THE PENNSYLVANIA STATE UNIVERSITY
SCHREYER HONORS COLLEGE

DEPARTMENT OF ENGINEERING SCIENCE AND MECHANICS

A STUDY OF CHIARI MALFORMATIONS USING MAGNETIC RESONANCE ELASTOGRAPHY

OSMAN VELEDAR

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Reviewed and approved* by the following:

Dr. Corina S. Drapaca
Assistant Professor in Engineering Science
Thesis Supervisor

Dr. Tony J. Huang
James Henderson Assistant Professor
Honors Adviser

Dr. Judith A. Todd
Professor
P. B. Breneman Deparment Head Chair

*Signatures are on file in the Schreyer Honors College and Engineering Science and Mechanics Office.

ABSTRACT

Magnetic Resonance Elastography (MRE), also called *palpation by imaging*, is a non-invasive, *in vivo* imaging technique used to measure the elasticity of a biological tissue subject to dynamic or static mechanical stress. The resulting strains are measured using magnetic resonance imaging (MRI) and the related elastic modulus is computed from models of tissue mechanics. Such a technique can be used not only as a non-invasive diagnostic tool for tumor detection, but also for gaining fundamental knowledge about the *in vivo* mechanical properties of normal biological tissues. In particular, brain MRE using the natural pulsations of the brain will help us better understand the brain mechanics. In this thesis we will investigate the changes in the stiffness of the brain tissue due to the presence of chiari malformations. We will use magnetic resonance images from Hershey College of Medicine of brains of patients with chiari malformations before and after the surgery to show that the brain tissue appears to be stiffer and more inhomogeneous before surgery, when the chiari malformation impedes the proper circulation of the cerebrospinal fluid in the brain, and that it is softer and more homogeneous after the surgery, with stiffness values close to normal ones known from in vivo MRE experiments.

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Chapter 1

Introduction

Clinical imaging is one of the most powerful techniques of modern medicine used in diagnosis, treatment planning, and assessment of rehabilitation outcome. However, the technique suffers from some inherent limitations such as limited field of view (ultrasound), exposure to dangerous radiations (CT), or radiologist's subjectivity. In recent years, a novel modality for analyzing pathologic conditions that couples classic medical imaging methods and information about the stiffness of tissues has been showing increasing promise to improve the outcome of radiological exams and reduce the high cost required by other diagnostic procedures. This new method is called image elastography.

An elastogram is the mapping of material parameters (the Young's modulus, for example) in an anatomically meaningful image. The approaches to date have been to use conventional imaging methods to measure the mechanical response of tissue to mechanical stress. The resulting strains have been measured using ultrasound, CT, or MRI and the related elastic modulus has been computed from biomechanical models of tissues. In particular, the MR elastography method (MRE) using harmonic shear waves offers direct visualization and quantitative measurement of tissue displacements, high sensitivity to very small motions, a field of view unencumbered by acoustic window requirements, and the ability to obtain full three dimensional displacement information throughout a volume.

Although MRE is still in its design and research stages, it has been recently approved to be used in clinical applications of the liver. In the clinical community it is well-known that a healthy liver is very soft, while a liver that has developed fibrosis is firmer, and if the condition progresses to cirrhosis, the liver can be almost rock-hard. If detected early, fibrosis of the liver can in many cases be treated. Once the disease progresses to cirrhosis, the condition is irreversible. Conventional imaging techniques are not effective in these cases. The traditional diagnostic is to obtain an actual specimen of liver tissue through a

needle biopsy which is a risky and painful surgical procedure. By using the MRE technique, a group of researchers from Mayo Clinic has shown that MRE will have sensitivity for diagnosing liver fibrosis of 98 percent and a specificity level (absence of false positives) of 99 percent [2]. Given these exceptional results, the MRE procedure and software for liver applications have been approved for use in hospitals and medical centers. Fig. 1 shows the difference in stiffness values between a healthy liver and a liver with stage 3 fibrosis.

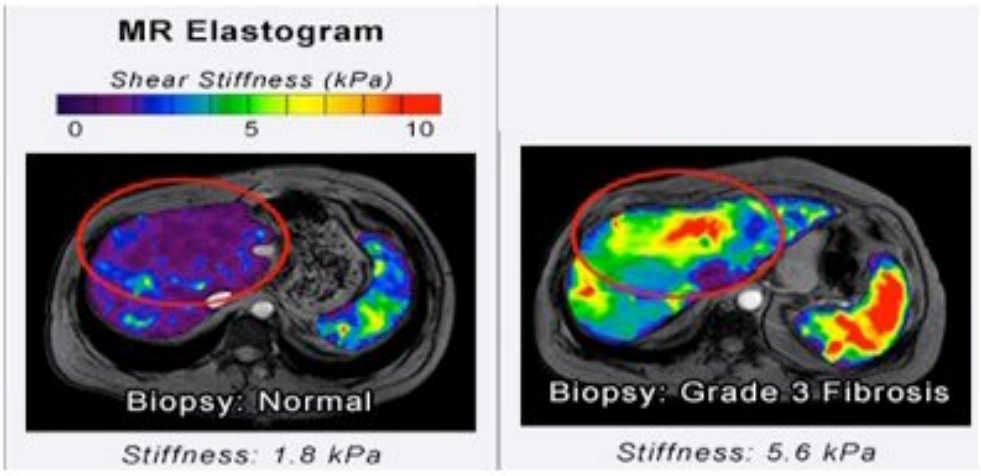


Fig. 1: Stiffness values of a normal liver (left) and at stage 3 fibrosis (right image) [2].

Inspired by the success of the MRE method in predicting the fibrosis in liver, we decided to investigate the stiffness of the brain tissue in patients with chiari malformations using MRE. The reason why we have chosen this particular condition of the brain will become apparent once we introduce and discuss the characteristics of these malformations.

Chiari malformation (CM) includes a complex group of disorders characterized by herniation of the cerebellum through the large opening in the base of the skull (foramen magnum) into the spinal canal [4]. The herniated tissue blocks the circulation of cerebrospinal fluid (CSF) in the brain and can lead to the formation of a cavity (syrinx) within the spinal cord. There are three main types of CM. CM1, the

simplest and most prevalent form is generally considered to be a congenital malformation, which is rarely apparent at birth (see Fig.2). CM2 and CM3 are more severe congenital malformations that are apparent at birth and associated with complex defects of the brain and spinal cord.

Patients with CM1 may experience no symptoms. When symptoms are present, they usually do not appear until adolescence or early adulthood, but can occasionally be seen in young children. The majority of patients complain of severe headache and neck pain. Other common symptoms are dizziness, vertigo, disequilibrium, visual disturbances, ringing in the ears, difficulty swallowing, palpitations, muscle weakness, impaired fine motor skills, chronic fatigue and painful tingling of the hands and feet. Because of this complex symptomatology, patients with CM1 are frequently misdiagnosed.

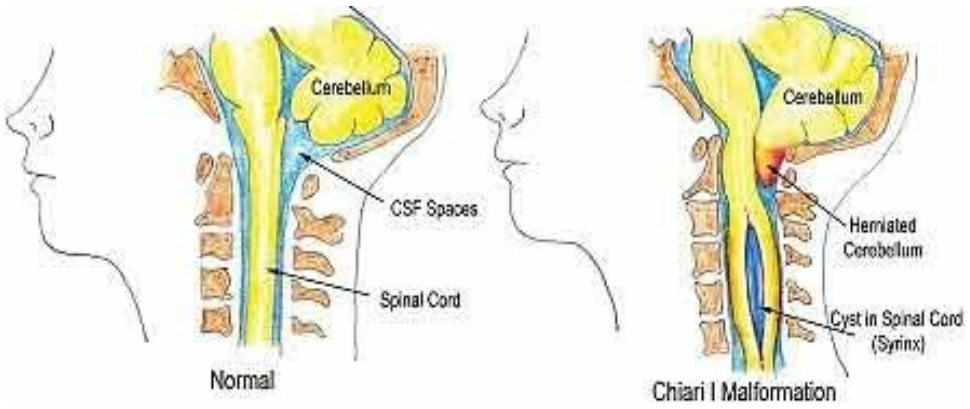


Fig.2: Picture of a normal brain (left) and a brain with chiari I malformation (right) [4].

Until recently, CM1 was regarded as a rare condition. However, with the increased availability of magnetic resonance imaging, the number of reported cases has risen sharply, with current estimates ranging from 200,000 to 2 million Americans with the condition. Approximately 3,500 Chiari operations are performed each year in the United States.

Although an MRI can show if the cerebellar tonsils are out of position, the diagnosis of Chiari remains challenging, due to the wide variety of reported symptoms. Unfortunately, there is no single, objective test which can clearly say that someone has a Chiari malformation which is causing problems.

Cine MRI is a type of MRI where the scanner is programmed to measure the flow of CSF. This procedure provides valuable information about the motion of the brain tissue and thus it can be used to see if the cerebellar tonsils are blocking the normal flow of CSF from the brain to the spinal area and back [4].

Our hypothesis is that when the CSF flow is impeded due to the presence of CM1, the pulsations of the brain are diminished and create the appearance of a stiffer brain tissue. The success of the CM1 surgery could be measured by the return of the Young modulus of the brain to normal values known from MRE measurements.

In this thesis we will use two data sets of cine MRI of a patient with CM1 before and after surgery, to show that the brain tissue appears to be stiffer and inhomogeneous before surgery, and softer and more homogeneous after the surgery, with stiffness values comparable with those known already from the MRE literature [1, 3]. We will use the fitting curve approach proposed in [3] to find the Young moduli of the brain tissue before and after surgery and then we will compare these results with the stiffness values found using the MREwave software developed by Mayo Clinic to analyze MRE data.

The proposed research lies at the frontiers between engineering science and medicine. Understanding the mechanics of the brain will have a tremendous impact on the development of advanced clinical diagnostic and treatment procedures not only for CM but also for other brain conditions, and on the design of improved head helmets and car protective devices. In addition, this study has the potential to play an important role in making cars and contact sports safer, thus drastically reducing both – the high number of deaths due to brain traumatic injuries (social component) and the very high health-related const for medical treatments (economic component).

Chapter 2

Literature Review

The process used so far in generating elastograms using MRI is as follows. MR images are recorded while a vibrating plate placed on the skin propagates mechanical shear waves in the tissue. By putting the magnetic field in tune with the mechanical vibrations, the wavelengths of the propagating shear waves can be calculated and used in a biomechanical model of the tissue to further calculate the corresponding Young moduli. In particular, to find the stiffness of the brain tissue, vibrations can be applied either as vertical displacements to the base of the head, or as horizontal displacements to mouth via a bite block (Fig. 3, [1]). The shear moduli of the white and gray matters are approximately 14.2kPa, and 5.3kPa, respectively. These values have been found by using the following formula for the shear modulus *G*:

$$G = \rho c^2 \qquad (1)$$

where ρ is the density of the brain and *c* is the shear wave propagation speed that is measured from MRE measurements. As most of the biological tissues, the brain is almost incompressible and thus its density can be assumed to be approximately equal to the density of water $1000\ \mathrm{Kg/m^3}$.

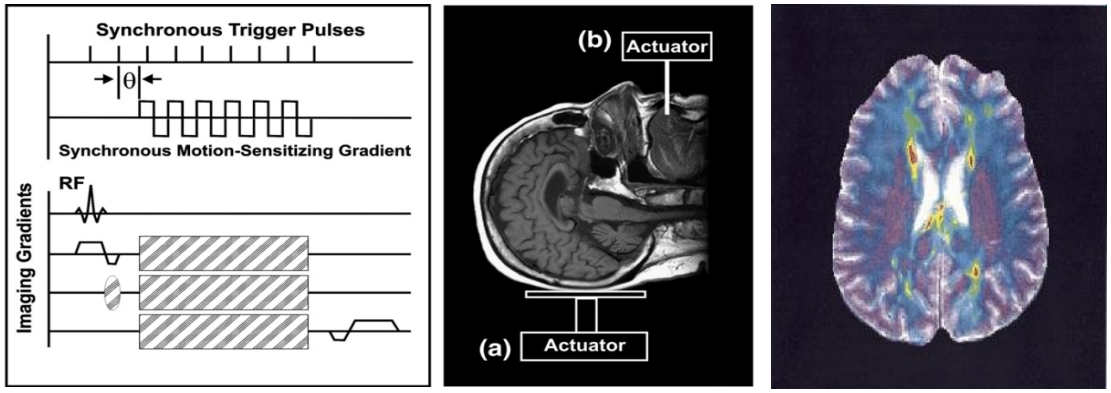


Fig. 3: MRE experiment setup (left and center) and a 2D elastogram (right) [1].

The same values of brain's shear modulus have been recently confirmed by [3], where the brain's natural pulsations under the influence of CSF and blood motion has been recorded using a phase contrast MRI technique. The total acquisition time was less than 5 minutes, and the imaging sequence has been performed with cardiac ECG gating. The damped oscillations of the brain have then been fit with a 6 parameter model of the form:

$$S(t,r) = A(r) + B(r)t + C(r)\exp(-\lambda(r)t)\cos(2\pi f(r)t + \Phi(r)) \qquad (2)$$

where *r* represents the spatial location in the brain, *A* is a constant component of the signal, *B* is the slope of the linear term, *C* is the amplitude of the damped oscillation term which has an exponential decay λ, a frequency *f* and a phase angle Φ. In this case the shear wave propagation speed is:

$$c = \frac{2\pi f \Delta y}{\Delta\Phi} \qquad (3)$$

with $\Delta y, \Delta\Phi$ a distance along the foot-head direction, and respectively, the phase difference. The shear modulus is calculated again from equation (1).

Chapter 3

Data Acquisition

We have obtained two 2D data sets of cine MRI from Hershey Medical Center of a patient with CM1 before and after the surgery (see Fig.4). An IRB protocol has given us permission to use and publish any results related to these data. Each cine MRI is made of 14 time sequences which represents a total of 5 sec. Since these images have been recorded for clinical rather than research purposes, not only that the total time acquisition was very small but also there was no cardiac gating. We expect that these limitations will affect our ability to properly process the data.

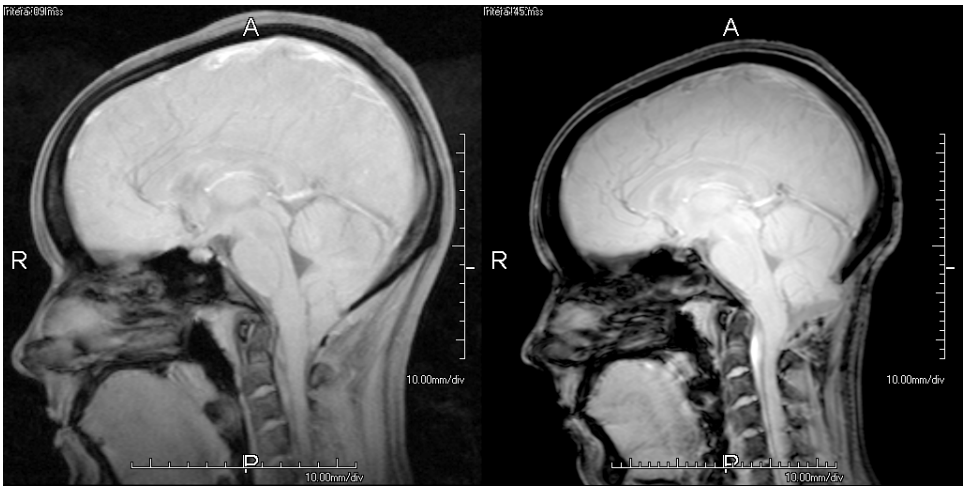


Fig. 4: First images of two sets of cine MRI of a patient with CM1 before (left) and after (right) surgery.

Chapter 4

Data Processing

Using Matlab (see Appendix A for the code), we have transformed the two cine MRI sets into two 400x400x14 matrices. Following the fitting curve technique in [3], we propose to fit these matrices to the following 4-parameter model:

$$S(t,r) = A(r)\exp(-\lambda(r)t)\cos(2\pi f(r) + \Phi(r)) \qquad (4)$$

The physical meanings of the 4 parameters in equation (4) are similar with the corresponding parameters used in equation (2). The reason we have chosen to use a 4-parameter rather than a 6-parameter model is due to the fact that, unlike [3], we have too few temporal data points. The shear wave propagation speed and the shear modulus will be calculated using formulas (2), and respectively (1).

Given the size of the matrices and the amount of noise in the data, we decided to fit model (4) to 20x20x14 matrices, selected from different parts of the brain. This is a good choice of processing the data since the brain tissue is a heterogeneous material with very different mechanical properties from one region to the next. In Fig.5 we show one such region and the shear moduli before and after the surgery. We note that the shear modulus after surgery has decreased almost 10 times which means that the CSF flow has returned to normal. Since the brain tissue is almost incompressible, the apparent stiffness (Young's modulus) is approximately three times the shear modulus. We call this an apparent stiffness rather than the true stiffness because the estimation of stiffness is done indirectly, using the rate of CSF flow. If the CSF flow is very slow (as in the case of CM1), then the pulsations (mechanical force) of the brain are very small and the brain tissue is almost force-free, there are no mechanical waves propagating through the brain that can be used to infer the stiffness value.

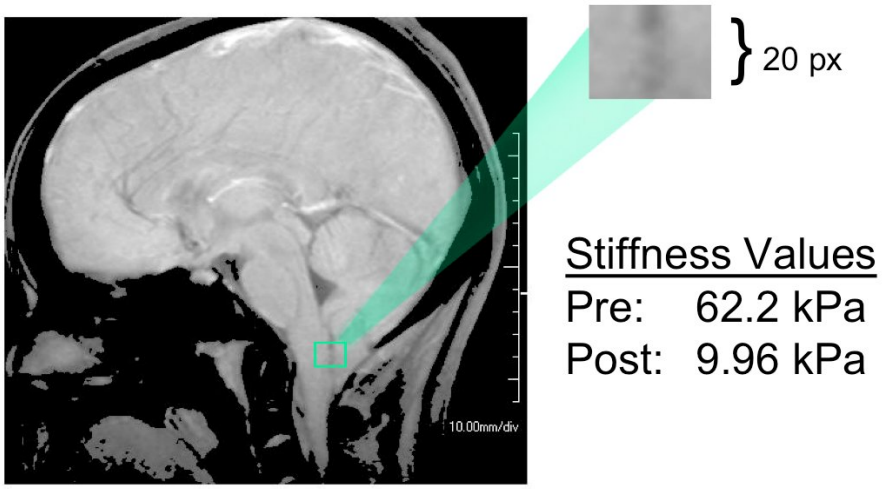
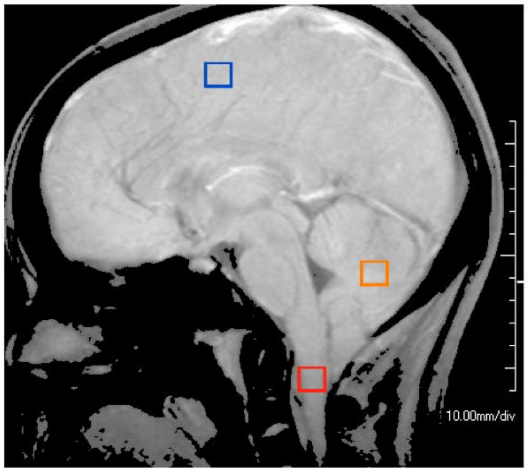


Fig. 5: Region of interest and estimated shear moduli pre- and post-surgery.

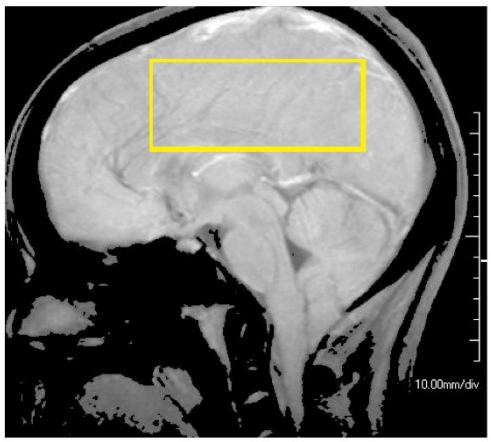
In Fig.6 we show other regions and their corresponding shear moduli before and after surgery. The much lower values of the shear moduli after the surgery indicate that the surgery has been successful; the CSF flow has been recovered and the brain functionality appears to be back to normal. By analyzing the values before the surgery we conclude that the brain tissue appears to be a stiffer and more inhomogeneous material. However, once the malformation has been removed, the brain tissue is softer and more homogeneous, with shear moduli approximately equal to 14 kPa, which was the value found by previous MRE measurements done on healthy patients [1, 3].



	Pre-Surgery	Post-Surgery
Red	60.4 kPa	12.4 kPa
Blue	11.4 kPa	18.8 kPa
Orange	26.9 kPa	10.9 kPa

Fig.6: Other regions of interest and their corresponding shear moduli pre- and post-surgery.

We have also compared the shear moduli obtained using our proposed 4-parameter model with the shear moduli obtained using the research software called MREwave [5]. MREwave is based on the direct algebraic inversion of differential equations method proposed in [6] where the Navier's equations in displacements corresponding to a linear visco-elastic solid are inverted to find the shear modulus. The results of our comparison are shown in Fig.7. Although we obtain comparable values, the frequency of the shear waves that have to be applied from outside to the head in order for the MREwave to give similar shear moduli as the 4-parameter model is huge. Such an MRE experiment cannot be performed in vivo on humans or animals.



	MREview	4-Parameter
Pre-Surgery	56 kPa	65 kPa
Post-Surgery	8 kPa	32 kPa

Fig.7: Region of interest used to compare the MREwave (also called MREview) and our 4-parameter model.

Chapter 5

Conclusion and Further Work

MRE is a powerful imaging technique that can help investigating the stiffness of biological tissues and any pathological conditions, such as tumors. Chiari malformation is a brain condition that alters the proper flow of CSF, resulting in an apparent stiffness of the brain tissue. In this thesis we studied the change in the apparent stiffness of the brain using two data sets of cine MRI of a patient with CM1 before and after surgery. We have shown that using a 4-parameter model we were able to analyze the stiffness of the brain. Before surgery, the brain tissue appears to be stiffer and more inhomogeneous, while after the removal of the CM1, the brain becomes softer and more homogeneous, with an average shear modulus of 14kPa, which is the same value that has been found from other MRE measurements on healthy patients [1, 3]. This finding could help measure the success of surgery of CM, in a non-invasive and safe way.

In our future work we plan to investigate other clinical conditions in the brain that affect the mechanical parameters of the brain tissue. We will also consider designing new biomechanical models for the brain that will help improve the estimated stiffness values.

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[5] Mayo Clinic Research, http://mayoresearch.mayo.edu/ehman_lab/mrw-wave.cfm

[6] Oliphant, T.E., Manduca, A., Ehman, R.L., Greenleaf, J.F. (2001). Complex-valued stiffness reconstruction for magnetic resonance elastography by algebraic inversion of the differential equation, *Magn.Reson.Med.*, 45, 299-310.

Appendix A
Matlab Code

%Matlab code provides conversion from cine MRI to matrices.

```
clear all;
clc;

a1=aviread('CSF 30 Pre_');

for i=1:15
    x1(:,:,:,i)=frame2im(a1(i));
end;

for i=1:14
    m1(:,:,i,1)=x1(35:386,35:476,1,i);
end;

Npre=size(m1,1);
Mpre=size(m1,2);

for i=1:Npre
    for j=1:Mpre
        for k=1:14
            if (m1(i,j,k,1)<100) m1(i,j,k,1)=0;
            end;
        end;
    end;
end;

write_binary_file(m1,'CSF_pre','float','l',0, 0);

%clear all;

a2=aviread('csf post_');

for i=1:15
    x2(:,:,:,i)=frame2im(a2(i));
end;

for i=1:14
    m2(:,:,i,1)=x2(35:386,45:426,1,i);
end;
```

```
Npost=size(m2,1);
Mpost=size(m2,2);

for i=1:Npost
    for j=1:Mpost
        for k=1:14
            if (m2(i,j,k,1)<100) m2(i,j,k,1)=0;
            end;
        end;
    end;
end;
write_binary_file(m2,'CSF_post','float','l',0, 0);
```

% Matlab code performing the fitting to the 4-parameter model

```
clear all;
clc;

a1=aviread('CSF 30 Pre_');

for i=1:15
    x1(:,:,:,i)=frame2im(a1(i));
end;

for i=1:14

    m1(:,:,i)=double(x1(380:400,290:310,1,i)); %anatomical structure
end;

write_binary_file(m1,'CSF_pre','float','l',0, 0);

a2=aviread('csf post_');

for i=1:15
    x2(:,:,:,i)=frame2im(a2(i));
end;

for i=1:14

 m2(:,:,i)=double(x2(370:390,285:305,1,i)); %same structure as in m1
end;

imshow(uint8(m1(:,:,1)));
figure, imagesc(uint8(m2(:,:,1)));

write_binary_file(m2,'CSF_post','float','l',0, 0);
```

```
T=14; % number of temporal sequences

xdata=1:1:T; %time sequence might need to be changed!

for i=1:size(m1,1)
    for j=1:size(m1,2)
        ydata(1:T)=m1(i,j,1:T);
        x=lsqcurvefit(@(x,xdata) x(1).*exp(-
x(2).*xdata).*cos(2*pi*x(3).*xdata+x(4)),...
            [1 0 0 0], xdata, ydata);
        ma1(i,j)=x(1);
        mb1(i,j)=x(2);
        mc1(i,j)=x(3);
        md1(i,j)=x(4);
    end;
end;

clear x ydata;

for i=1:size(m2,1)
    for j=1:size(m2,2)
        ydata(1:T)=m2(i,j,1:T);
        x=lsqcurvefit(@(x,xdata) x(1).*exp(-
x(2).*xdata).*cos(2*pi*x(3).*xdata+x(4)),...
            [1 0 0 0], xdata, ydata);
        ma2(i,j)=x(1);
        mb2(i,j)=x(2);
        mc2(i,j)=x(3);
        md2(i,j)=x(4);
    end;
end;

clear x ydata;

%apply a gaussian filter on the phase data md1, md2

h=fspecial('gaussian', [7 7], 0.5);
md1_h=imfilter(md1,h, 'replicate');
md2_h=imfilter(md2,h, 'replicate');

dx1=120/512; %12*10mm/512 size in x of x1
dy1=120/512; %12*10mm/512 size in y of x1

s1=0;

for i=1:20
    s1=s1+mc1(i,10);
end;

dx2=240/512; %24*10mm/512 size in x of x2
dy2=240/512; %24*10mm/512 size in y of x2
```

```
s2=0;

for i=1:20
    s2=s2+mc2(i,10);
end;


dist1=dy1*20;
dist2=dy2*20;

c1=2*pi*s1/20*dist1/(md1(1,10)-md1(20,10));
c2=2*pi*s2/20*dist2/(md2(1,10)-md2(20,10));

density=1000; %Kg/m^3

E1=density*(c1)^2;
E2=density*(c2)^2;
```

Osman Veledar

ozv101@psu.edu

Campus Address
1003 W. Aaron Dr. #2D
State College, PA 16803
United States
(717) 725-6979

Permanent Address
1859 Harrington Dr.
Lancaster, PA 17601
United States
(717) 569-5959

EDUCATION

Bachelor Degree of Science in Engineering Science (Honors)
Minor: Bioengineering
The Pennsylvania State University, State College, PA
Expected Graduation: May 2010

Core Courses

Medical Instrumentation	Biomaterials
Cell Biology/Physiology	Physics in Modern Medicine

EXPERIENCE

Learning Center Assistant/Calculus & Physics Tutor (Sp07 – Sp08)
Penn State University, York, PA

- Assisted Penn State students with their academic needs
- Managed a heavy schedule with school and tutoring
- Helped new tutors get acclimated with the tutoring system

Skills learned: Communication, mentoring, working with others, planning

Research Assistant (Summer09)
Penn State University, State College, PA

- Analytical simulations in MatLab
- Modeled heat propagation through finite slab

COMPUTER SKILLS

Microsoft Excel, Microsoft Word, Adobe Photoshop CS4, C++, HTML, MatLab, Propellerhead Reason 4.0, SolidWorks

AWARDS/ACTIVITIES

Schreyer Honors College
Penn State Tutoring Certificate
AP Scholar

INTERESTS

Medical Imaging
Understanding biological mechanisms
Applying techniques for early diagnosis