to differentiate bulk motion to physiological contributors of noise. Because a phantom lacks the ability to breathe or experience cardiac cycle effects, factors that cause signal noise are primarily bulk motion. Being able to repeat the experiments of comparing traditional MRE to restricted MRE can further characterize the behavior of signal noise in MRE. Furthermore, phantoms are commonly used to verify MRE techniques, so understanding signal noise contributions in phantoms provides better utilization of the tool.

2.1.2.1 Phantom Creation

Three agarose phantoms were created. The methods were based on previously published work from the lab group. [64] Salt (5 grams) and agar (1.0%wt) were added to 1000 mL of water in a beaker. The water with the agar and salt were placed on a hotplate, with a stir bar. The hot plate was turned on and foil covered the top of the beaker, allowing only a thermometer to be inserted into the glassware. The temperature was monitored and when it reached 90 degrees, the solution was carefully
poured into a Tupperware container. This container was then placed inside a refrigerator for the material to form.

2.1.2.2 Imaging Methods for Phantom MRE

The experimental setup was very similar to the Brain MRE experiments (Figure 9). Three identical phantoms were scanned. To simulate a traditional MRE experiment, the phantom was placed on top of the passive driver. Three pieces of tape were used to secure the container loosely to the head coil, which is commonly done when working with MRE phantoms. The configuration for a “Head Restricted MRE” was redefined in the Phantom experiments as “Restricted MRE”. To setup this configuration, small foam pillows were placed around the phantom in the head coil. An additional two pieces of tape connected the top of the Tupperware container to the head coil to further restrict left-right motion.

Imaging methods for the Phantom MRE were very similar to brain MRE as well. The phantoms received three unique MRE scans twice, once in the traditional MRE configuration and once in the Restricted MRE setup, just like the Brain MRE experiments. In the first sequence, the MEG was set to 0.1 mT/m and the vibration as turned off to assess image noise. In the second scan, the MEG was set to 10 mT/m and the vibration was turned off to assess physiological noise. This sequence was designed to have the motion encoding set for a typical MRE scan, while the vibration continued to not be used. For the third scan, the MEG remained on at 10 mT/m and the 50 Hz vibration (set at 6 waveform cycles) was turned on to assess motion noise. The amplitude of the vibration for the traditional MRE scans was 5% while for the restricted MRE it was at 10% to accommodate for the inherent limited mobility with additional foam pillows. All sequences were EPI at 3 mm³ resolution and had 40
slices, 20 repetitions, and 3 directions which include the Phase \((y)\), Read \((x)\), Slice \((z)\).

Further imaging details include TR = 4800 ms and TE = 65 ms. The total scan time for a phantom was approximately 40 minutes without standard imaging and shimming.

Figure 9. Comparison of experimental setup for Traditional MRE and Restricted MRE for Phantoms.

### 2.1.2.3 Statistical Methods for Phantom MRE

Statistical assessments for Phantom MRE were very similar to the Brain MRE. Further details of these methods can be described in those Statistical Methods. The net matrix of average noise was plotted for each direction of each scan in MATLAB. The distribution of noise was evaluated. The histogram for the matrix of the net average noise for individual directions, \(x\), \(y\), and \(z\) for each scan was computed using the \texttt{histfit} MATLAB function. The full-width half maximum (FWHM) of the distribution of noise in \(x\), \(y\), and \(z\), was computed in order to understand the spread of noise during a scan. Subsequently, the net mean and standard deviation of noise across all three subjects to observe global differences. Additionally, kurtosis was computed to assess the shape of the distribution of data.
2.2 Aim 2: Isolate and quantitatively assess cardiac cycle signal noise in the in vivo brain.

The purpose of these experiments is to understand the influence of cardiac cycle noise in the raw MRE data. Experiments were designed to isolate physiological noise and coordinate MRE images with the cardiac cycle to determine a relationship between the two.

2.2.1 Imaging Methods

Three subjects, two female and one male, whose average age was 23.7 +/- 1.5 years were scanned for cardiac pulsation experiments. The imaging sequences utilized had the motion encoding gradients on at 70 mT/m and not the vibrational component of an MRE scan. These settings would allow only physiological noise to be observed. Three scans were completed with the MEG turned on for each scanning direction. All scans were EPI at 3.0 mm³ resolution. 8 slices of the brain were scanned, with 250 repetitions per slice in order to observe changes in signal noise due to cardiac pulsation. A small number of slices was scanned in order to speed up the acquisition. Additional MRI settings include FoV read 240 mm, TR 1120 ms, TE 65.0 ms. Total scan time for sequence was approximately 25 minutes.
Each human subject wore a pulse oximeter device while in the Prisma scanner (Figure 10A). Meanwhile, an Arduino Uno device was connected to the external trigger capabilities of the Prisma scanner (See Appendix A for additional details on the Arduino Uno). The Arduino device would send to external log on the Prisma scanner when MEG triggers. Meanwhile, the Prisma scanner software contained the ideacmdtool that is able to write log outputs from external triggers, which would include the Arduino and pulse oximeter signal. These files were exported along with imaging data.
2.2.2 Cardiac Binning

In post-processing, the recorded pulse oximeter signal was adjusted to be aligned with the MRI images that were repetitions of an individual slice. The raw pulse oximeter signal was first trimmed such that it only contained pulse-oximeter signal that occurred during the MRE scans. Then, the signal was normalized to have a variance between 0 to 1. The timing of peaks of the cardiac cycle were determined through the peak-detector function on MATLAB. From one peak to one peak was considered one cardiac cycle (Figure 10B). To correct for delays between data acquisition and pulse-oximeter signal due to physiology and hardware, the timing of the peak was delayed between 1000 to 1600 ms due to physiological and hardware delays.

For the signal between the timepoints of one peak and the subsequent on, that length of the signal was divided into 10 areas which were considered “Cardiac Bins” (Figure 10B). If the division of the bins was uneven, the remaining timepoints were assigned to an additional 11th bin which would then be discarded. Meanwhile, the MEG recording via the Arduino was aligned with the images taken at identical time points. The pairing of the MEG signal with the image was aligned with the pulse-oximeter readings. The assignments of the pulse-oximeter signal to a cardiac bin were subsequently also assigned to the MRE images at the same timepoints. Thus, Cardiac Bin assignment took place for all repetitions of a slice across all eight slices.

2.2.3 Statistical Methods

Once images for an individual slice were divided into cardiac bins, the average noise and standard deviation was computed for the cardiac bin. The mean and standard deviation of noise was computed for an individual subject as well as across all three
subjects to have a net mean and standard deviation. For a single cardiac bin across all
subjects, the net mean and standard deviation were also computed, such that the bin
for one slice was assigned a singular value for both measurements.

To assess trends in cardiac cycle across cardiac bin in all slices, a global
average and standard deviation of noise in a cardiac bin was computed across all slices
for a cardiac bin. These two sets of data were then plotted to assess whether changes in
noise across cardiac bins aligned with the patterns associated with systole and diastole.

2.3 Aim 3: Quantify noise effects on NLI Stiffness Calculations

To understand the 3-dimensional spatial extent of noise events which can
influence NLI outcomes, the correlations between a voxel of interest in an image and
surrounding points were analyzed. Understanding how noise present in images relates
to one another can help improve NLI’s ability to calculate mechanical properties.
Highly correlated noise in adjacent voxels can lead to bias and artifacts in the
algorithm.

2.3.1 Imaging Methods

The data used to quantify noise effects was from the acquired data in the
Traditional Brain MRE experiments in Aim 1. The scans selected captured MRE-
specific noise such as the physiological and vibrational noise. Specifically, the two
traditional MRE scans that were used were (1) when the MEG was on and the
vibration was off and (2) when both the MEG and the vibration were both turned on.
The scan where the MEG and vibration both turned off was not used because it only
contains image noise which would be variable in all calculations. Image noise is also
primarily gaussian noise which is well-handled by NLI. Therefore, the two scans were
used per subject, and three subjects total were scanned. Complete details regarding image acquisition of these scans can be found in Imaging Methods for Brain MRE in Aim 1’s methods.

2.3.2 Correlation Analysis

![Correlation Analysis Diagram](image)

Figure 11. Visual of piece-wise correlation. For a voxel of interest in one image, the correlation was calculated between each subsequent voxel in x and y, and across multiple repetitions in z. This process is repeated for motion encoding direction that were taken during the scan.

The calculated noise from the two Traditional MRE scans with the MEG on were used for the correlation analysis. To measure between pixel correlation for a voxel of interest in an image, the MATLAB corr function was utilized. To implement the function, first a point was identified in the MRE image based on the MEG direction. Within this image, the correlation coefficient was calculated for all points in-plane horizontally (X points), vertically (Y points), and out-of-plane across all slices (Z points). A visualization of these three vectors can be seen in Figure 11. Thus,
for one image in one encoding direction, correlation coefficients were calculated along x, y, and z planes of the image.

The resultant paired-correlation coefficients for x, y, and z image planes were then plotted on a semi-logarithmic graph. The coefficients were plotted at the absolute distance from which the paired pixel was located relative to the voxel of interest (Figure 12). From this plot, the correlation length can be computed, which is indicative of the distance that pixels remain very correlated. Short range correlations can be approximated by the following equation:

\[ C(r_1, r_2) \sim e^{-|r_2-r_1|/r_c} \]  

Equation 5. 

In the above equation, \( C \) is the correlation coefficient, \( r_c \) is the correlation length, and \( r_2 - r_1 \) is the distance between paired pixel and the voxel of interest. In order to calculate the correlation length, the log of both sides of the equation can be taken such that the equation is now:

\[ \log(C(r_1, r_2)) \sim -\frac{1}{r_c}|r_2-r_1| \]  

Equation 6.

This new equation can be used to fit the paired-correlation coefficients that were plotted on the semi-logarithmic graph. Thus, in order to measure the correlation length, a piecewise linear fit was implemented. This fit was selected because the noise is expected to be highly correlated at some distance close to the initial point, in which Equation 6 holds true, and drastically less correlated at some distance further away from the initial point. Because the slope of the line is approximated by \(-\frac{1}{r_c}\), the inverse of the slope of the first line of the piecewise fit is the correlation length:

\[ r_c \sim \frac{1}{m} \]  

Equation 7.

The piecewise fit was applied using lsqcurvefit Matlab function, a nonlinear least-squares solver. The function starts at the pixel and finds coefficients to best fit a
nonlinear function to the correlation coefficients that are plotted. The inverse of this slope was then taken to determine the correlation length. This process was repeated for each image plane for the three motion encoding directions for both the no vibration and vibrational scans.

![Graph of correlation coefficients](image)

Figure 12. Model plot of correlation coefficients for a voxel of interest in an image plane. The two lines part of the piecewise fit are the grey and green lines. The inverse of the slope of the grey line is the correlation length for signal noise for the point.

To analyze the correlation across several subjects in both the no vibration and vibration scans, a small region of an image was selected to iterate this process (Figure 13). A 6x6 pixel square in the upper central region of an image was selected to calculate the correlation lengths along the voxels in all three encoding direction’s images. The slices that were selected were central in the brain. Once the correlation length was computed for both experimental configurations in all three subjects, the global average and the standard deviation of the correlation length were calculated.
The net average and standard deviation were taken for both in-plane directions and out of plane.

Figure 13. 6x6x6 voxel region selected. Yellow box shows region in plane selected and a sample of the six slices with noise profiles in the Motion Encoding Y direction are shown above. Noise profiles were also analyzed in the x and z directions.
Chapter 3
RESULTS

3.1 Aim 1: Characterize bulk motion noise in the in vivo brain and in phantom models

It was observed that restricting subject movement with foam pillows reduced the signal noise present in images. This trend was observed in both human subjects and agarose phantoms.

3.1.1 Head Motion

Figure 14. Average noise for all subjects in both Traditional MRE and Head Restricted MRE. Averages for all three scan types are shown. Samples of brain slices can be seen to the right of the image.
Overall noise was observed to be reduced during the head restricted MRE (Figure 14). Without the MEG and the vibration, noise did not vary between conditions. When the MEG was turned on, there was an increase in signal noise due to now capturing physiological noise. Traditional MRE and Head Restricted MRE scans had slight differences in noise. During the vibrational scan of a Traditional MRE, the noise is distributed in x, y, and z in relatively evenly. There appears to be minimal differences in noise across slices in a singular scan, in both Traditional and restricted MRE experimental setups. However, in the restricted MRE condition, the y motion does not change and may in fact be a little higher. Noise is also reduced in both the x and z directions in this scan MRE. The random motion in x and z is reduced due to restricted movement, but that motion is partially compounded into y, which is the direction of applied actuation. The motion noise is distributed evenly amongst slices such that no one slice experiences a relatively greater volume of noise than another.

Figure 15. Histogram of distribution of total noise for both a typical MRE and Head Restricted MRE conditions. Noise is averaged across all three subjects. A normal distribution fit of the distribution of noise is displayed over each scan as well.
Histogram of the net noise in Traditional MRE and Head Restricted MRE were generated and can be seen in Figure 15. The spread of noise in the Traditional MRE scan was observed to be greater than the Head Restricted MRE scans. In the scan where the MEG and Vibration are both turned off, the noise distribution is quite narrow, with most points close to no noise. This narrowness was observed in both the Traditional MRE and the Head Restricted MRE configurations. In the scan where the MEG was turned on but the vibration remained off, the spread of noise reached -0.2 to 0.2 radians. The distance noise spread when the MEG was turned off was similar between Traditional and Head Restricted MRE, but the shape of the distribution differed as most of the noise in the Head Restricted MRE was closer to zero. However, in the third scan, in which the MEG and vibration are both turned on, the most noise is observed, with tails reaching -0.4 to 0.4 radians. The Head Restricted MRE with the vibration turned on had a narrower spread of noise, with more noise close to 0. Meanwhile, the noise in the Traditional MRE had a greater spread such that more noise was present in the tails. Overall, the Head Restricted MRE pushes more noise to zero rather than to the tails of the curves. The change of distribution of noise is best seen in the third scan, where both the vibration and MEG are turned on and head restriction reduces spurious motion that results in noise.

The distribution of noise was also evaluated in x, y, and z directions separately for each of the six scans. The net histograms can be seen in Figure 16. The Head Restricted MRE noise distribution remained similar to the Traditional MRE distribution when the MEG was turned off and the vibration was turned off. When vibration was turned on, the use of foam pillows in the restricted MRE made a big difference. The noise in y during the head restricted MRE had a greater spread of
noise than x and z. Thus, the x and z noise was forced closer to zero while the y noise continued to stay spread out. In the Traditional MRE, these three directions had relatively similar distributions of noise. The greater spread of noise in y in the Restricted MRE corresponds to the experimental setup, where the subject is only able to move in the y direction. Because of the use of the foam pillows, the subject has very limited mobility in the x and z directions, leaving the head to propagate freely in y and thus also allow for more motion that will lead to noise.

![Histograms of noise in three directions for the three different scans performed in both the Traditional MRE and Head Restricted MRE scans.](image)

The Net FWHM, standard deviation, and mean were assessed across all three subjects. The net FWHM paralleled the trends visualized in the histograms of the distribution of noise (Table 1). When both MEG and vibration were turned on in the traditional MRE, the FWHM was greatest in z. However, in the Head Restricted MRE, the y direction experienced about a 30% greater width relative to the x and z directions. Compared to a Traditional MRE scan, the Head Restricted scan where the
vibration was turned on had a 44% increase in FWHM width in the y direction. The maximum FWHM observed was 0.316 which was reported in the y direction of the Head Restricted MRE with the vibration turned on.

Table 1. Net FWHM for Traditional and Head Restricted MRE

<table>
<thead>
<tr>
<th>Condition</th>
<th>Scan</th>
<th>All</th>
<th>x</th>
<th>y</th>
<th>z</th>
</tr>
</thead>
<tbody>
<tr>
<td>Traditional MRE</td>
<td>MEG off, Vibration off</td>
<td>0.147</td>
<td>0.119</td>
<td>0.156</td>
<td>0.161</td>
</tr>
<tr>
<td></td>
<td>MEG on, Vibration off</td>
<td>0.199</td>
<td>0.197</td>
<td>0.201</td>
<td>0.12</td>
</tr>
<tr>
<td></td>
<td>MEG on, Vibration on</td>
<td>0.218</td>
<td>0.183</td>
<td>0.22</td>
<td>0.246</td>
</tr>
<tr>
<td>Head Restricted MRE</td>
<td>MEG off, Vibration off</td>
<td>0.174</td>
<td>0.167</td>
<td>0.131</td>
<td>0.215</td>
</tr>
<tr>
<td></td>
<td>MEG on, Vibration off</td>
<td>0.171</td>
<td>0.167</td>
<td>0.176</td>
<td>0.169</td>
</tr>
<tr>
<td></td>
<td>MEG on, Vibration on</td>
<td>0.248</td>
<td>0.177</td>
<td>0.316</td>
<td>0.231</td>
</tr>
</tbody>
</table>

The trends in the variance and average total noise were similar to those of the FWHM. The Net Standard deviation can be found in Table 2 and the Net Average noise in Table 3. The greatest variance occurred when the MEG was turned on with the vibration. There was a 60% increase in noise in the y direction in the Head Restricted MRE setup relative to the Traditional MRE configuration in the scan where the MEG and vibration are both turned on. A 20% increase in the mean noise occurred as well between the two scans. The Net Average noise present in an experimental setup increased when the MEG was turned on and then again when the vibration was on. However, the Head Restricted MRE scans had a lower average of noise present compared to the equivalent traditional MRE scan. In the traditional MRE scan, When the vibration is turned on, there is a decrease in the net mean noise x and z, but not in y, which is about 25% greater than in the Traditional MRE scan.
Additionally, it was necessary to not only understand the changes in the variation and mean volume of noise, but also further analyze the shape of the curve. Kurtosis was used to characterize the nature of the distribution of signal noise. All Kurtosis values were greater than three for all six scans in each of the respective directions. A kurtosis of greater than three can thus be characterized as leptokurtic, meaning the distribution has a greater kurtosis than a normal distribution and thus has more noise concentrated near the mean. Kurtosis between an identical Traditional MRE scan and a Head Motion MRE scan showed a decrease in Kurtosis in the Head Restricted MRE relative to the Traditional MRE. However, within a series of Traditional MRE scans and Head Restricted MRE scans, the Kurtosis declined for x, y, and z. However, the kurtosis during the Head Restricted MRE when both the MEG

Table 2. Net Standard Deviation for Traditional & Head Restricted MRE

<table>
<thead>
<tr>
<th>Condition</th>
<th>Scan</th>
<th>All</th>
<th>x</th>
<th>y</th>
<th>z</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Traditional MRE</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MEG off, Vibration off</td>
<td>0.0586</td>
<td>0.046</td>
<td>0.063</td>
<td>0.065</td>
<td></td>
</tr>
<tr>
<td>MEG on, Vibration off</td>
<td><strong>0.0733</strong></td>
<td>0.072</td>
<td>0.077</td>
<td>0.071</td>
<td></td>
</tr>
<tr>
<td>MEG on, Vibration on</td>
<td><strong>0.0683</strong></td>
<td>0.057</td>
<td>0.065</td>
<td>0.08</td>
<td></td>
</tr>
<tr>
<td><strong>Head Restricted MRE</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MEG off, Vibration off</td>
<td><strong>0.0711</strong></td>
<td>0.068</td>
<td>0.053</td>
<td>0.088</td>
<td></td>
</tr>
<tr>
<td>MEG on, Vibration off</td>
<td><strong>0.0618</strong></td>
<td>0.059</td>
<td>0.065</td>
<td>0.061</td>
<td></td>
</tr>
<tr>
<td>MEG on, Vibration on</td>
<td><strong>0.087</strong></td>
<td>0.062</td>
<td><strong>0.105</strong></td>
<td>0.083</td>
<td></td>
</tr>
</tbody>
</table>

Table 3. Net Average Noise for Traditional & Head Restricted MRE

<table>
<thead>
<tr>
<th>Condition</th>
<th>Scan</th>
<th>All</th>
<th>x</th>
<th>y</th>
<th>z</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Traditional MRE</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MEG off, Vibration off</td>
<td><strong>0.021</strong></td>
<td>0.02</td>
<td>0.022</td>
<td>0.02</td>
<td></td>
</tr>
<tr>
<td>MEG on, Vibration off</td>
<td><strong>0.042</strong></td>
<td>0.044</td>
<td>0.037</td>
<td>0.046</td>
<td></td>
</tr>
<tr>
<td>MEG on, Vibration on</td>
<td><strong>0.062</strong></td>
<td>0.053</td>
<td>0.067</td>
<td>0.067</td>
<td></td>
</tr>
<tr>
<td><strong>Head Restricted MRE</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MEG off, Vibration off</td>
<td><strong>0.021</strong></td>
<td>0.021</td>
<td>0.019</td>
<td>0.023</td>
<td></td>
</tr>
<tr>
<td>MEG on, Vibration off</td>
<td><strong>0.038</strong></td>
<td>0.039</td>
<td>0.036</td>
<td>0.038</td>
<td></td>
</tr>
<tr>
<td>MEG on, Vibration on</td>
<td><strong>0.059</strong></td>
<td>0.042</td>
<td>0.083</td>
<td>0.052</td>
<td></td>
</tr>
</tbody>
</table>
and Vibration are turned on is greater than the traditional MRE scan. A summary of kurtosis values can be found in Table 4.

Table 4. Average Kurtosis for Traditional & Head Restricted MRE

<table>
<thead>
<tr>
<th>Condition</th>
<th>Scan</th>
<th>All</th>
<th>x</th>
<th>y</th>
<th>z</th>
</tr>
</thead>
<tbody>
<tr>
<td>Traditional MRE</td>
<td>MEG off, Vibration off</td>
<td>385</td>
<td>128</td>
<td>363</td>
<td>434</td>
</tr>
<tr>
<td></td>
<td>MEG on, Vibration off</td>
<td>251</td>
<td>118</td>
<td>580</td>
<td>41</td>
</tr>
<tr>
<td></td>
<td>MEG on, Vibration on</td>
<td>19</td>
<td>10</td>
<td>10</td>
<td>25</td>
</tr>
<tr>
<td>Head Restricted MRE</td>
<td>MEG off, Vibration off</td>
<td>254</td>
<td>196</td>
<td>114</td>
<td>243</td>
</tr>
<tr>
<td></td>
<td>MEG on, Vibration off</td>
<td>77</td>
<td>65</td>
<td>109</td>
<td>50</td>
</tr>
<tr>
<td></td>
<td>MEG on, Vibration on</td>
<td>100</td>
<td>52</td>
<td>86</td>
<td>79</td>
</tr>
</tbody>
</table>

3.1.2 Phantom Motion

The phantom motion experiments allowed the ability to assess signal noise in a model that lacked physiological sources of noise in order to further understand bulk motion noise. Signal noise was overall reduced in the Restricted MRE (Figure 17). When the MEG was turned off and vibration was turned off, there was little difference in noise between the Traditional and Restricted MRE. Because this scan assesses only image noise, the noise is expected to not differ between the two scans. However, when the MEG is turned on and the vibration is turned off there is a greater volume of noise observed in the y direction in the Restricted MRE and white noise is reduced in the z direction compared to the Traditional MRE. The noise in the x direction remains constant. When the MEG and Vibration are both turned on, the motion is dampened in the Restricted MRE. In the traditional MRE it is very evident that the greatest amount of noise is observed in the y direction, because this is the direction of vibration. This trend is dampened in the Restricted MRE, although a greater volume of noise is still observed in the y direction. Across slices of the phantom in a scan, the amount of
noise remained relatively similar as well, such that one slice does not have significantly more than nearby slice.

Figure 17. Comparison of Traditional MRE and Restricted MRE across all Phantom experiments for the three unique scans. Noise averaged across all three phantoms for each scan. Lack of noise present in the z direction aligns with the lack of physiological noise in the phantom.

The histograms of signal noise for the six scans in phantoms are displayed in Figure 18. The distribution of noise when both the MEG and vibration are turned off, follows a similar pattern between Traditional and Restricted MRE. When the MEG is turned on and vibration is off, noise in x and z directions maintain similar distribution shapes. The noise in y is a bit more in the tails in the Restricted MRE. When the MEG and vibration is turned on, the spread of noise in the Restricted MRE is less than in the
Traditional MRE. Thus, more of the noise is centered around zero than in the tails. The y noise has a much greater spread in the Traditional MRE than the Restricted MRE. Therefore, the noise in y in the Traditional MRE was more in the tails, reaching upwards of 0.05 radians from the center. The Restricted MRE had tails extend only to approximately 0.03 radians from zero.

![Histograms of signal noise in Phantom experiments in x, y, and z for both Traditional MRE and Restricted MRE.](image)

Figure 18. Histograms of signal noise in Phantom experiments in x, y, and z for both Traditional MRE and Restricted MRE.

The Net FWHM was computed for the distributions that were generated (Table 5). In both Traditional MRE scans and Restricted MRE scans, the FWHM increased as the when the MEG was turned on and again when vibration was turned on. In the scan where both the MEG and vibration were turned off, the FWHM was relatively similar between the Head Restricted and Traditional MRE. This scan also had the smallest reported FWHM at 0.007 radians. When the MEG was turned on and vibration was turned off, the Restricted MRE had decrease in the FWHM in the x direction, an
increase in the y direction, and a decrease in the z direction compared to the Traditional MRE. The use of the foam pillows limited x and z motion, thus the noise in those directions is closer to zero than at the tails of the distributions. When additional vibration was turned on, the FWHM of the Restricted MRE was less than the Traditional MRE. The greatest FWHM was in the y direction of the Traditional MRE scan where both the MEG And vibration was turned on at 0.038 radians. The FWHM in the same direction and equivalent scan in the Head Restricted MRE was 0.021 radians, which was 44% less than the Traditional MRE scan.

Table 5. Net FWHM for Traditional and Head Restricted Phantom MRE

<table>
<thead>
<tr>
<th>Condition</th>
<th>Scan</th>
<th>x</th>
<th>y</th>
<th>z</th>
</tr>
</thead>
<tbody>
<tr>
<td>Traditional MRE</td>
<td>MEG off, Vibration off</td>
<td>0.007</td>
<td>0.008</td>
<td>0.007</td>
</tr>
<tr>
<td></td>
<td>MEG on, Vibration off</td>
<td>0.016</td>
<td>0.014</td>
<td>0.013</td>
</tr>
<tr>
<td></td>
<td>MEG on, Vibration on</td>
<td>0.019</td>
<td>0.038</td>
<td>0.021</td>
</tr>
<tr>
<td>Restricted MRE</td>
<td>MEG off, Vibration off</td>
<td>0.008</td>
<td>0.008</td>
<td>0.007</td>
</tr>
<tr>
<td></td>
<td>MEG on, Vibration off</td>
<td>0.014</td>
<td>0.017</td>
<td>0.01</td>
</tr>
<tr>
<td></td>
<td>MEG on, Vibration on</td>
<td>0.016</td>
<td>0.021</td>
<td>0.016</td>
</tr>
</tbody>
</table>

The average noise in the Traditional and Restricted MRE confirmed the trends observed in the FWHM (Table 6). Overall, the Restricted MRE scans had a lower average of noise compared to the Traditional MRE equivalent. However, when the MEG was turned on and the Vibration was turned off, the average noise in the y direction in the Restricted MRE was 50% greater than the Traditional MRE, due to the limitation of left-right movement in the experimental configuration. However, when the vibration was turned on, the Restricted MRE had a lower average amount noise in all three directions, approximately 30% less than the equivalent Traditional MRE. When the vibration was turned on, the y direction continued to have the largest
average noise, in both Traditional MRE and Restricted MRE experiments. But, the noise in the Traditional MRE configuration was approximately 70% greater than the average noise in the Head Restricted MRE.

Table 6. Net Average Noise for Traditional and Restricted Phantom MRE

<table>
<thead>
<tr>
<th>Condition</th>
<th>Scan</th>
<th>All</th>
<th>x</th>
<th>y</th>
<th>z</th>
</tr>
</thead>
<tbody>
<tr>
<td>Traditional MRE</td>
<td>MEG off, Vibration off</td>
<td>0.00242</td>
<td>0.002</td>
<td>0.003</td>
<td>0.002</td>
</tr>
<tr>
<td></td>
<td>MEG on, Vibration off</td>
<td>0.00455</td>
<td>0.005</td>
<td>0.004</td>
<td>0.004</td>
</tr>
<tr>
<td></td>
<td>MEG on, Vibration on</td>
<td>0.00798</td>
<td>0.006</td>
<td>0.012</td>
<td>0.006</td>
</tr>
<tr>
<td>Restricted MRE</td>
<td>MEG off, Vibration off</td>
<td>0.00244</td>
<td>0.002</td>
<td>0.002</td>
<td>0.002</td>
</tr>
<tr>
<td></td>
<td>MEG on, Vibration off</td>
<td>0.00449</td>
<td>0.005</td>
<td>0.006</td>
<td>0.003</td>
</tr>
<tr>
<td></td>
<td>MEG on, Vibration on</td>
<td>0.00552</td>
<td>0.005</td>
<td>0.007</td>
<td>0.005</td>
</tr>
</tbody>
</table>

Kurtosis was also used as an indicator of how close the distribution of noise represented a gaussian curve (Table 7). All kurtosis values were greater than 3, which indicates that the distribution of noise spread more in the tails of the curve. This trend can be described as leptokurtic. Within Traditional and Restricted MRE scans, the kurtosis increased when the MEG was turned on versus when it was off. The greatest kurtosis was in the Traditional MRE scan where the MEG was turned on and the Vibration was off. This value was approximately 50% greater than the Restricted MRE scan where the MEG was turned on the Vibration was off. In the Restricted MRE scan, the largest kurtosis was when both the MEG and the vibration was turned on.
Table 7. Kurtosis for Traditional and Head Restricted Phantom MRE

<table>
<thead>
<tr>
<th>Condition</th>
<th>Scan</th>
<th>All</th>
<th>x</th>
<th>y</th>
<th>z</th>
</tr>
</thead>
<tbody>
<tr>
<td>Traditional</td>
<td>MEG off, Vibration off</td>
<td>4.03</td>
<td>4.18</td>
<td>4.05</td>
<td>3.75</td>
</tr>
<tr>
<td>MEG on, Vibration off</td>
<td>6.53</td>
<td>4.26</td>
<td>5.22</td>
<td>12.42</td>
<td></td>
</tr>
<tr>
<td>MEG on, Vibration on</td>
<td>6.42</td>
<td>4.66</td>
<td>3.82</td>
<td>11.73</td>
<td></td>
</tr>
<tr>
<td>Restricted</td>
<td>MEG off, Vibration off</td>
<td>4.04</td>
<td>4.64</td>
<td>3.63</td>
<td>3.75</td>
</tr>
<tr>
<td>MEG on, Vibration off</td>
<td>4.42</td>
<td>3.35</td>
<td>4.10</td>
<td>3.41</td>
<td></td>
</tr>
<tr>
<td>MEG on, Vibration on</td>
<td>6.07</td>
<td>3.69</td>
<td>4.82</td>
<td>9.65</td>
<td></td>
</tr>
</tbody>
</table>

3.2 Aim 2: Isolate and quantitatively assess cardiac cycle signal noise in the in vivo brain.

For the cardiac cycle experiments, motion encoding remained on while vibration was off in order to observe physiological noise. Figure 19 shows the average noise in each cardiac bin per slice in one subject. The noise in the cardiac bins for the three imaging directions, x, y, and z, can be seen. The greatest noise was observed in the first cardiac bin. Noise in bins 5-8 were less than those in bins 1-3 (Figure 19). The noise in bins 9 and 10 are slightly greater than bins 5-8 but less than bin 1. This noise
parallels the pulse oximeter signal, which peaks at systole and then decreases to a trough to recover signal prior to systole occurring again.

To observe the pattern of noise within a bin, images were also assessed within a single cardiac bin (Figure 20). It can be seen that the patterns of noise in the first cardiac bin is not only greater than latter bins (such as Bin 7) but have a similar pattern of noise. The noise in these images skew slightly negative. Bin 7 was selected to assess against the peak cardiac bin as it aligned with the trough in the cardiac cycle pulse oximeter signal. The noise is very similar across images in bin 7 and the volume of noise is closer to zero relative to the first bin as well.

![Figure 20. Comparison of images in the first and seventh Cardiac Bin in the x direction. Each bin has approximately the same number of images in each bin.](image)

Similarly, the average noise in Bin 1 and Bin 7 was compared across multiple slices of the brain (Figure 21). It can be seen that there is a greater volume of noise in
the first bin than the seventh bin. This pattern was apparent across all three imaging
directions. The average noise in the seventh bin was very similar across all three
directions and slices. In the z direction the noise in bin 1 was very similar between
slices. The pattern of noise varied across slices in bin 1 when comparing imaging
directions in x, y, and z. When comparing noise across slices in one imaging direction,
noise in bin 1 differed greatly in the x and y directions but not in z.

![Image of noise comparison]

Figure 21. Comparison of average noise in Cardiac Bin 1 and Bin 7 for four slices for
Subject #1. Changes are observed in all three directions, with the greatest average
noise in the z direction.

The standard deviation was calculated for each cardiac bin in individual
subjects (Figure 22). The standard deviation served as an indication of the variation
between bins within a slice in one subject. The greatest observed variation of noise
was in bin 1 which occurred at the same time as systole (Figure 22). The standard
deviation of noise in a cardiac bin drops off after the first bin and increases slightly
again in bin 4. The variation then decreases again in bins 5-7. From bins 8 -10 the
noise begins to slightly increase again. This trend is observed in all three gradient directions.

Figure 22. Standard deviation of each cardiac bin in each direction in a slice in Subject #1. Greatest variance observed in Cardiac Bin 1 which corresponds to systole.

Figure 23. Comparison of Cardiac Bin 1 and Bin 7 for four individual slices. Variation greater in first cardiac bin compared to latter points in the cardiac cycle.
Similarly, the standard deviation of noise was compared specifically within Bin 1 and Bin 7 as the first bin corresponds with the peak of the cardiac cycle and the seventh bin corresponds to the trough (Figure 23). It can be observed that bin 1 has the greatest noise and has 50% greater noise compared to bin 7. This trend is reflected across all three directions, x, y, and z. The pattern of standard deviation of noise in bin 7 is very similar across directions and slices. The pattern of noise in the x direction across slices remains very similar with an area of high variation located at the top of the slice. In the z direction there is also a pattern of high variation located on the right side of a slice that occurs in every slice.

![Net Average Noise](image)

Figure 24. Average noise in a cardiac bin across five slices in all three subjects. Absolute value of the noise was taken for an individual scan prior to the overall average.

The net average noise was calculated across all subjects in order to compute a global average. The noise for an individual cardiac bin in a specific slice across all three subjects were averaged to have a net amount of noise. It is observed that the first cardiac bin generally has the most volume of noise, and the seventh cardiac bin has a
lower volume (Figure 24). The similar trend was viewed within individual subjects. The ability to visualize the trends in cardiac bins across all slices can help evaluate differences in the net average noise between slices. In general, the greatest average noise occurs in the first slice, as well as the 7th, and 8th slices, which corresponds to the top and bottom parts of the brain.

Figure 25. Net standard deviation of noise in cardiac bins for all three subjects. Trends in all eight slices are displayed.

The net standard deviation was calculated from subject standard deviations to provide a global value on the variation in specific slices and bins. The net standard deviation supports the trends in the net average physiological noise. The peak in variation in the cardiac cycle across all slices occurs in the first cardiac bin. The variation in noise then declines across the cardiac bins and recovers prior to systole occurring again. The greatest variance is observed in the first slice in the net standard deviation (Figure 25). The 7th and 8th slices of the brain experience more variation in
noise as well. The middle slices of the brain have less variance in noise. The aggregate standard deviation of noise across all subjects followed the peak and trough of the cardiac cycle but also differed in the level of variation of noise between different slices.

The aggregate and individual trends in the volume of noise across cardiac bins were assessed (Figure 26). The average noise in cardiac bins were plotted across all eight slices for the three individual subjects and the net total. In general, the noise in individual directions paralleled the same pattern of the cardiac cycle. The peak average occurred in the first cardiac bin with the minimum average noise occurring around approximately bin 7. There is also a slight peak in the signal noise in bin 4. While this peak is not as great as in bin 1, it may have physiological implications.

![Average Noise](image)

Figure 26. Average noise in cardiac bins across all 8 slices. Plots for individual subjects as well as a group average are displayed together.

Similarly, the net standard deviation was plotted for each cardiac bin alongside subject specific standard deviations. This plot can be seen in Figure 27. The peak variation of noise occurred in the first cardiac bin. There is a slight increase in the variation of noise between bin 3 and bin 4. The standard deviation then declines from
bins 4–8 before increasing slightly again in bins 9 and 10. This trend remained true in both the global standard deviation and in individual subjects.

**Figure 27.** Standard deviation in cardiac bins across all 8 slices for individual subjects. Net standard deviation is indicated by the bolded blue line.

### 3.3 Aim 3: Quantify noise effects on NLI Stiffness Calculations

The correlation length of noise from a voxel of interest was used to determine the extent to which noise influences NLI calculations. Non-gaussian noise can behave as very correlated and NLI is only equipped to filter gaussian noise. Because NLI constructs a series of subregions to estimate mechanical properties, the more area that contains correlated noise, the greater impact noise will have on calculations. The correlation length from the voxel of interest to other voxels in plane horizontally (x), vertically (y), and out-of-plane across all slices (z) was calculated for a small rectangular region across several slices. The purpose of assessing this small area of an image was to evaluate the effects of correlated noise between points in an image.
Figure 28. Comparison of Noise and calculated Correlation for voxel of interest in a brain slice from one test subject’s scan where the MEG was turned on, but vibration remained off. Voxel of interest selected for correlation comparison is starred (X=30, Y=35).

Although the process of calculating correlation length was iterated over several pixels, one voxel of interest was used in order to demonstrate trends (Figure 28). The voxel of interest selected was located in the 24th slice (Z), and X = 30, Y = 35. The correlation was first assessed in the non-vibration scan, in which the MEG was turned on and vibration was turned off. The correlation calculated across the entire slice can be seen in Figure 28. Noise along the x motion encoding direction near the point appears less correlated, while there is a higher correlation in the peripheral of the slice. In the y encoding direction, the noise appears strongly correlated on the right and left sides of the slice. For the motion encoding in the z direction, the voxels have a similar pattern of correlation to y, with correlation between 0.5 to 0.8.
Figure 29. Correlation for MEG on, Vibration off Scan of one subject for voxel of interest $X = 30, Y = 35, Z = 24$. Plots are shown for all three encoding directions. Best fit line can be seen in red, with the indicated cutoff for the fit.

After calculating the correlation coefficients across an entire image, the correlation coefficients for this voxel of interest were plotted on a semi-log scale in plane and out of plane for all three encoding directions (Figure 29). The points were fitted with a line with a negative slope which became horizontal when correlation became random. The slope of the curve was shallower for pixels that remained correlated a further distance apart from the voxel of interest compared to a curve where it flattened at a smaller distance from the voxel of interest. In Figure 29, the fit of the correlation coefficients demonstrates the distance that noise remains highly correlated. For each motion encoding direction, the correlation in $z$ was the smallest length, with the fitted line levelling out less than 2 pixels away. This is to be expected
because each slice is acquired separately, so physiological noise is not expected to be similar from slice-to-slice. In the x motion encoding direction, noise remained correlated at a further distance from the initial point in plane horizontally than vertically where the horizontal line began at just over 10 pixels in x and around 10 pixels in y. In the y motion encoding direction, the correlation in plane was relatively similar horizontally and vertically where it levelled around 10 pixels away. In the motion encoding in the z direction, the fit levelled off at a greater distance in x than in y, as the best fit line levelled out at almost 30 pixels away in x versus the 4 pixels in y.

Figure 30. Comparison of noise and calculated correlation for a voxel of interest in a brain slice from one test subject’s scan where the MEG and Vibration were on. Voxel of interest selected for correlation comparison is starred (X=30, Y=35).

The correlation coefficients were also calculated for a subject’s vibrational scan as well, in which the MEG and vibration were both turned on (Figure 30). The noise correlation in the x motion encoding direction was less uniform than in y or z. In the y direction, the noise was strongly correlated near the voxel of interest and over a large portion of the central part of the image. This direction had the highest correlation
near the selected voxel of interest. In the z motion encoding direction, the correlation pattern was very similar to that of the y direction. Pixels were highly correlated near the voxel of interest, but were less correlated as the distance increased with the initial voxel of interest.

![Correlation – MEG on, Vibration on](image)

Figure 31. Correlation for MEG and Vibration on Scan of one subject for voxel of interest X = 30, Y = 35, Z = 24. Plots are shown for all three encoding directions. Best fit line can be seen in red, with the indicated cutoff for the fit.

The correlation coefficients in-plane vertically and horizontally, and across slices were plotted and fitted with a curve to estimate the correlation length (Figure 31). The slope of the fitted line is used to calculate the correlation length of noise. Like the no vibration scan, across all motion encoding directions, the correlation out-of-plane across slices had the quickest drop off in correlation. The distance where the correlated fit ended was approximately 2 slices away from the selected slice. In the x
motion encoding, in plane, points vertically and horizontally were more correlated at similar distances of 5 pixels. In the motion encoding direction y, the slope of the line of correlation vertically was much shallower than the x direction with the line extending to a distance of 26 pixels while horizontally the line flattened around 5 pixels. Thus, points remained more highly correlated longer vertically than horizontally. In the motion encoding in the z direction, the slope of the line was smaller in plane vertically than horizontally. The fit leveled in the x direction at 6 pixels and in the y direction at approximately 15 voxels. These fits that had longer distance before a horizontal line corresponded to a correlation of 5 and 8 respectively in x and y.

From the slopes of the curves generated in each direction of the image, the correlation lengths could be calculated for a voxel of interest. Table 8 shows the calculated correlation length for voxel of interest in one subject with the MEG turned on and no vibration and vibration scans. When the MEG is turned on and vibration is off, the motion encoding in the x direction has the smallest correlation lengths out of all three motion encoding directions, with an average correlation length of less than one voxel (0.65). Within an image, the correlation length across slices remains low as well. The motion encoding in the y direction has the longest correlation along the y axis while in the z motion encoding direction the longest length is in the x direction (Table 8A). When the MEG and vibration are both turned on, the motion encoding in the x direction has the least correlated noise across all image axis (Table 8B). However, the correlation length between slices remains around 1 slice away across all three imaging gradients. Overall, the motion encoding gradient in the y direction’s vertical imaging axis had the longest correlation length out of all gradients. It should
be noted that the motion encoding in the y direction is the same direction as the induced vibration. The z gradient direction had a longer correlation length in y than in the x imaging axis in plane. In both the no vibration and vibration scans, the x motion encoding direction had the lowest correlations out-of-plane, with the correlation length average around 1 slice away. In addition, the correlation lengths were longer when the vibration was turned on relative to when it was off. For example, the average correlation length in the motion encoding x direction in plane without vibration was 0.64 while with vibration on was 1.78. The greatest correlation length between the two scans occurred along the vertical axis in plane on the vibration scan in the y motion encoding direction. The correlation length was estimated to be almost 17 pixels.

Table 8. Summary of correlation length for MEG on and (A) Vibration off and (B) Vibration on for a selected voxel of interest (X = 30, Y = 35, Z =24) in one image for an individual subject.

<table>
<thead>
<tr>
<th>A) MEG on, Vibration Off</th>
<th>Image Axis</th>
<th>B) MEG on, Vibration On</th>
<th>Image Axis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gradient</td>
<td>x</td>
<td>y</td>
<td>z</td>
</tr>
<tr>
<td>MEG X</td>
<td>0.69</td>
<td>0.68</td>
<td>0.59</td>
</tr>
<tr>
<td>MEG Y</td>
<td>7.50</td>
<td>10.85</td>
<td>1.10</td>
</tr>
<tr>
<td>MEG Z</td>
<td>12.80</td>
<td>7.04</td>
<td>0.56</td>
</tr>
</tbody>
</table>

The correlation lengths were also calculated over a region of 6x6 pixels in 6 slices central in the brain. This region was assessed in scans no vibration and vibration in the traditional MRE configuration for three subjects. The correlation length of an imaging axis along each motion encoding gradient direction was averaged across all three subjects in order to assess the difference in correlation length between the two types of scans. The net average correlation length can be found in Table 9 and the
standard deviation of the correlation length can be seen in Table 10. Individual subject averages for the no vibration and vibration scans can be found in Appendix C in Table 11 and Table 12. The average correlation length overall when the MEG was on, but vibration turned off was approximately 3.5 pixels while when the vibration was turned on it was 4.5 pixels in length. Thus, the average correlation length with the vibration was greater than without the vibration. In plane correlation length was approximately 350% greater than out-of-plane correlation across both the no vibration and vibration scans.

Table 9. Average Correlation Length Across all three subjects

<table>
<thead>
<tr>
<th>Average Correlation Length</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>MEG on, Vibration off</strong></td>
</tr>
<tr>
<td>Image Axis</td>
</tr>
<tr>
<td>MEG X</td>
</tr>
<tr>
<td>MEG Y</td>
</tr>
<tr>
<td>MEG Z</td>
</tr>
</tbody>
</table>

Different motion encoding directions experienced varying correlation lengths. Although the correlation length along the z imaging axis, out-of-plane, remained around 1 pixel for the three gradient directions, the correlation varied for in-plane noise. The motion encoding in the x direction had the smallest correlation length of noise in-plane, both in the horizontal and vertical directions. The correlation length averaged approximately 3 pixels for the no vibration scan and 3.5 pixels for the vibration scan. For the motion encoding in the y direction, the in-plane noise averaged 3.5 pixels for the no vibration scan and approximately 7 voxels for the vibration scan.
When the vibration is turned on, the head is propagating in the y direction which is compounds the amount of noise in-plane. The motion encoding in the z direction was most similar between the no vibration and vibration scans. The correlation length averaged approximately 7.5 pixels for both directions.

Table 10. Standard deviation of Correlation Length Across all three subjects

<table>
<thead>
<tr>
<th>Gradient</th>
<th>Image Axis</th>
<th>MEG on, Vibration off</th>
<th>MEG on, Vibration on</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>x</td>
<td>y</td>
</tr>
<tr>
<td>MEG X</td>
<td></td>
<td>0.78</td>
<td>1.25</td>
</tr>
<tr>
<td>MEG Y</td>
<td></td>
<td>0.28</td>
<td>0.45</td>
</tr>
<tr>
<td>MEG Z</td>
<td></td>
<td>4.97</td>
<td>5.36</td>
</tr>
</tbody>
</table>
Chapter 4
DISCUSSION

4.1 Aim 1: Characterize bulk motion noise in the in vivo brain and in phantom models

Overall, bulk motion noise was observed to vary between Traditional MRE and Restricted MRE in Brain and Phantom models. Both experiments demonstrated how image noise, physiological noise, and vibrational noise contribute to lower quality images in MRE. Isolating these different sources of signal noise is valuable in being able to determine the factors that are attributed to each type of signal noise. This provides the foundation to take the first steps towards methods to correct these issues.

4.1.1 Brain MRE

Between Traditional MRE and Head Restricted MRE, there was little difference in the level of noise in the scans for image noise (both MEG and Vibration off) and physiological noise (MEG turned on). This trend occurred because the addition of foam pillows would not change the nature of the signal noise present or some aspect of physiological noise. Image noise also would not change as a result of patient motion. Physiological sources of noise are dependent primarily on intrinsic movement, such as the cardiac cycle or breathing, which would continue regardless of head restriction being implemented. Therefore, the utilization of foam pillows to restrict head movement really only has an effect on patient motion and not physiological movement. Foam pillows would reduce small head motions by the subject, however, and this data indicates that it can be a small problem in MRE.

When the vibration was turned on the greatest amount of noise was observed in the y direction. In MRE, the vibration is in the y direction, starting at the posterior of
the head. Thus, the greatest noise observed was in the same direction as the vibration in y. This occurred in both Traditional MRE and to a greater extent in the Head Restricted MRE. The utilization of foam pillows limits the x and z bulk motion, thus leaving the head to move freely in the y direction, which contributes to additional signal noise in this direction, though less in others. Limiting motion in the x and z directions but not in y is optimal for MRE. The y motion contains the MRE wave propagations, which is what the modality is trying to capture. Motion in the x direction is left-right motion while z motion is the rotation of the head, which are not the forms of motion to prioritize in MRE. Furthermore, the nature of the noise with the restriction is altered as the noise in the y direction had a greater spread. This means that less noise is centered around zero. The noise likely does not follow a normal distribution, but the images acquired in the Head Restricted MRE may in fact be more accurate than Traditional MRE. Incorporating the use of foam pillows to restrict head movement has been incorporated in fMRI and diffusion imaging studies to reduce subject movement.[65], [66] It is particularly advantageous to incorporate the use of foam pillows to restrict motion in protocols in pediatric studies where the subject’s head size is significantly smaller than the coil and the subject is prone to move. [67]

With restriction of the x and z motion to reduce noise, there is some unintended loss of signal. However, as it is the signal to noise ratio that is relevant in making MRI images, this is a compromise that must be made and may be advantageous in the long run. For the purpose of these experiments, the restrictions were very extreme. The use of pillows to this extent may dampen the actual MRE motion and thus alter the stiffness calculations. This may not necessarily be problematic, as the reduced noise model may in fact have a more accurate stiffness
calculation. It was observed that the nature of the signal noise in the y direction changed, referring to indicators such as the distribution of the data. The altered signal noise may reflect changed signal being observed as well. Furthermore, the incorporation of physical restrictions of movement will not solely correct motion errors in MRE. Sequence navigators and retrospective motion correction have been shown to produce larger changes than physical restrictions. [65] All in all, the use of some restraints of movement would definitely be beneficial especially in clinical populations prone to present greater head motion. [68]

Several limitations can be considered for this series of experiments. The Head Restricted MRE may compromise signal for reducing noise. The addition of the foam pillows may be uncomfortable for subjects, depending on the degree to which the pillows are added in the head coil. A threshold may need to be determined in the future to properly assess the degree to which the foam pillows are utilized in a protocol. Additionally, for these experiments, a subject always was scanned with the Head Restricted MRE first and then the Traditional MRE. Because the Traditional MRE was at the end of the scanning duration, subject movement may have been more pronounced.

Overall, the brain MRE experiment demonstrates the ability to characterize image noise, physiological noise, and vibration noise factors separately. Subject motion likely does not contribute as much to image noise and physiological noise; however, it is very predominant in vibration. The use of foam pillows to prevent subject movement has been shown to be effective in reducing the signal noise, but the use of the pillows must not reduce subject comfort or limit the y motion that is necessary in calculating brain mechanical properties.
4.1.2 Phantom MRE

The understanding of noise in Phantom MRE is an important aspect to consider because Phantom MRE models are commonly used to validate sequences and techniques. Knowing what the nature of noise in phantom MRE is like can help develop denoising techniques and further improve the model as a verification tool to test new methods.

The Phantom MRE noise had several similarities to the Brain MRE. When the MEG and vibration was both turned on, the greatest amount of noise was observed in the y direction for both Traditional and Restricted MRE. The greater noise in the y direction is likely due to the addition of the foam pillows that prevent x and z motion. However, it was very apparent in the Phantom MRE model that the restricted MRE had a significant lower volume of signal noise overall. The movement in the Phantom MRE was reduced due to the restriction from not only the foam pillows, but was compounded by taping the phantom to the head coil.

The phantom experiments also confirmed what noise was observed in the Brain MRE experiments. Approximately the same amount of signal noise is observed when the MEG and vibration were both turned off in the Restricted MRE and Traditional MRE configurations. Thus, only image noise is represented in this scan, similar to what was observed in vivo. However, when the MEG was turned on, differences in the amount of noise occurred. In the z direction, the Restricted MRE had less noise than the Traditional MRE. Like the in vivo model, the decrease in noise is likely due to the addition of the foam pillows which limits movement. Noise in the z direction when the MEG is turned on was a lot less than in vivo models probably because the phantom lacks physiological noise, such as the cardiac cycle or breathing. These factors often propagate the brain in the z direction on a scale of hundreds of
microns. [9], [45] Because the phantom does not pulsate, likely the only factor affecting noise in the Restricted MRE is table shaking. When the MEG and vibration are both turned on, the Traditional MRE and Restricted MRE configurations experience the greatest volume of noise in the y direction. However, the volume of noise in the Restricted MRE is less than the Traditional MRE setup. This decrease in noise is likely due to the additional limitations of movement in the restricted MRE. Interestingly, the noise in the z direction remains relatively constant between the Traditional and Restricted MRE scans when the vibration is turned on. This is likely because the phantom lacks physiological sources of movement, so only external factors contribute to movement in the z direction.

It is also important to evaluate how restricting movement alters the wave motion that is used in NLI for stiffness calculations. Comparing the wave images between the Traditional and Restricted MRE, the wave motion is less in the Restricted MRE. This event is probably due to the nature of taping the container more to the surface of the head coil. However, because the vibration in the y direction has least restraint, it does not decline as much relative to x and z. The decrease in wave motion observed was in light of increasing the amplitude of the motion in the Restricted MRE from 5% to 10%. Thus, it is likely that in order to achieve proper MRE motion in a Restricted MRE configuration in phantoms that the vibration amplitude must be increased. A potential challenge of the altering wave motion is that the smaller wave motion in the Restricted MRE can result in differing stiffness calculations in NLI. Nonetheless, changes in wave motion are not too much of an issue in NLI calculations, as long as the noise in the image is low as well. If the SNR remains above a threshold, the calculations can still be made.
Because phantoms are part of MRE experiments, it is necessary to provide a threshold to which someone may add restrictions of movement in the model. It is necessary to balance restricted movement with the ability to properly propagate shear waves through the material. It is recommended to insert foam pillows to prevent movement during phantom experiments, but that the fit should not be tight such that the phantom has no movement. Furthermore, to compensate for more restricted movement, vibration should be increased to 10% amplitude rather than 5% which is typically used. [64] Future experiments studying noise in phantom models can compare differences in volume, materials, and viscoelasticity to closer mirror brain tissue and the signal noise present.

4.2 Aim 2: Isolate and quantitatively assess cardiac cycle signal noise in the in vivo brain.

The purpose of assessing cardiac cycle signal noise was to observe the presence of cardiac related signal noise in MRE. The grouping of repetitions of the same slice into bins allows the ability to assess the prediction that a greater noise is observed at the peak of the cardiac cycle. Both the computed standard deviation and average across the cardiac bins confirmed that the cardiac cycle physiological noise was present in MRE images.

The pattern of physiological noise observed in these experiments corresponds to the pulse-oximeter signal. Because the pulse-oximeter signal is used to measure cardiac activity, it can be inferred that the physiological noise that is primarily observed is associated with cardiac cycle processes. The cardiac cycle is closely linked to intracranial pressure and fluid flow, which can alter the blood pressure over the course of the cardiac cycle. This likely causes the pulsatile nature of the brain,
which results in unwanted motion in MRE. [69] Although other factors that may contribute to physiological noise such as breathing or table shaking, the pulsation of the brain due to the cardiac cycle is on a scale of hundreds of microns. [45] While the MRE sequence is only weakly sensitive to motion in the frequency range of cardiac pulsation, such large motion only results in noise terms, but they are large enough to be significantly correlated.

The peak amount of signal noise in the first bin potentially aligns with the start of systole in the cardiac cycle. During the beginning of systole, the aortic valve opens, and blood is ejected from the left ventricle. Aortic pressure also increases, which would alter the blood flow in the brain. [38] When the inflow of blood occurs, the pressure rises exponentially, thus blood flow changes, despite no changes in blood volume in the heart. This behavior leads to a slight increase in cranial pressure, as the pulse wave dissipates to surrounding tissue in microvascular and venous pulsations. [69] The cranial blood flow movement likely leads to unwanted tissue movement, and thus the MEG records this error. Therefore, the first cardiac bin is likely to be coordinated with the beginning of systole in the cardiac cycle, causing the greatest signal errors in the brain.

A secondary peak in average and variation of noise was observed in bin 3 to bin 4. This secondary peak is possibly occurring at the same time relative to the secondary peak that can be observed in the pulse-oximeter signal. This peak does not share the same amplitude as the systolic peak, but does coincide with the slight increase in the average signal noise in bin 3. This smaller peak is known as the dicrotic beat, which is associated with the elastic recoil of the aorta and aortic valve. [70] This event would slightly alter the blood pressure and flow, which may be reflected in
changes of brain arteries. These changes could cause a slight increase in noise errors. Once the aortic valve closes, the diastolic phase of the cardiac cycle takes place.

The lower average and variation of signal noise in bins 4-9 is likely associated with the diastolic phase in the cardiac cycle. During this phase, the blood vessels are returning blood to the heart in anticipation for the next contraction. [38] Because blood is leaving the brain instead of being pulsed to the brain, it could possibly be associated with a decline of signal noise which was observed in cardiac bins 4-9. In other words, the blood flow is much more passive during diastole than when blood is forced into the brain in systole. During diastole, the pressure in the heart also remains relatively low as the blood volume refills. The lack of dynamic changes in pressure is associated with a lack of electrical signal captured on ECG as well. [41] Because of a lack of dynamic pressure changes during this period of the cardiac cycle, it is likely that there would be less signal noise as well.

While noise within a slice mirrors the pattern of the cardiac cycle, it is also necessary to evaluate how the physiological noise varies between slices. The eight slices were distributed evenly across the brain in order to evaluate differences in physiological noise. The variation and average noise were greater in outer slices of the brain. The increase in noise on outer slices is likely due to the fact that in these regions of the brain there is slightly more room to move. These slices are also associated with regions of the brain which have previously been shown to be affected by cardiac motion related artifacts. The brain stem and corpus callosum are regions which have been observed to experience greater displacement due to cardiac pulsation in the brain. [46], [59] In a previous study, it was reported that the peak mean displacement of the brain stem was approximately 186.7 µm, the corpus callosum was 65.3 µm and the
cerebellum was 105.2 μm. [46] These structures are located lower in the brain and thus are most susceptible to displacements that can be attributed to the cardiac cycle. Therefore, an increase in physiological noise in these regions, slice 1 and 2 of the scans, can likely be attributed to the cardiac motion that occurs in the area. The eighth slice also experienced a greater volume of noise. Slices 7 and 8 only capture a small area of the brain. The periphery of the brain in MRI is susceptible to field inhomogeneity and lower signal-to-noise ratio, so it is likely that these events cause an increase in signal noise for these slices. [71]

It is also necessary to understand which motion-encoding direction experiences the greatest physiological noise. The scans in these experiments were where the MEG was turned on, but the vibration was turned off, thus the only noise present would be related to physiological processes. The most physiological noise is observed in the z direction, which is probably due to the pulsatile motion of the brain during the cardiac cycle primarily taking place in the z direction. [46] These experiments therefore may show that physiological noise is most problematic in the z direction and efforts to correct physiological artifacts should target this motion encoding direction.

To use this information in practice, it is necessary to evaluate the timing of the cardiac cycle relative to the MRE vibrational frequency. The vibration is delivered at 50 Hz, which means the vibration occurs every 20 ms. Additionally, the average heart rate is between 60 to 90 beats per minute, or the duration peak-to-peak of the cardiac cycle is 600 - 1000 ms. [72] However, the sampling rate of the MRI scan is the echo time, which is 65 ms for these scans. The different periods of times between cardiac cycle peaks, vibration, and acquisition of data mean that not every data point is associated with the peak in the cardiac cycle. For every cycle, approximately 15
images are acquired. Thus, interference of the cardiac cycle may only occur in a handful of images, rather than an entire data set. Cardiac cycle is particularly an issue because it propagates the brain hundreds of microns while the MRE displacement is only on a scale of ten microns. [9], [45] NLI tries to focus on only the 50 Hz signal; however, if the cardiac cycle happened to align with the 50 Hz vibration it may not capture the accurate motion, especially because the amplitude of the cardiac cycle changes is much greater than the MRE vibration. The timing of physiological processes are important factors to consider when developing methods mitigate physiological noise in MRE images.

In these experiments the work primarily focused on cardiac cycle noise. Other physiological sources of noise were not assessed, as the assumption was that cardiac motion is the most predominant source. In reality, other sources of internal movement are factors that contribute to physiological noise. Subtle table movement can be recorded when the MEG is turned on. In phantom models, this is on the of the factors that contributes to physiological noise that appears in the z motion encoding direction. Breathing is another physiological factor that displaces the brain. A person takes between 12 to 16 breaths per minute, which is one breath approximately every 3.75 to 5 seconds. [73] Therefore, if the acquisition and/or vibration coincides with the breath, this event may lead to increased sources of error. Previous studies have demonstrated how respiratory pulsation is in the ventricular and cortical cerebrospinal fluid, which can contribute to motion errors in the region. [28], [36], [74] Future projects can assess the impact of respiration and other physiological disturbances on signal noise in MRE.

Other limitations of this experiment are the timing between the cardiac cycle, MRI system, and pulse-oximeter device. The pulse-oximeter data is recorded in a text
file at a 50 Hz frequency, or one point every 20 ms. [75] The pulse-oximeter is placed at the finger so there are inherent physiological delays between when the heart beats and when the device records a signal. Furthermore, the lag in blood volume changes in the brain can be upwards of 100-150 ms. [69] Although efforts were made to coincide the maximum noise in the first cardiac bin with the peak in the cardiac cycle, slight discrepancies lead to this process being imperfect.

Overall, physiological noise measured was observed to be closely related to the systolic and diastolic phases of the cardiac cycle. The peak amount of noise in bin 1 is likely associated with the start of systole in the cardiac cycle. Additionally, lower slices of the brain that were captured had the greatest amount of physiological noise, which possibly corresponds to regions of the brain that experience the greatest influence of the cardiac cycle, such as the brainstem. The larger amount of noise observed in the topmost slice of the brain also has a high volume of noise, which is likely due to more space for the brain to move and the lower SNR that is common in the periphery of the brain. Understanding the influences of cardiac physiological noise provides a foundation to implement effective corrective techniques to limit brain physiological motion.

4.3 Aim 3: Quantify noise effects on NLI Stiffness Calculations

The purpose of the third aim was to evaluate how much of an issue non-gaussian signal noise is in the NLI calculations. The NLI algorithm solves over a 10x10x10 pixel region. Thus, if noise is highly correlated between voxels over the entirety of this space, the noise has non-gaussian behavior. Gaussian noise would typically appear as random, such that the correlation between voxels would be low. Having an understanding of how much correlated noise exists can help researchers
better design NLI to correct for non-gaussian signal noise. Because the algorithm solves only a set matrix size, correlated points that are far away from the point of interest would not affect the stiffness calculation. However, in-plane pixels that are nearby a point of interest and are highly correlated could cause miscalculation.

Images of the correlation of one voxel of interest to the entire image demonstrate how non-gaussian noise varies across the three motion encoding directions (Figure 28). When the MEG is on, but the vibration is off, the noise in x is very random, thus it is likely there is a higher amount of Gaussian noise present in the x motion encoding direction. Because noise in the x direction is associated with left-right head movement, it is only when a subject shifts their head that spikes in signal noise would occur in this direction, so it is likely to be less correlated than other directions. This trend is further shown in the image of the correlation of one voxel of interest across an entire image. In the x motion encoding direction, the correlation coefficient appear more random near the region of the voxel, thus the noise is probably more gaussian in nature. Thus, it may not impact the stiffness calculation. Meanwhile, the y and z motion encoding directions appear to have much more correlated noise near a selected point. The higher correlation of noise in the y and z motion encoding directions may correspond to the presence of the more applied motion in the y direction, and physiological motion in the z direction.

When the MEG and vibration are both turned on, not only does the amount of noise present in a slice increase, but there is a higher correlation across images between voxels compared to the scan without the vibration. Noise continues to remain more random in the x motion encoding direction, with correlation coefficients near the selected point slightly positive around approximately 0.2. On the other hand,
correlation in the y motion encoding direction remains highly correlated. Because the y motion encoding gradient direction is the same direction of the MRE vibration, it is likely that additional subject motion is the cause of this highly correlated noise. The z motion encoding direction has the highest amount of noise and similarly had a higher correlation of noise between voxels. In the same direction as this motion encoding, physiological processes, such as the cardiac cycle, propagate the brain. These sources of noise likely contribute to non-gaussian noise present in images, thus a greater correlation between voxels is present.

To assess noise more quantitatively, the correlation length was calculated both in plane and out-of-plane. More noise was correlated in plane than out-of-plane for both the nonvibrational and vibrational scans. This is likely due to how data is acquired in images. Images are constructed entirely in plane first before progressing to the next plane. When capturing a slice in an EPI sequence, the information is collected in plane at once in a single pass. Once the data for that entire image is acquired, we move to the next plane to acquire another series of in-plane information. Because the event of progressing between slices, through plane, does not occur immediately adjacent to a voxel, the noise would probably be less related across slices. However, because in-plane voxels are collected at the same time and include the same motion, it is anticipated that these adjacent voxels could be highly correlated. This is the trend that was observed in the no vibration and vibration scans. Out of plane noise, which was represented by the correlation length through plane in z, remained on average approximately 1 pixel both for vibration and no vibration scans. Meanwhile, the x and y correlation lengths, which represent the distance pixels remain highly correlated vertically and horizontally from a voxel of interest, were approximately 5 and 4.5
pixels respectively for the no vibration scan and 6 voxels in each direction for the vibration scan. This trend was consistent in images in all motion encoding gradient directions because the images are acquired identically.

The x motion encoding direction experiences the lowest correlation length across all imaging axis for both the no vibration and vibrational scans. The average correlation length for scans was about 2.5 pixels. The longest correlation occurred in the y (vertical) imaging axis in plane around 4 pixels, while the z direction, out-of-plane had the smallest correlation length of approximately one voxel. There is also probably more gaussian noise present in this motion encoding direction. The motion encoding in the x direction is associated with left-right movement. This movement may not contribute as much to signal noise as other factors in the y and z directions.

The motion encoding in the y direction had longer correlation lengths along the imaging axis than the motion encoding in the x direction. When the vibration was turned off the average across imaging planes was approximately 3 pixels while when the vibration was turned on the correlation was about 5 pixels. This difference in correlation length is likely due to the additional vibration which propagates the head more in y direction. This may lead to a greater volume of correlated signal noise, thus a higher correlation between pixels in plane. In plane, the correlation length in the vibration scan reached almost 7 pixels in length. This distance could begin to be an issue in the NLI stiffness calculation as NLI uses a 10x10 matrix. That would imply that almost 50% of the pixels in that matrix have highly correlated non-gaussian noise which the algorithm would not correct for.

The z motion encoding direction had the longest correlation lengths out of all three encoding directions. On average, the correlation length in the no vibration scan was 5
pixels while in the vibration scan it was 5.5 pixels. The correlation length reached upwards of 8 voxels in plane. There are likely higher correlation lengths in this motion encoding direction than in the others because more non-gaussian noise may occur in this direction. Along the z axis, physiological sources of noise, such as the cardiac cycle, breathing, and table shaking propagate the brain. Like the other motion encoding gradients directions, out-of-plane pixels had the shortest correlation length. This is likely because the timing of the acquisition is not as close as pixels in-plane. Thus, if the cardiac cycle is at its peak during systole at the same time an image is acquired, the error will likely occur very similarly over a group of pixels in-plane. A correlation of upwards of 8 pixels in-plane could potentially lead to calculation errors in NLI. In the 10x10 matrix, 64% of the voxels would contain highly correlated, non-gaussian noise. Thus, it may be necessary to focus on non-gaussian filtering techniques in the z motion encoding direction to reduce the noise present in estimations.

Although the correlation length was calculated, there were several limitations within the methods. Because these correlation lengths were calculated using the piecewise function, the fit may be imperfect. The slope of the best fit line could have been inaccurate. Moreover, we were unable to use every pixel in an image as a voxel of interest. Rather only a small region of an image was used. However, because calculated correlation lengths had relatively small standard deviations, we can infer that are results are consistent across an entire image. Further work on assessing the correlation within specific regions of the brain can help identify how prevalent non-gaussian noise is in different slices. In addition, in-place noise was only assessed vertically and horizontally from a point. In reality, points diagonal from a voxel of
interest could be highly correlated as well. While it may be more accurate to measure more in-plane relationships, selecting only two in-place directions helped simplify the problem and reduce the amount of time to compute the correlation length. Also, in the experimental setups in the scanner, foam pillows were not used to reduce head movement. It may be worthwhile to calculate the correlation lengths when foam pillows are implemented to reduce head motion. It is expected that the correlation length would be even less in motion encoding directions as the use of foam pillows was observed to reduce signal noise. The correlation length may inform us on how noise is changed with the use of foam pillows.

4.4 Future Directions

This project was the first in-depth assessment of sources of signal noise in MRE. The understanding and knowledge gained from this project can extend into future work in developing techniques to limit image, physiological, and vibrational signal noise in MRE. Future work can focus on developing navigators in MRE sequences to correct for motion. Acquiring higher quality images limits the need to do retrospective motion correction, which can potentially save researchers more time. It is also advised to utilize foam pillows to lightly restrict the left-right movement of an individual’s head. However, it is important to ensure that the subject is still comfortable and that the desired vibration can still be achieved. To compensate for the added restriction, the amplitude of the MRE vibration should increase in order to still meet the desired shear wave propagation.

Future work can also focus on techniques to work with images that are captured at the peak of systole. One option is to oversample the brain and identify images that were captured at the start of systole in the cardiac cycle. These images
could then be removed without compromising the data set. As an alternative, these images could be weighed less relative to images captured during diastole such that no data is loss in the post-processing pipeline. However, both of these proposed methods would increase the duration of the scan; therefore, it is a balance between data quality and scan time. Developing and contrasting these techniques can help further correct for physiological noise that occurs due to the pulsation of the brain during systole.

Because the correlation length has been estimated for pixels acquired in images in all three encoding directions, there is a higher understanding of the degree to which non-gaussian noise is a problem. NLI can be adjusted to not capture only voxels corrupted by highly correlated noise. Some potential solutions could be enlarging the matrix that NLI uses such that it would capture more uncorrelated noise between voxels and thus improve the estimation. The correlation length is an informative metric to researchers to further improve the NLI calculation’s accuracy and reduce the influence of non-gaussian related noise present in images. The correlation length can also be used to estimate how other proposed methods improve the quality of images. Calculating the correlation length of noise in experimental configurations with foam pillows, new sequences, or removing images occurring during systole, can provide a metric for how noise influences mechanical property calculations.
Chapter 5

CONCLUSION

Signal noise alters the quality of images in MRE. Image noise is inherently present in all images, but techniques are developed to mitigate the effects. Physiological noise is also present because MRE uses motion encoding gradients to capture motion. Different sources of physiological noise include the cardiac cycle, breathing, and table shaking. The cardiac cycle is the most predominant physiological noise because it displaces parts of the brain up to hundreds of microns while MRE motion induces displacements on the scale of a couple of microns. The vibrational noise is present when the motion of MRE is turned on. This work is one of the first extensive projects detailing the effects of image, physiological, and vibrational noise in MRE as well as how it influences mechanical property maps calculations.

In assessing the noise related to head motion, the noise is evenly spread in the three motion encoding gradient directions. However, when foam pillows are implemented to restrict movement, the noise in x and z is reduced. This is likely because the foam pillows restrict left-right motion. Because motion is reduced in these two directions, there is an increase in signal noise in the y direction, which is the same direction as the induced MRE mechanical vibration. These observations were demonstrated in both in vivo and phantom models.

For characterizing cardiac cycle noise, images were acquired with the MEG on, but MRE vibration turned off to only assess physiological noise. Images retrospectively aligned with the cardiac cycle, which was recorded through the pulse-oximeter device. The noise is likely greater in images captured at the start of systole, when blood flow is drastically altered and pressure in veins and arteries increase.
More noise occurred during systole and a lower volume of noise was observed during diastole. Because both the cardiac cycle and MRE vibration are harmonic motion, when these two events occur simultaneously, it is likely when the increase in errors occurs. Filtering or removing images captured during systole may mitigate this effect.

Once signal noise was observed quantified in raw images, it was necessary to then evaluate how much of an issue non-gaussian noise causes in NLI calculations. Non-gaussian noise is likely to be highly correlated between pixels while gaussian noise would not. Correlation length is a metric used to determine how far pixels are correlated from each other. Voxels out of plane from one-another were probably not likely to have non-gaussian noise errors as the length of the correlation averaged around 1 voxel. However, in-plane, voxels were highly correlated on average 5 pixels away with a maximum length of over 8 pixels. These significant differences between in-plane and out-of-plane noise can likely be attributed to how images are acquired entirely in one plane and then progress to the next image, such that only points near each other in plane may experience a similar source of noise and thus be highly correlated to one another.

Overall, signal noise causes lower quality images in MRE. Understanding how head motion and the cardiac cycle affect images can help researchers further develop and implement methods to reduce the effects of these images. Assessing the degree of non-gaussian noise present in images provides a tool to inform on noise effects in NLI. The pairing of assessing raw non-gaussian sources of noise with an understanding of the relation between voxels provides a novel assessment of the extent to which noise affects mechanical property calculations. The understanding gained by this work is critical in the development of MRE as a tool for assessing brain health.
REFERENCES


Sep. 1996.


[71] N. I. Avdievich, H. P. Hetherington, A. M. Kuznetsov, and J. W. Pan, “7T head


Appendix A

ARDUINO DESIGN

The Arduino was utilized in order to record the MEG simultaneously with recording pulse-oximeter data. The Arduino was connected to the Siemens 3T MRI system via data cable through a patch panel. The Arduino was programmed in the Arduino IDE to record when the motion encoding gradient was turned on. Figure 32 shows how the Arduino UNO was integrated within the MR system while Figure 33 shows the electrical configuration of the Arduino Uno. Figure 35 and Figure 36 show the engineering drawings of the box to contain the Arduino components. The base and lid were printed via a 3D printer.

Figure 32. Fritzing Diagram for Arduino
Figure 33. Engineering drawing of Arduino. [76]

```c
int outPin = 13; // output is attached to digital pin 13
int inPin = 7;  // input is connected to digital pin 7
int tDelay = 100;  // 100 ms stretching
int val = 0;

void setup() {
  pinMode(outPin, OUTPUT); // set output to computer
  pinMode(inPin, INPUT);   // set input to MRI system
}

void loop() {
  val = digitalRead(inPin);
  if (val == HIGH)  // MEG signal
    {
    digitalWrite(outPin,HIGH); // send MEG signal as external trigger to system
    delay(tDelay);
    }else{
    digitalWrite(outPin,LOW);  // no MEG signal
    }
}
```

Figure 34. Screenshot of script written in Arduino IDE to deliver a signal to the MRI system when the MEG is turned on.
Figure 35. Engineering drawing of container for Arduino designed used Solidworks CAD software.

Figure 36. Engineering drawing of lid for Arduino container. Solidworks software was used to create the software.
Appendix B

Aim 1: Brain MRE Additional Results

Individual subject data for the average noise in an image can be found below. Because of the similarity between subject profiles for scans, the average noise across all scans were taken and statistics were calculated off of the net average.

Figure 37. Comparison of Traditional MRE and Restricted MRE for Subject #1 for the three unique scans.
Figure 38. Comparison of Traditional MRE and Restricted MRE for Subject #2.

Figure 39. Comparison of Traditional MRE and Restricted MRE for Subject #3.
Aim 3: Correlation Length Averages for Individual Subjects

To investigate whether the trends observed in one voxel of interest was consistent with an entire image, a region of 6 pixels x 6 pixels x 6 slices was chosen to measure the average correlation length across several voxels. The results for each the three individual subjects can be found below. Average correlation length was computed for individual subject prior to averaging across all three subjects. Scans that were used were where the MEG was turned on and (1) vibration is off and (2) vibration is on with a traditional MRE configuration.

Table 11. Average Correlation length for three subjects when MEG is on and Vibration is off.

<table>
<thead>
<tr>
<th>Gradient</th>
<th>x</th>
<th>y</th>
<th>z</th>
</tr>
</thead>
<tbody>
<tr>
<td>MEG X</td>
<td>2.70</td>
<td>2.08</td>
<td>1.08</td>
</tr>
<tr>
<td>MEG Y</td>
<td>4.36</td>
<td>3.24</td>
<td>0.99</td>
</tr>
<tr>
<td>MEG Z</td>
<td>7.43</td>
<td>4.14</td>
<td>1.01</td>
</tr>
</tbody>
</table>

Table 12. Average Correlation length for three subjects when MEG is on and Vibration is off.

<table>
<thead>
<tr>
<th>Subject 1</th>
<th>MEG on, Vibration On</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gradient</td>
<td>x</td>
</tr>
<tr>
<td>MEG X</td>
<td>4.27</td>
</tr>
<tr>
<td>MEG Y</td>
<td>6.16</td>
</tr>
<tr>
<td>MEG Z</td>
<td>7.87</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Subject 2</th>
<th>MEG on, Vibration On</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gradient</td>
<td>x</td>
</tr>
<tr>
<td>MEG X</td>
<td>2.33</td>
</tr>
<tr>
<td>MEG Y</td>
<td>10.02</td>
</tr>
<tr>
<td>MEG Z</td>
<td>5.58</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Subject 3</th>
<th>MEG on, Vibration On</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gradient</td>
<td>x</td>
</tr>
<tr>
<td>MEG X</td>
<td>3.25</td>
</tr>
<tr>
<td>MEG Y</td>
<td>4.63</td>
</tr>
<tr>
<td>MEG Z</td>
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</tr>
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