EXPERIMENTAL AND COMPUTATIONAL MODELING OF ULTRASOUND CORRELATION TECHNIQUES

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CORRELATION TECHNIQUES

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Thesis

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ABSTRACT

Space travel has placed humans in an interesting physiological situation that makes it necessary to secure the health of the astronauts. In space, due to the lack of gravity, there is a fluid shift toward the upper body that results in a decrease in plasma volume. As a result, there is a significant drop in red blood cell mass over the flight period, which could result in space flight anemia. To monitor this change, ultrasound must be used, since it is the most trusted and only flight surgeon approved imaging/detecting modality for space flight. Continued research into the use of ultrasound for monitoring hematocrit levels can improve the lives of humans both in space and on Earth.

A physical means to examine the viability of a cross-correlation detection method for ultrasound (originally demonstrated for optical light scattering) that minimizes multiple scattering effects [23] was demonstrated by conducting a Young’s two-pinhole experiment. This was implemented using a pinhole mask on the receiving transducer to affect cross-correlation. The resulting interference pattern should have a period predicted by the pinhole size, spacing, and frequency of the ultrasound signal. Interference patterns were produced for a series of masks with different pinhole sizes and pinhole separations. The fringe patterns were analyzed, with the measured period compared to the predicted
period, and the 300/700(pinhole diameter/separation) mask was determined as the most optimal.

A two-dimensional computer model was developed using the Comsol Multiphysics software package (Comsol AB.). The model was created to analyze the physical cross correlation method and help explain the experimental results, accounting for some of the effects not captured by the analytical model. The simulations showed that the masks with smaller pinholes (~100μm) had periods that were not consistent with the analytic predictions, indicating the presence of effects that were not properly modeled analytically. One of these effects was evanescent wave coupling with the two-pinhole mask. In addition, the signal attenuation and energy were determined for a blood mimicking fluid in a tissue flow phantom. The signal characteristics of the flow model were the first step in determining the optimal spacing of the multiple transducer array prototypes, which will be based on the scattering geometry of the scatterers.

Overall, these methods demonstrated that the two-detector multiple scattering suppression cross-correlation technique is a feasible approach to non-invasive hematocrit determination using ultrasound.
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CHAPTER I
INTRODUCTION

1.1 Ultrasound

Animals such as bats and dolphins have been using ultrasound in the form of SONAR long before it was discovered by humans. Sonography, or imaging with ultrasound, allows for the visualization of static structure as well as dynamic events in the human body [1]. Doppler ultrasound has been used to evaluate the condition of tissue, whether healthy or diseased, with examples being studies of myocardial ischemia, cardiac aging, myocardial infarction, and myocardial hypertrophy [2]. Alternative uses include the quantification of echo-contrast agents in macroscopic vessels and cardiac chambers and tissue microvasculature [2]. Because of this, Doppler ultrasound is widely used for the diagnosis and treatment planning of vascular disease. However, the information that ultrasound provides regarding blood flow dynamics typically associated with these diseases is often limited or difficult to interpret [3].

The pulse-echo technique uses ultrasound pulses to isonify the tissue and monitors the back-reflected sound (or echoes). The echoes are received and processed to determine physiological parameters or form anatomical images. The ultrasound frequency range begins just out of the range of human hearing, at approximately 20 kHz, but most medical devices operate in the range of 2 – 10MHz. The sound velocity, or propagation speed, depends on the physical characteristics of the medium, specifically...
the density and compressibility [4]. The velocity of ultrasound is approximately 1580 m/s in human blood, 3500 m/s in bone, 1450 m/s in fatty tissue, and 1540 m/s in soft tissue [4, 50]. The ultrasonic energy received by the transducer is dependent on the intensity of the transmitted wave packet and the scattering and absorption properties of the tissue [2].

The three types of ultrasound techniques are A-mode, B-mode, and Doppler ultrasound. A-mode ultrasound measures the amplitude of the echoed sound wave as a function of time (depth). B-Mode or “brightness” mode uses the same information to create a two-dimensional image composed of a transverse stack of A-scan. The Doppler technique uses the ultrasonic pulse and measures frequency shift due to dynamic scattering events (i.e. moving targets) [2]. The difference between the transmitted and received frequency is the Doppler frequency.

A coupling medium such as a gel is used to provide a good sound path from the transducer to the skin to help minimize reflection losses at the air/tissue interface. The attenuation, or weakening of the sound as it propagates, increases with propagation distance and medium density limiting the depth and effectiveness of ultrasound. This is also dependent on frequency, lower frequency sound is attenuated less (and propagates farther) than higher frequency sound. The attenuation is due to absorption, reflection, and scattering [1]. Absorption, in which sound is turned into other forms of energy most notably heat, is the largest contributor to attenuation while reflection and scattering are secondary losses that occur as the sound wave interacts with tissue interfaces and internal structures. Scattering is the redirection of sound in different directions occurring because of an acoustic impedance difference between two objects (e.g. the medium and imbedded inhomogeneities [1]. The scattered intensity depends on the frequency of the sound wave
and size of the scatterer or inhomogeneity. Speckle is an interference phenomenon due to
the superposition of the echoes from several different scatterers. These echoes may result
in total or partial reinforcement (constructive interference) or cancellation (destructive
interference).

1.2 Hematocrit

Blood is formed of elements including red blood cells (erythrocytes), white blood
cells (leukocytes), and platelets (thrombocytes) suspended in plasma. Plasma is a
yellowish fluid primarily made up of a saline solution with three major dissolved
proteins: fibrinogen, globulin, and albumin. The cellular portion makes up approximately
45% volume of the whole blood while the rest is plasma with a range of 36% to 54%
[50].

Normal red blood cells (RBCs) are biconcave discs that have a diameter of
approximately 7.8 micrometers and a thickness of 2.5 micrometers at the sides and 1
micrometer at the center [5]. This results in a typical volume between 90 to 95 cubic
micrometers [5]. RBC’s occupy 40-45% by volume (42-54% for adult males and 38-46%
for adult females) of the whole blood. Clinically the volumetric ratio of RBC volume to
volume of whole blood is termed the blood hematocrit. A blood hematocrit in the normal
range (40%-45%) correlates to between 4,700,000 and 5,200,000 RBCs per cubic
millimeter of whole blood.

RBCs contain hemoglobin, a compound of protein and iron, which allows the
RBCs to carry oxygen. The concentration of RBC in the circulatory system is controlled
by a feedback loop that controls the production of erythropoietin, a hormone produced in
the kidneys. When erythropoietin production stimulates the red bone marrow, stem cells differentiate into reticulocytes that escape from the bone marrow into the blood stream. These then shed their nucleus to become fully functional RBCs. The production of RBCs occurs in response to the demand for oxygen by tissue and the regulation of fluid homeostasis in the circulatory system. RBC production occurs in the bone marrow of all bones at a young age. As a person ages, the RBC production decreases in the long bones until about the age of 20 and then is continued only by membranous bones [5].

When the hemoglobin content in the bloodstream drops below that in the hematocrit range of 33-39, the result is anemia. Anemia can be caused by rapid blood loss, bone marrow aplasia, loss of stomach mucosa (megaloblastic anemia), fragile RBCs (hemolytic anemia), or a diet lacking iron-rich foods, all of which result in the reduction of RBCs [5]. Anemia has a drastic effect on the function of the circulatory system [6]. The effects can range from a change in the viscosity of the blood causing an unwanted increase in cardiac output, to secondary polycythemia causing the extreme production of RBCs, to polycythemia vera causing an increase in hematocrit which results in an increased total blood volume [5].

Hematocrit is determined by centrifuging the whole blood for a period of time and measuring the percentage of the total volume occupied by packed red blood cells compared to the total amount. This requires that blood be drawn from peripheral locations and the test performed ex-vivo.
1.3 Relevance of the Study

The quest to journey into space and travel to the moon and other planets, such as Mars, has placed humans in an interesting physiological situation. Because of the microgravity environment, the human body does not function as it does on Earth and certain physiological changes occur [7, 8]. For example, during a shuttle launch astronauts experience up to 3 times the force of gravity for several minutes and then almost immediately experience complete weightlessness for an extended period [8]. The main acute symptoms of the microgravity environment include motion sickness, back pain, nasal congestion, vision changes, and urinary retention [8]. Chronic physiological problems that occur over time as human physiology adjusts to the lack of gravity include loss of muscle and bone mass, increased heart rate, and significant reductions in blood plasma levels leading to orthostatic intolerance on return to a gravity environment [7, 8].

Another physiological issue that astronauts have to deal with due to the loss in blood plasma is the decrease in overall RBC mass. Astronauts experience an average 10-15% decrease in red blood cell mass leading to potential spaceflight induced anemia [9, 10]. There are several contributing factors for this behavior. These include muscles requiring less oxygen because of muscle mass loss and the need to balance the oxygen carrying capacity of whole blood with the reduction in overall blood plasma levels to maintain hematocrit and blood viscosity [11]. No matter what the cause of the reduction in RBC mass, it is agreed that it is a concern for long duration space flight. The first step to the correction of the problem is to provide easy to use physiological monitoring tools for the astronauts.
Not only is easy to use, non-invasive physiological monitoring desirable in space due to the extreme consequences that might occur if medical evacuation was needed, but it is also desirable here on Earth. Constant patient monitoring is needed in hospitals and assisted living situations. To solve this problem both in space and on Earth, a smart medical system needs to be implemented. In a smart medical device, the key component step is detection because it allows for an accurate diagnosis. Ultrasound can be that key detection modality. Ultrasound is a safe and inexpensive method for imaging and detection and has been used for many years on the International Space Station and other space missions [8]. Continued research into the use of ultrasound for monitoring hematocrit levels can improve the lives of humans both in space and on Earth.

1.4 Research Hypothesis

1. The two-pinhole mask physical cross-correlation technique was able to measure field correlations.

2. A predicted period method can be used to optimize the pinhole size and spacing for the physical two-pinhole mask cross correlation technique to isolate the interference.

3. The signal speckle noise caused by multiple scattering effects that are similar to RBC ultrasound scattering in blood can be suppressed by a physical cross-correlation technique.
1.5 Objectives

This study was conducted to investigate a method for suppressing multiple scattering effects so that single scatter attenuation could be related to hematocrit and then developed a device for the non-invasive determination of hematocrit using low power Doppler ultrasound. The optimal method for suppressing multiple scattering effects, as implemented and validated for optics by Meyer [23], would be to use a multiple transducer array. This method was not feasible due to budget reasons. A multiple pinhole mask would be used as a secondary method to validate the multiple scatter suppression technique for ultrasound.

A simple interference test, similar to a Young’s double-slit experiment, was to be conducted using the two-pinhole mask as a means to demonstrate the physical cross-correlation technique of ultrasound. The output peak-to-peak voltages were to be plotted against the angle of rotation to determine a fringe pattern for each mask. The fringe pattern peaks were to be compared to the predicted period in order to determine the optimal pinhole mask size and spacing from the tested masks.

A two-dimensional computer model was to be developed to computational model the pinhole mask experiment in a finite element method in order to investigate the limitations and explain any unknown phenomena. The computer model would demonstrate and confirm the two-pinhole mask cross-correlation technique for ultrasound.

In addition, a blood mimicking fluid flow experiment would be conducted to determine the characteristics of the forward scattering Doppler ultrasound signal. These characteristics would be used as a baseline for future blood mimicking fluid experiments.
2.1 Purpose

Space travel has always been associated with great risk. Not only are there dangers involved with making the trip out of the Earth’s atmosphere, but there are also great health risks. As the time duration of space flight increases, for extended missions to visit other planets such as Mars, it will be necessary to secure the health of the astronauts [7]. Without the ability to examine the astronauts first hand and with the limited amount of time for health communications, a sensory system will need to be designed that can constantly monitor as many physiological conditions as possible. In addition, such a system would be beneficial to health care on Earth [9].

Soller et al. explored the possibilities of advanced medical systems that relate directly to the nutrition and fitness of humans in space [9]. It was determined that there should be three components to smart medicine. The first is a sensing element that is able to determine physiological conditions or the medical status of the patient. The smart medicine system encompasses a feedback control system that originates with the sensory elements. Without the development of the sensory elements, the smart medicine system cannot be constructed. The second is a processing unit to analyze the sensor inputs and determine if the health status is normal or if treatment is needed, and if so, what type of treatment. The third and final component is a suite of treatment effectors that are
embedded in the intelligent system and can supervise the application of the treatment. The final implementations of a smart medicine system would allow constant, real-time monitoring with minimal input from the astronauts.

The development of a constant, real-time health monitoring system is an important step in solving space flight anemia [9 - 13]. Space flight anemia has been observed in almost all space flight missions, which could potentially result in harmful consequences to the astronauts and the mission. Anemia is the decrease in the ability of the blood to carry oxygen due to either a decrease in the total number of RBCs or a decrease in the concentration of hemoglobin per RBC, or a combination of both [5,14]. Most cases of anemia result in a reduction of oxygen transport in the blood causing fatigue and diminished physical capacity [15]. Over time, anemia can cause a reduction in endurance and in severe cases, can cause a reduction in the lungs' ability to absorb oxygen. This can lead to secondary organ dysfunction or damage, which includes heart arrhythmias and congestive heart failure [15]. Any symptoms associated with anemia can endanger not only the astronaut but his/her crewmembers as well.

Previous studies [9 - 13] have revealed a 10-15% decrease in RBC mass over a period of approximately 2 weeks, equaling a loss of about 1% per day. It has also observed that there is an elevation of urinary antidiuretic hormone (ADH) during the first day of flight, mostly due to acceleration exposures and other launch stresses, which leads to a reduction in plasma volume and RBC mass [10 - 13, 16]. In fact, the body adjusts quickly to the microgravity environment by reducing the plasma volume by 17% within 22 hours of flight and increasing the plasma protein concentration by 9% within the first day [16]. As the plasma volume decreases, the hematocrit increases because it is a
percentage of the RBC within the whole blood volume. Over time, the body’s homoeostasis causes a reduction in the RBCs and a return of hematocrit to near preflight levels. This reduction is called “space anemia.”

There are several different theories as to why there is a decrease in RBC mass in a microgravity environment. One explanation is based on the increased cabin partial pressure of oxygen, which existed in early flights before Skylab [13]. It is thought that if the ambient oxygen level is higher than normal, the body no longer needs as many RBCs, so they are destroyed. Another theory suggests the suppression of erythropoiesis by the decrease in reticulocyte count [12, 13]. Even without a definitive cause, space anemia can still create many problems for the astronauts.

The determination and monitoring of hematocrit for astronauts is only one example of how hematocrit determination is beneficial to human health care. By monitoring hematocrit, Gan et al. concluded that it is an early, simple, and useful predictor of severe pancreatitis [17]. By carefully watching a patient’s hematocrit, it may be possible to detect acute pancreatitis before it occurs, as compared to current predictor tests, which take up to 48 hours to return results. Another example includes the relationship between low hematocrit and contrast-induced nephropathy (CIN) [18]. Currently, the relationship between low hematocrit and CIN has not been investigated but Nikolsky et al. has argued that it should be, since CIN is one of the most frequent causes of in-hospital renal function impairments [18]. In fact, he believes that correcting the hematocrit level might decrease the rate of CIN. This might be possible if a constant hematocrit monitoring system could be implemented.
2.2 Other Possible Methods for Hematocrit Detection

Pulse oximetry is a non-invasive real-time method to determine the amount of oxygen held by a patient’s hemoglobin. A sensor is placed on either the fingertip or earlobe of an adult or across the foot of a small child. Near infrared light at two wavelength passes through the anatomical feature and the absorption is measured. The ratio of light intensity at the two wavelengths is caused by the difference between oxygen-bound and oxygen unbound blood hemoglobin [19, 20]. From this the oxygenation level or percentage of hemoglobin molecules bound with oxygen can be calculated. This technique is particularly useful for patients under anesthesia and in the intensive care [20]. Advantages of this technique include real-time data acquisition that results in quick and timely responses to the patient’s condition and the possibility of small size components. Some difficulties include detecting the development hypoxemia and detection when carboxyhemoglobin (COHb) and methemoglobin (MetHb) are present, which require more than two wavelengths of light for accurate detection [19]. In hematocrit detection, pulse oximetry is limited by the assumption of specific levels of hemoglobin on each blood cell and in the inability to measure large vessel RBC levels, which maybe differ from capillary blood, depending on location.

A related technique for hematocrit detection is near-infrared spectroscopy (NIRS). NIRS is based on the same principle as pulse oximetry, the difference being the use of more than two wavelengths and a multiple receiver-detector configuration for improved spatial resolution. A NIRS system was created by Jeon et al. [21] that measured hemoglobin with five light-emitting diodes, with wavelengths in the range of 569 to 975 nm, to an accuracy of approximately 1g/dL. Zhang et al. [22] also used near-infrared
radiation to measure hematocrit. His group used full-spectrum near-infrared spectroscopy
coupled to partial least-squares multivariate calibration algorithms to noninvasively
measure hematocrit [22]. Even though these two methods using NIR light are designed to
determine hemoglobin, the process and design are similar for determination of
hematocrit.

2.3 Backscatter and Suppression in Dynamic Light Scattering

Dynamic light scattering (DLS) is a technique for determining dynamic properties
of a given scattering system, such as the size distribution profile of small particles in
solution [23]. One of the difficulties with using DLS techniques, however, is that multiple
scattering by the sample can result in unreliable and skewed data. Consequently, it is
necessary to suppress the multiple scattering components while preserving the single
scattering signal, which is directly correlated with the sample dynamics. Several studies
[23 - 26] have focused on the suppression of multiple scattering effects. Phillies et al.
[24] used a method of homodyne cross-correlation to suppress the multiple scattering
signals in quasielastic light scattering spectroscopy. In this study, a “Gaussian two-
detector correlation experiment,” the detection volumes for each detector overlapped
such that the correlation of the multiple scattering signals at the two detectors averaged to
zero while the correlation of the single scattering signal averaged to a nonzero value. This
reduction in the “double-scattering” effect by using a two-detector system demonstrated
that strongly scattering systems could be studied with this method. The two beam/two
detector light scattering spectrometer as proposed was tested experimentally and proven
to be valid [24,25].
Dhont et al. developed a method to correct static and dynamic light scattering data for double scattering and developed expressions for the field strength of higher order scattered light [27]. Dhont et al. found that the cross correlation technique was incomplete because important second order contributions were overlooked but concluded that the cross correlation was nonetheless valuable for suppressing double scattering contributions [24, 28, 29]. They also noted that the modified approach yielded better results.

More recently, research and experimentation has confirmed that multiple scattering can be suppressed by cross-correlation [23]. It was determined that when dynamic light scattering occurs in an intermediate regime where higher-order scattering is significant, the most effective technique for dealing with multiple scattering is the cross correlation method developed by Phillips [24,25] and extended by others [28,29]. Meyer concluded that, if two closely spaced detectors are used to collect light, they will collect both single and multiple scattering contributions and the single scattering contributions will be strongly correlated with each other at all times, while the multiple scattering components will be only weakly correlated. Specifically, scattered light emanates from a given interaction volume where singly scattered light produces correlated patches of light, or time-dependent speckle, that are much larger in the plane transverse to the incident beam and smaller parallel to the beam. The multiple scattered light, on the other hand, produces speckle that is much smaller than the single scattering speckle in the transverse plane, illustrated in Figure 1. This is the method used to distinguish single and multiple scatterers by utilizing two, closely spaced optical fibers as detectors.
Fig. 2.1: Relative speckle size for single and multiple scattering [23].

The spacing of the fibers was calculated so that a given multiple scattering speckle would be detected by only one detector but not both, and so both detectors could detect the single scattering (Eq.2.1 and 2.2 in Fig.1). Similar to previously mentioned techniques [24-29], the temporal auto-correlation and temporal cross-correlation technique was then calculated (Eq. 2.3 and 2.4) with 256 different time delays (τ), with $n_a(t)$ and $n_b(t)$ being the resultant pulse streams.
\[ G(\tau) = \langle n(t + \tau)n(t) \rangle \] (2.3) [23]

\[ G_{AB}(\tau) = \langle n_A(t + \tau)n_B(t) \rangle = \langle n_B(t + \tau)n_A(t) \rangle \] (2.4) [23]

It was concluded that the method allowed for the suppression of multiple light scattering but as the weight percentage increased, the suppression became less effective. The auto-correlation results showed a greater decrease in multiple scatter suppression as the weight percentage increased as compared to the cross-correlation results. The principles and techniques of multiple scatter suppression in DLS can be similarly applied to ultrasound.

2.4 Ultrasound and Hematocrit

Ultrasound backscattering has been studied since early World War I with its use in SONAR, but over the past 30 years, it has been implemented as a medical tool [48]. Much research has been done to perfect ultrasound techniques that use backscattered signals for detection or imaging [2, 3, 6, 8, 17, 21, 30-47]. Reid et al. determined that the ultrasound backscatter from blood was due to erythrocytes [37]. Specifically, the backscattered signal is associated with the properties of the blood, such as hematocrit and level of aggregation [46]. The attenuation of ultrasound in blood is mainly due to absorption, at frequencies below 15MHz, where scattering can be neglected, while above 15MHz both scattering and absorption contributions are comparable [50].

The description of scattering in blood involves the wave propagation through a dense distribution of scatterers [30]. The general solution to this problem requires knowledge of the pair distribution function \( P(r_s, r_t) \), or the probability of finding the \( s \)th particle at \( r_s \) and the \( t \)th particle at \( r_t \). Twersky developed a method to solve the scattering
of waves by random distribution of scatterers in terms of the one particle distribution function [36]. The method was later improved on by Sigelmann and Reid who calculated the scattering coefficient of blood from the RMS value of the gated scattered wave [49]. Shung et al. demonstrated using this method that the scattering of ultrasound by blood was proportional to the fourth power of the frequency as predicted by the wave scattering theory for small scatterers and dependent upon the hematocrit of the blood [30]. In a later paper, Shung et al. stated that the relationship between scattering and hematocrit could not be accounted for by simple scattering theory because the scatterers are dependent when the fractional volume is large [37]. However, it was also noted in the same paper that the non-linear relationship between scattering and hematocrit is not due to multiple scattering effects [37]. Shung et al. noted that when the concentration of scatterers is low, single scattering could be characterized by the amount of scatterers per unit volume. Conversely, when the concentration of scatterers is high, a multiple scattering mechanism was required to address the gradual disappearance of the random nature of the scattered signal.

From these studies, it was generally accepted that ultrasound scattering is dependent on hematocrit; and it was therefore possible to determine the amount of hematocrit by measuring the backscattered ultrasound from blood. Mo et al. found that there are two difficulties in forming a theoretical model of the backscattered Doppler signal from blood [40]. The first problem encountered was that because of interference of the dense suspension of RBCs, the Doppler signal received is a random process that has a power spectrum with large random fluctuations that is Doppler speckle. Second, Doppler signal can vary greatly with changes in flow disturbances and turbulence [40]. There are
three broad categories of Doppler Ultrasound models: (1) scattering models, which deal with the physical mechanisms that generate the Doppler signal in blood, (2) signal models, which are mainly concerned with the analysis and synthesis of the stochastic nature of Doppler signals, and (3) parametric spectral models, which provide Doppler spectral estimations [40].

Doppler ultrasound is more commonly used for clinical studies and research of blood flow. It has been shown that the backscattered power does not represent a fitting relationship with hematocrit [37, 39]. Mo et al. stated that the backscatter coefficient (BSC) initially increases with hematocrit up to 15-20% and then decreases as hematocrit approaches 50% [39]. Little research has been conducted with blood of hematocrit above 50% [39]. Shung et al. and Sigel et al. showed that blood echogenicity is influenced by the local shear rate and that a low shear rate results in a high echogenicity [42]. It was assumed that echogenicity is related to shear-rate-dependent state of aggregation. De Kroon et al. reported cyclic changes in echogenicity during the cardiac cycle and it was suggested that these variations might be related to changes in the state of red blood cell aggregation, which are induced by the varying shear rate [42].

Secomski et al. studied the noninvasive monitoring of hematocrit due to its importance in clinical applications [32, 33]. Their method of determining hematocrit was based on the ultrasonic Doppler blood flowmeter and previous work done by Johner et al. Johner et al. showed that the change in velocity of ultrasonic wave propagation in the blood plasma depends on the RBC count [35]. From this, it was possible to determine the power of the Doppler signal for two volumes and calculate the attenuation coefficient, which could be correlated to hematocrit [32]. Later, Secomski et al. [33] would determine
that hematocrit is a function of ultrasonic wave attenuation in blood while the Doppler
corrected power spectrum is used to calculate the attenuation coefficient. The methods included
both pulse-echo and transmission techniques with a 2-gate and multi-gated measurement
system. Results from the in vivo experiments showed that the attenuation coefficient was
could be calculated using a multi-gated pulsed Doppler insonation, which also made
placement of the probing beam easier. However, it was noted that the relationship
between hematocrit and ultrasonic wave attenuation only existed up to 15-20% and was
very inconsistent thereafter. It was hypothesized that the inconsistencies were due to
multiple scattering effects given that multiple scattering effects increased as the number
of scatterers in the fluid increased.

Tortoli et al. also investigated an ultrasound multi-gated instrument with a device
capable of computing real time fast Fourier transforms of Doppler signal detected from
64 equally spaced range cells [44]. The development of ultrasound flow analysis led the
way for Balocco et al. to develop a 3D model reproducing the biomechanical behavior of
the human blood vessel [34]. The model geometry consisted of a series of right
generalized cylinders that were connected to represent the complex blood vessel
geometry. The signal from a simulated blood flow was calculated using a dynamic
displacement of scatterers within the Field II Simulation Program software [58, 59]. Field
II was used to create the acoustical aspects of the model in M mode, B mode and color
Doppler mode for imaging. Three physiological phantoms were created of the carotid
artery to model healthy and unhealthy situations: healthy, 50% stenosis, and a carotid
bifurcation. A finite element technique was utilized to model arterial pulsation and the
dynamic displacement of scatterers within the artery while the arterial region is
acoustically characterized by radio frequency echo signals. An isotropic elastic model was used to demonstrate wall membrane displacements. Overall, Balocco et al. reported that the dynamic 3D model was able to reproduce the physical and acoustic behaviors of the selected blood vessel [34]. The model allowed for the expansion of assumptions previously made about steady flow conditions so that the model could incorporate other geometries similar to actual human arteries.

Most recently, ultrasound backscattering and light scattering cross-correlation theories have been combined with the aim of creating an accurate noninvasive ultrasound blood hematocrit detection technique. Preliminary work done at the NASA Glenn Research Center in Cleveland, Ohio (David Fischer, Jerry Myers, Jeff Mackey, and Michael Phelan) demonstrated a method for achieving this using ultrasound correlation measurements. The idea was presented at the 2007 Third World Ultrasound Congress held in Paris, France. The proof of concept testing consisted of measuring a correlated signal analogous to a single scatter signal. It utilized a two-pinhole masking technique. Two ultrasound transducers were aligned in a head-to-head configuration with a two-pinhole mask placed on one transducer while the other transducer had no mask or a single pinhole mask. The transmitting transducer was rotated the center point of the two-pinhole mask (Fig. 1.2).
The use of a two-pinhole mask allows the scattered field to be sampled and the correlation of the field to be measured through analysis of the resulting interference pattern. This enables one to separate the correlated part of the signal from the incoherent background, which does not give rise to interference fringes. As stated earlier, multiple scattering speckles are smaller than single scattering speckles [23]. It was determined that when the distance between the pinholes centers in the mask is smaller than the single scattering speckle but larger than the multiple scattering speckle, the single scattering signal will be correlated at the two pinholes while the multiple scatter scattering signal will not. Consequently, by performing two-point detection and cross-correlation, multiple scattering can be suppressed. The concept that ultrasound correlation could be measured was demonstrated using a simple Young’s two-pinhole interference test, resulting in a sinusoidal interference pattern having a fringe with period equal to $\lambda/d$, where $\lambda$ is the wavelength of the transmitting transducer and $d$ is the distance between the pinholes.

$$\text{period (radians)} = \frac{\lambda}{d} \quad (2.3)$$
The experimental results illustrated a periodic fringe pattern with decreasing amplitude (or fringe visibility) with increasing angle due to the finite size of the pinholes. The study was limited to preliminary testing for proof of concept.
3.1 Pinhole Mask Experiment General Configuration

Two transducers were aligned face-to-face with one transmitting transducer connected to a commercial ultrasound system modified for these tests and a receiving transducer connected to a data-recording oscilloscope. A two-pinhole mask was placed on the receiving transducer while the transmitting transducer was rotated through 46 degrees in the positive and negative directions off the center alignment (Fig. 3.1).

Fig. 3.1: Illustration demonstrating the rotation of the transmitting transducer relative to the stationary receiving transducer.
3.2 Pinhole Mask Experiment Equipment

The ultrasound transducers (Indus Instruments, Webster, Texas) were 3mm diameter, 10 MHz semi-water tight tubing mounted transducers that were applied externally to the target location (Appendix A). The Ultrasonic Measurement System was constructed and specifically modified for our service by Dr. Craig J. Hartley of the Baylor College of Medicine, Houston, Texas. The transmitting transducer was connected to the Baylor College of Medicine (BCM) Multichannel Ultrasonic Measurement System with the 10 MHz pulsed Doppler module (Appendix A).

The input signal from the BCM Ultrasonic System and the received signal were monitored using an oscilloscope (Tektronix TDS3014B, Appendix A). Channel 1 recorded the output from the ultrasonic system, or what is the input signal to the transmitting transducer, and channel 2 recorded the output from the receiving transducer. The signal from the ultrasonic system was split so that the output could be recorded by the oscilloscope and be transmitted through the transducer. The Ethernet port on the oscilloscope was utilized to export both channels’ signal waveforms from the oscilloscope for storage and post processing via e*Scope.

The pinhole masks were milled out of copper with two identical holes drilled into the top of the mask (Fig. 3.2). The pinhole mask parameters, pinhole size and spacing, were chosen based on the equations to determine the estimated speckle size [23]. The ultrasound beam diameter was estimated by the diameter of the transducers and the diameter of the scatterers was estimated by the diameter of the blood mimicking fluid particles.
The diameter of the pinholes and their (inner distance) separation were measured to characterize the masks by the parameters of P and S (Fig. 3.3).
The masks were designed to fit over the tubal transducers and were fixed into position by a screw on the side of the mask. The two-pinhole mask sheath had an outer diameter of 3.6mm and an inner diameter of 3.2mm. The length of the pinhole mask was 4.4mm. Three pinhole masks were fabricated for the experiment that had varying pinhole sizes and spacing (Table 3.1).

<table>
<thead>
<tr>
<th>Mask Number</th>
<th>Pinhole Size (μm)</th>
<th>Pinhole Inner Spacing (μm)</th>
<th>Pinhole Spacing (μm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>300</td>
<td>400</td>
<td>700</td>
</tr>
<tr>
<td>2</td>
<td>100</td>
<td>400</td>
<td>500</td>
</tr>
<tr>
<td>3</td>
<td>100</td>
<td>600</td>
<td>700</td>
</tr>
</tbody>
</table>

The pinhole masks were referred to by the ratio of the pinhole size to the pinhole spacing, i.e. the pinhole mask with 300μm pinhole size and 700μm pinhole spacing was pinhole mask 300/700.

In order to create an acoustic bridge between the transducers, an ultrasonic gel was used (Aquasonic 100 ultrasound gel). The gel had a wave transmission speed around 1520 m/s, with sound frequency impedance between 1.5*10^6 Pa*s/m, sound attenuation of 0.05 dB/cm/MHz, and pH of 5.5-8 [62].

3.3 Pinhole Mask Experimental Setup

The experimental setup (Fig. 3.4) consisted of a transducer on a rotational stage focused at a stationary transducer over which specific pinhole masks were placed.
The transducers were separated by a distance of 2mm, measured from the face of the transmitting transducer to the edge of the pinhole mask on the receiving transducer. The positive angles were measured clockwise from the out-looking face of the receiving transducers, while negative angles were measured counterclockwise.

3.4 Pinhole Mask Experiment Procedure

For each of the two-pinhole masks, the transducers were cleaned using de-ionized water and an optical cleaning cloth prior to measurement. The receiving transducer was
then fixed in its stationary position aligned with the center of the rotational stage. To complete an acoustic bridge between the transducers, ultrasound gel was used. The gel was placed inside the pinhole mask before it was placed on the receiving transducer. The two-pinhole mask was then placed on the receiving transducer. The transmitting transducer was fixed onto the rotational stage and the tip was placed 2 mm from the front of the pinhole mask, measured with calipers. The ultrasound gel was then added between the pinhole mask and the transmitting transducer to complete the acoustic bridge. The ultrasonic system was then powered on, along with the oscilloscope. Measurements were taken every 2 degrees in both the positive and negative directions from center up to 46 degrees for two trials over the range of angles (i.e. 47 total angles in each trial). The peak-to-peak voltages were recorded from the oscilloscope.

3.5 Pinhole Mask Experiment Post Processing

The peak-to-peak voltages were recorded for each angle with respect to the transmitting transducer, were averaged for the two trials, and the average voltage was plotted versus the angles. The plots were created to compare the fringe patterns for each of the two-pinhole masks. The predicted fringe pattern period was calculated for each pinhole mask (Eq. 2.3) and the observed fringe pattern period was determined using the first major peak as the basis for determining the period. The criterion for a major peak was that the two values before the peak must increase to the peak while the two values after the peak must decrease. Next, a backward calculation was done to determine the pinhole spacing using the observed period (Eq. 2.3), solving for parameter “d”. The wavelength needed as input to Eq. 2.3 was calculated using the values for the speed of
sound and frequency, 1520 m/s and 10 MHz respectively. The pinhole spacing was taken to be 500μm, or 700μm. In addition, the first and second peaks were recorded for comparison.

Error was analyzed in the alignment of the transmitting transducer to the pinhole mask. The error in angle measurement was calculated by taking the difference in the measured angle and the error-shifted angle. The maximum angle error was used as the overall error for the measurements.

3.6 Pinhole Mask Computer Simulation General Configuration

A computer simulation of the two-pinhole mask model was created to analyze and validate the model’s physical process. Comsol Multiphysics software (Comsol AB.) was used to develop a two-dimensional pressure acoustics transient model. The model scenario consisted of sixteen model variations that encompassed the transducers full range of orientation.

3.7 Pinhole Mask Computer Simulation Model Design

The model was created by using the Comsol Acoustics Module. A two-dimensional pressure acoustics application mode was chosen. Within this mode, the transient analysis option was chosen for acoustic modeling using the wave equation, with ‘p’ being the acoustic pressure, cs the speed of sound in the medium, and ρ₀, the equilibrium density, while q and Q are dipole and monopole sources respectively (Eq. 3.1).
\[ \frac{1}{\rho_0 c_s^2} \frac{\partial^2 p}{\partial t^2} + \nabla \cdot \left( -\frac{1}{\rho_0} (\nabla p - q) \right) = Q \]  

(3.1)

The acoustic pressure, \( p = p(\mathbf{r},t) \), is solved for in the wave equation (Eq. 3.1) using parameters such as \( c_s, \rho_0, q, \) and \( Q \). The domain of the model included the area between the input transducer and the two-pinhole masks, as well as the area between the two-pinhole mask and the receiving transducer (Figs. 3.5-3.7)

Fig. 3.5: Pinhole Mask Computer Simulation Domain (21-degree angle with mask of 300/700 with units of \( 10^{-3} \)m).
Fig. 3.6: Pinhole Mask Computer Simulation Domain (21-degree angle with mask 100/500 with units of $10^{-3}$ m)

Fig. 3.7: Pinhole Mask Computer Simulation Domain (21-degree angle with mask 100/700 with units of $10^{-3}$ m)
The computer model was constructed using the dimensions of the pinhole mask experiment. Given this, the transducer faces were 3mm in diameter with a distance of 2mm between the transducers face to the pinhole mask. The domain area represents the acoustic bridge created by the ultrasound gel.

The model was constructed with the receiving transducer (edge 20 in Fig. 3.8) being stationary and the transmitting transducer (edge 3 in Fig. 3.8) rotating from zero to forty-fifty degrees with measurements being taken every three degrees. This resulted in sixteen different models. The pinhole mask edge boundaries were labeled one through twenty-one (Fig. 3.8)

![Fig. 3.8: Boundary edges of the pinhole model at 21 degrees with mask 300/700 (units in figure 10^{-3} m for x and y-axis).]
The model for zero degrees was slightly different from the other fifteen models because boundary edge number 13 was not needed since there was no angle of rotation.

The boundary conditions were selected to mimic the experimental conditions as best as possible. The transmitting transducer (edge #3) had Dirichlet boundary conditions set to “Radiation condition” with wave type “plane wave” where the incident pressure ‘p₀’ was equal to ‘pᵢ.’ The value of ‘pᵢ’ was set to the specified signal level, either from the ultrasound signal equation or a data file containing signal data. The radiation condition allowed an outgoing wave to leave the domain without reflections and was the ratio between the sound pressure and the normal particle velocity. Boundary edges #1,2,4,5,13,19,20, and 21 were set to impedance boundary conditions with the input impedance ‘Z’ set equal to 1050*1520 (units Pa*s/m) (Eq. 3.2).

\[ n \cdot \left( \frac{1}{\rho_0} (\nabla p - q) \right) + \frac{1}{Z} \frac{\partial p}{\partial t} = 0 \]  

(3.2)

The remaining boundary edges, 6-12 and 14-18, had boundary conditions of a homogenous Neumann type hard sound boundary where the normal derivative of the pressure at the wall becomes zero (Eq. 3.3).

\[ \frac{\partial p}{\partial n}\bigg|_{wall} = 0 \]  

(3.3)

Two specific parameters for the subdomain were used to define the properties of this domain-fluid density (\(\rho_0 = 1050 \text{ kg/m}^3\)) and speed of sound (\(c_s = 1520 \text{ m/s}\)), or the speed of sound in the medium. The subdomain is controlled by the equation chosen in the acoustics transient analysis application mode (Eq. 3.1).

The free mesh (Fig. 3.9) was constructed as an unstructured grid using triangular elements. The number of elements in each model ranged from 18,000 to 20,000 elements.
depending on the size of the domain; the degrees of freedom ranged from 37,000 to 40,000; and the number of mesh points ranged from 9000 to 11,000.

Fig. 3.9: Mesh of 21-degree model with 300μm pinhole size and 700μm pinhole spacing (units in figure 10⁻³ m).

The mesh settings were not changed between models; however, due to the movement of the transmitting transducer, each model contains a slightly different number of elements. The solver was time dependent and had computational times that ranged from 5*10⁻⁶ to 6.5*10⁻⁶ seconds with time steps of 1*10⁻⁹ seconds beginning at time zero. The final time ranged in values due to the limitations in processing power with a finer mesh.

The output signal was obtained using the Comsol’s built-in boundary integration function. The boundary integration function integrated across each boundary edge’s length with respect to each time step. Two plot probes were established before each simulation so that the transmitting transducer and receiving transducer output signals
were recorded. The signals were saved as text files for later analysis. The domain properties were observed via animation. A movie of the total wave pressure over time was created for certain pinhole mask models to observe wave propagation and scattering effects.

3.8 Pinhole Mask Computer Simulation Model Scenarios

The pinhole mask computer simulation was created to mimic the pinhole mask experiment with four model scenarios representing the four different pinhole masks in the experiment. Each scenario consisted of sixteen different models with each model representing an increment of three degrees as the transmitting transducer rotated from zero to forty-five degrees. The domains for the 300μm pinhole size and 700μm mask model scenario are shown in Appendix C.

Three different signals were used as input to the computer models. A continuous ultrasound signal was created to mimic the BCM Ultrasonic System input, with $f_0$ and $f_c$ being sinusoidal frequencies, 0.9 MHz and 10 MHz respectively (Eq. 3.4).

$$p_{ucpr}(t) = 18 \left( 1 + 18 \cdot \sin \left( 2 \cdot \pi \cdot f_0 \cdot (t - (3 \cdot 10^{-7})) + \frac{p_0}{q} \right) \right) \cdot \sin \left( 2 \cdot \pi \cdot f_c \cdot (t - (3 \cdot 10^{-7})) \right) \cdot \exp \left( -100 \cdot \frac{\left( t - (2.5 \cdot 10^{-7}) \right)^2}{(1 \cdot 10^{-11})} \right)$$  \hspace{1cm} (3.4)

By using an amplitude-modulated signal, it was possible to recreate the ultrasound signal and solve for acoustic pressure. This signal was used for all the standard ultrasound pinhole model analysis.

A random (white) noise signal was created over the same time period as the input ultrasound signal. A third signal was created by adding the white noise signal to the clean
ultrasound signal at a 10% level (S/N = 10) to create a noisy ultrasound signal. The signals were created in Matlab (The Mathworks) and exported as text files (code shown in Appendix J). The files were imported into Comsol using the function creation option that allowed a function to be created using text file parameters. Specifically, the input function was created directly from the file points, and all values outside the text file time values were allowed to be zero, as no signal would be transmitted.

3.9 Pinhole Mask Computer Simulation Convergence Study

In order to demonstrate that the mesh resolution was at an appropriate level for accurate results, a convergence study was conducted [57, 61]. A mesh convergence study was conducted by varying the mesh resolution until the error converges to an acceptable level for the metrics under investigation, in this case, less than ten percent error for the variation in the measured signal at the receiving transducer. It was assumed that the highest mesh density in the study was the most accurate and the percent error was calculated based on the value associated with that configuration. A pinhole mask model was chosen as the base model, in this case, the two-pinhole mask model at 15 degrees with 100μm size pinholes and 500μm hole spacing. The mesh density was increased by increasing the number of mesh points from 3647 to 12669, which increased the number of mesh elements and the degrees of freedom within the model from 6852 to 24172 and 14146 to 49510, respectively. A change in the distribution of mesh points on the transducer faces (edges 3 and 20) and pinhole faces (edges 7 - 10, 12, 16) was used as a method for a controlled increase in mesh resolution. After the mesh was initiated at the
given values, it was refined once, resulting in a higher mesh density and increased boundary mesh distributions (Table 3.2).

Table 3.2: Convergence Study Mesh Data.

<table>
<thead>
<tr>
<th>Edge 3: # mesh points (initial)</th>
<th>Edge 3: # mesh points (refined)</th>
<th>Pinhole edges: # mesh points (initial mesh)</th>
<th>Pinhole edges: # mesh points (refined mesh)</th>
<th>DOF (final)</th>
<th># of elements (final)</th>
<th># of mesh points (final)</th>
</tr>
</thead>
<tbody>
<tr>
<td>45</td>
<td>90</td>
<td>9</td>
<td>18</td>
<td>14146</td>
<td>6852</td>
<td>3647</td>
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<td>120</td>
<td>12</td>
<td>24</td>
<td>19400</td>
<td>9424</td>
<td>4988</td>
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<td>30</td>
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<td>11592</td>
<td>6122</td>
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<td>42</td>
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<td>16812</td>
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</tr>
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<td>48</td>
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<td>19604</td>
<td>10289</td>
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</tr>
<tr>
<td>150</td>
<td>300</td>
<td>30</td>
<td>60</td>
<td>49510</td>
<td>24172</td>
<td>12669</td>
</tr>
</tbody>
</table>

Each mesh density resulted in a different output signal. The peak-to-peak voltage of the boundary integrated over the face of the receiving transducer per unit time was calculated and plotted against the number of points in the mesh for the different mesh densities. The percent error was calculated and plotted against the mesh densities (Matlab code is shown in Appendix I). From this study, an optimal mesh can be chosen based on accuracy and computing power needs and the chosen mesh density can be evaluated for accuracy.
3.10 Pinhole Mask Computer Simulation Post Processing

Peak-to-peak output pressure values were calculated from the receiving transducer output signal. Fringe patterns of the signals were plotted using the peak-to-peak pressure versus the angle of rotation. Fringe plots were created for all pinhole masks. In addition, comparative plots for the random noise and ultrasound noisy signal along with plots of the experimental, random noise, noisy ultrasound signal, and computer simulated fringe patterns were constructed. The convergence study analysis consisted of integrating the output pressure waveform and plotting the values versus the number of mesh elements. The percent error was calculated and plotted versus number of mesh points.

3.11 Blood Mimicking Fluid (BMF) Signal Characterization General Configuration

A flow loop containing a pulsatile pump, tissue mimicking phantom, and reservoir were connected inline. A blood mimicking fluid was pumped through the system with ultrasound transducers placed externally on the tissue phantom to record the forward scatter signal.

3.12 BMF Signal Characterization Equipment

A custom arterial analog flow system was created that utilized a tissue mimicking flow phantom and blood mimicking fluid. The tissue mimicking flow phantom (Blue Phantom Division of Advanced Medical Technologies, LLC) consisted of four flow tubes (top to bottom in Fig. 3.10): 7.6mm diameter straight tube, 9mm diameter straight tube, 7.6mm diameter with stenosis, and 7.6mm diameter angled downward. The flow
phantom provided surrounding medium with acoustic characteristics similar to soft tissue.

A Series 1400 (1423) Pulsatile Blood Pump (Harvard Apparatus) was used as the piston type pump to produce the pulsatile waveform of the fluid. With this pump, it was possible to regulate the amount of fluid pumped during each cycle by changing the output phase ratio and strokes per minute as the RPM. During all experiments, the output phase ratio was 30/70, which represented percent systolic divided by percent diastolic. The strokes per minute were 45 and the stroke volume was approximately 50ml. The specific data for the pump is shown in Appendix D.

The blood mimicking fluid (BMF) consisted of 5μm diameter polystyrene microspheres that were suspended in a pre-mixed fluid that contained of water, glycerol,
dextran, and a surfactant [60]. The fluid had acoustical properties that matched blood serum, contained preservatives that inhibited bacterial and fungal growth, and had a viscosity similar to blood at high sheer, approximately 4.1 mPa*s. The density of the particles was 1.03 g/cm³.

The same 10 MHz tubal transducers were used as in the previous pinhole experiment. The transmitting transducer was setup to transmit the ultrasound signal; the receiving transducer was set to receive. In addition, the same BCM Ultrasonic system was used. The Tektronix 3014b oscilloscope was used to acquire two signals: channel 1 was the direct output from the BCM Ultrasonic System split from the 10 MHz pulsed Doppler module, and channel 2 was the forward scatter receiving transducer signal from the phasic output of the BCM system. All output data was acquired through the e*Scope program.

3.13 BMF Signal Characterization Experimental Setup

The flow phantom, pulsatile pump, and BMF reservoir were connected inline by plastic tubing (Fig. 3.11). Ball values were used throughout the flow loop in order to change the path of the flow and isolate specific areas of the loop.
The transducers were externally placed on the flow phantom’s 7.6mm straight tube with an angle of 45 degrees off the center alignment or a total of 90 degrees between transducers (Fig. 3.10 and Fig. 3.12).
3.14 BMF Signal Characterization Procedure

The pre-run checklist included inspection and preparation. The flow loop was first inspected for any leaks on the pump, reservoir, or tubing. The reservoir tank was then stirred with a magnetic stirrer to mix the microspheres inside the fluid for approximately five minutes. As the reservoir was mixing, the transducers were arranged in the tissue-mimicking phantom at a 45-degree angle from center or 90 total separation angle, the transmitting transducer was a negative 45 degrees and the receiving transducer was positive 45 degrees. Each was externally placed transducers on phantom surface with acoustic gel added. The transducer distance into the tissue phantom was adjusted until maximum signal peak-to-peak voltage was obtained at stationary flow. The adjustments were made physically to the transducers and with the ‘Range’ adjustment on the ultrasonic device while the ultrasonic system was powered on.

All valves were checked to be open with the exception of the water reservoir, which was closed during each experiment. The main particle reservoir was then opened and the pump was powered on. The pump was run for a minimum of five minutes to ensure uniform particle distribution.

Five different concentrations were used in the experiment. For each concentration, a small amount of polystyrene particles was added to the blood mimicking fluid. After each trial, 10ml and 50ml samples were taken from the particle reservoir for analysis of concentration. The concentrations were then determined by centrifuging the samples and measuring the amount of particles in relation to the total amount of fluid resulting in a percentage of total particles. Finally, ten signals were recorded for each concentration via e*Scope.
3.15 BMF Signal Characterization Post Processing

The signal characteristics calculated for the fluid flow experiment were energy, amplitude, and attenuation of energy and amplitude. The energy of the input and forward scattering signal was evaluated using a discrete time energy equation (Eq. 3.5)

\[ E = \sum_{n=-\infty}^{\infty} (|x(n)|^2) \]  \hspace{1cm} (3.5)

The peak amplitude was determined from the maximum value of the signal each signal. Then, the attenuation was calculated by using Equation 3.6 and was also calculated with amplitudes; input amplitude and forward scatter amplitude were substituted for the energies.

\[ \text{attenuation}_{\text{energy}} (dB) = 20 \times \log_{10} \left( \frac{E}{E_0} \right) \]  \hspace{1cm} (3.6)

Since ten trials were recorded for each concentration, the final energy and attenuation values are the average of all ten-trial energy and attenuation values. The standard deviations were calculated for attenuation and energy for each of the concentrations.
CHAPTER IV
RESULTS

4.1 Pinhole Mask Experimental Results

An ultrasound signal pulse was transmitted through the transducer from the BCM Ultrasonic System (Fig. 4.1)

Fig. 4.1: BCM Ultrasonic System ultrasound output signal (10MHz).
After the ultrasound pressure wave passed through the pinhole mask, it was received by a second transducer that was connected to an oscilloscope to observe and record the signal (Fig. 4.2).

![Output Signal from BCM Ultrasonic System - Mask 100/500 @ 4 degrees](image)

Fig. 4.2: Output signal recorded with transmitting transducer at 36-degree angle and receiving transducer 100/500 pinhole mask.

The received output signals were analyzed for peak-to-peak voltage (Appendix F). The peak-to-peak voltages were recorded, averaged, and plotted versus the angle of insonation for each pinhole mask (Figs. 4.3- 4.6).
Fig. 4.3: Fringe pattern for pinhole mask with 100μm pinhole size and 500μm pinhole spacing.

Fig. 4.4: Fringe pattern for pinhole mask with 100μm pinhole size and 700μm pinhole spacing.
Fig. 4.5: Fringe pattern for pinhole mask with 300μm pinhole size and 700μm pinhole spacing.

Fig. 4.6: Fringe pattern plot for all three pinhole masks.
The period of the fringe patterns were calculated using the predicted period equation (Eq. 2.3) (Table 4.1).

**Table 4.1: Predicted angle for the 1st peak of the period.**

<table>
<thead>
<tr>
<th>Mask</th>
<th>Predicted Angle for 1st Peak of the Period</th>
</tr>
</thead>
<tbody>
<tr>
<td>100/500</td>
<td>17.42</td>
</tr>
<tr>
<td>100/700</td>
<td>12.44</td>
</tr>
<tr>
<td>300/700</td>
<td>12.44</td>
</tr>
</tbody>
</table>

The periods were estimated using the observed the first peak in the fringe pattern for each mask (Table 4.2).

**Table 4.2: Peak values for pinhole mask fringe patterns.**

<table>
<thead>
<tr>
<th>Mask</th>
<th>1st Peak (degrees)</th>
<th>2nd Peak (degrees)</th>
</tr>
</thead>
<tbody>
<tr>
<td>100/500</td>
<td>24</td>
<td>34</td>
</tr>
<tr>
<td>100/700</td>
<td>22</td>
<td>34</td>
</tr>
<tr>
<td>300/700</td>
<td>14</td>
<td>26</td>
</tr>
</tbody>
</table>

The predicted and observed periods were plotted over the fringe pattern for two periods (Figs. 4.7 – 4.9, square =observed, circle =predicted).
Fig. 4.7: Pinhole Mask (100/500) fringe pattern with observed and predicted periods plotted.

Fig. 4.8: Pinhole Mask (100/700) fringe pattern with observed and predicted periods plotted.
Fig. 4.9: Pinhole Mask (300/700) fringe pattern with observed and predicted periods plotted.

Given the observed period of the fringe pattern for each mask, the mask pinhole spacing could be back-calculated assuming the first major peak of the fringe pattern represented the period (Table 4.3). The Matlab code for data analysis is shown in Appendix L.

Table 4.3: Predicted mask pinhole spacing based on observed period.

<table>
<thead>
<tr>
<th>Mask</th>
<th>First Peak (degrees)</th>
<th>First Peak (radians)</th>
<th>Predicted Mask Pinhole Spacing</th>
</tr>
</thead>
<tbody>
<tr>
<td>100/500</td>
<td>24</td>
<td>.419</td>
<td>363</td>
</tr>
<tr>
<td>100/700</td>
<td>22</td>
<td>.384</td>
<td>396</td>
</tr>
<tr>
<td>300/700</td>
<td>14</td>
<td>.244</td>
<td>623</td>
</tr>
</tbody>
</table>
It was estimated that the transmitting transducer could have been misaligned by ±0.01mm. The error was calculated by finding the difference between the actual angle and the angle caused by alignment error. The distance between the center point of the transmitting transducer and the centerline of alignment parallel to the pinhole mask face was calculated using the known rotation angle and basic trigonometric functions. In addition, the distance perpendicular to the pinhole mask of the transmitting transducer was calculated. Then, the alignment error distance was subtracted from the total parallel distance and that total was divided by the perpendicular transducer distance. The cotangent of this value was taken to be the estimated angle error (Appendix D). The error was plotted versus the angle of insonation (Fig. 4.10).

![Estimated Error from Angle Alignment](image)

*Fig. 4.10: Estimated error from angle misalignment based on the angle of insonation.*
The maximum error occurred at the largest angle and was $\pm 0.7812^\circ$. The maximum error was then used as the assumed error for the experiment.

4.2 Pinhole Mask Computer Simulation Results

The input signal to the Comsol model was an ultrasound input signal that was created to resemble the continuous BCM ultrasound signal (Fig 4.11).

![Computer Simulation Ultrasound Signal](image)

**Fig. 4.11:** Computer simulation clean ultrasound signal.

Two other signals were generated for the computer simulation and input signals. The second overall signal was a random (white) noise signal that was created in Matlab using the random number function (Fig 4.12).
The third signal generated was a combination of the clean ultrasound signal with added noise. The random function was again used but with each term being multiplied by 10% of the maximum amplitude of the clean ultrasound signal and then added to the clean ultrasound signal (Fig 4.13).
Fig 4.13: Computer simulation noisy ultrasound signal.

Each model scenario contained sixteen pinhole models. The program yielded a contour plot of each time step depicting total wave pressure (Fig. 4.14). The figures could be used to create a video of the pressure wave motion. Seven time steps are shown to demonstrate the propagation of the pressure wave (Appendix G.).
After each model was run, the peak-to-peak pressure value was determined from the boundary integration over time of the receiving transducer. The peak-to-peak pressure values were obtained for each of the sixteen pinhole models and four pinhole model scenarios. The first maximum value, or peak, was assumed to begin the cosine waveform. The values were plotted versus the angle of the transmitting transducer (Figs. 4.15 – 4.17).

Fig. 4.14: Post processing contour plot of total pressure of pinhole mask 300/700 at time 5μs. 
Fig. 4.15: Computer simulation fringe pattern for mask 100/500.

Fig. 4.16: Computer simulation fringe pattern for mask 100/700.
Fig. 4.17: Computer simulation fringe pattern for mask 300/700.

The same procedure was done for the noisy ultrasound signal and the random noise signal. All pinhole fringe patterns (experimental, clean ultrasound, noisy ultrasound, and random noise) were plotted in the same figure (Figs. 4.18 -4.20).
Fig 4.18: Experimental and computer simulation (CS) fringe pattern for pinhole mask 100/500 (normalized to the maximum value for each signal).

Fig. 4.19: Experimental and CS fringe pattern for pinhole mask 100/700 (normalized to the maximum value for each signal).
The observed angles at which the fringe pattern peaked were recorded for the three signals (Tables 4.4 – 4.6)

Table 4.4: Computer simulation peak values for pinhole mask fringe pattern ultrasound signal.

<table>
<thead>
<tr>
<th>Mask</th>
<th>1st Peak</th>
<th>2nd Peak</th>
<th>3rd peak</th>
</tr>
</thead>
<tbody>
<tr>
<td>100/500</td>
<td>18</td>
<td>36</td>
<td>-</td>
</tr>
<tr>
<td>100/700</td>
<td>12</td>
<td>27</td>
<td>42</td>
</tr>
<tr>
<td>300/700</td>
<td>12</td>
<td>27</td>
<td>36</td>
</tr>
</tbody>
</table>
Table 4.5: Computer simulation peak values for pinhole mask fringe pattern ultrasound signal with noise.

<table>
<thead>
<tr>
<th>Mask</th>
<th>1\textsuperscript{st} Peak</th>
<th>2\textsuperscript{nd} Peak</th>
<th>3\textsuperscript{rd} peak</th>
</tr>
</thead>
<tbody>
<tr>
<td>100/500</td>
<td>6</td>
<td>15</td>
<td>30</td>
</tr>
<tr>
<td>100/700</td>
<td>15</td>
<td>18</td>
<td>36</td>
</tr>
<tr>
<td>300/700</td>
<td>15</td>
<td>21</td>
<td>36</td>
</tr>
</tbody>
</table>

Table 4.6: Computer simulation peak values for pinhole mask fringe pattern random noise signal.

<table>
<thead>
<tr>
<th>Mask</th>
<th>1\textsuperscript{st} Peak</th>
<th>2\textsuperscript{nd} Peak</th>
<th>3\textsuperscript{rd} peak</th>
</tr>
</thead>
<tbody>
<tr>
<td>100/500</td>
<td>6</td>
<td>30</td>
<td>39</td>
</tr>
<tr>
<td>100/700</td>
<td>15</td>
<td>18</td>
<td>27</td>
</tr>
<tr>
<td>300/700</td>
<td>15</td>
<td>24</td>
<td>36</td>
</tr>
</tbody>
</table>

After each simulation run, contour plots of the total output pressure were displayed. The contour plots were created for each time step within the simulation. The plots could be chosen for anytime in the simulation, specifically to demonstrate diffraction for the fringe pattern (Figs. 4.21 and 4.22).
Fig 4.21: Pressure contour plot of 30-degree angle with mask 100/500.

Fig 4.22: Pressure contour plot of 30-angle with mask 100/500 expanded view of pinholes and fringe pattern.
The convergence study was conducted to demonstrate that the mesh density is of sufficient quality for the simulation. The number of mesh elements was increased for the same model with the peak-to-peak signal output being calculated. From the output, a percent error was calculated (Table 4.7).

<table>
<thead>
<tr>
<th># of mesh points</th>
<th>Peak-Peak Signal Output (x10^-8) (Pa)</th>
<th>Percent Error (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>3647</td>
<td>-0.169803</td>
<td>1599.3</td>
</tr>
<tr>
<td>4988</td>
<td>0.090528</td>
<td>699.3</td>
</tr>
<tr>
<td>6122</td>
<td>-0.058993</td>
<td>620.9</td>
</tr>
<tr>
<td>7410</td>
<td>0.011050</td>
<td>2.4</td>
</tr>
<tr>
<td>8839</td>
<td>0.011417</td>
<td>0.8</td>
</tr>
<tr>
<td>10289</td>
<td>0.011208</td>
<td>1.1</td>
</tr>
<tr>
<td>11321</td>
<td>0.011392</td>
<td>0.6</td>
</tr>
<tr>
<td>12669</td>
<td>0.011326</td>
<td>0</td>
</tr>
</tbody>
</table>

As the mesh densities were increased, the mesh domain plots were recorded as images (Appendix E). The signal output was integrated over time and the magnitude was plotted against the number of mesh points in the model (Fig. 4.23).
Fig. 4.23: Magnitude of integrated convergence study signal versus number of mesh points.

The percent error was then calculated assuming the model with the highest number of mesh points is most accurate and plotted versus the number of mesh points (Fig. 4.24)
4.3 BMF Signal Characterization Experimental Results

The oscilloscope recorded two signals: the input signal at 4.0μs per division and the forward scatter signal at 400ms per division. There were ten divisions recorded in each file.

The microsphere particle concentrations in the fluid were determined by centrifuging the samples and measuring the ratio of the amount to the total sample size. The estimated volumes of the samples were 0.35ml, 0.4ml, 0.6ml, 0.7ml, and 0.9 ml, from concentration trial one to five, respectively. These concentrations corresponded to 7%, 8%, 12%, 14% and 18% particle to fluid ratio. The energy, amplitude, and
attenuation were calculated (Tables 4.8 and 4.9) along with the standard deviation of the four concentrations (Table 4.10).

**Table 4.8: Energy and amplitude values for the five concentrations.**

<table>
<thead>
<tr>
<th></th>
<th>Conc. 1</th>
<th>Conc. 2</th>
<th>Conc. 3</th>
<th>Conc. 4</th>
<th>Conc. 5</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amplitude</td>
<td>0.2512</td>
<td>0.2460</td>
<td>0.2328</td>
<td>0.2740</td>
<td>.4000</td>
</tr>
</tbody>
</table>

**Table 4.9: Energy and amplitude attenuation for the five concentrations.**

<table>
<thead>
<tr>
<th>Attenuation (dB)</th>
<th>Conc. 1</th>
<th>Conc. 2</th>
<th>Conc. 3</th>
<th>Conc. 4</th>
<th>Conc. 5</th>
</tr>
</thead>
<tbody>
<tr>
<td>Energy</td>
<td>-76.7942</td>
<td>-73.0791</td>
<td>-78.1233</td>
<td>-75.3455</td>
<td>-69.4240</td>
</tr>
<tr>
<td>Amplitude</td>
<td>-41.7461</td>
<td>-41.8016</td>
<td>-42.4258</td>
<td>-41.0981</td>
<td>-39.1472</td>
</tr>
</tbody>
</table>

**Table 4.10: The standard deviation for energy, amplitude, and both attenuation values for within each concentration.**

<table>
<thead>
<tr>
<th></th>
<th>Conc. 1</th>
<th>Conc. 2</th>
<th>Conc. 3</th>
<th>Conc. 4</th>
<th>Conc. 5</th>
</tr>
</thead>
<tbody>
<tr>
<td>Energy</td>
<td>1.4589</td>
<td>1.2536</td>
<td>1.2118</td>
<td>1.0450</td>
<td>3.7152</td>
</tr>
<tr>
<td>Amplitude</td>
<td>1.1654</td>
<td>0.8538</td>
<td>0.8202</td>
<td>0.8424</td>
<td>4.8755</td>
</tr>
<tr>
<td>Attenuation (Energy)</td>
<td>2.1754</td>
<td>1.9446</td>
<td>1.7545</td>
<td>2.023</td>
<td>16.0952</td>
</tr>
<tr>
<td>Attenuation (Amplitude)</td>
<td>0.0362</td>
<td>0.0247</td>
<td>0.0224</td>
<td>0.0269</td>
<td>0.2867</td>
</tr>
</tbody>
</table>
CHAPTER V
DISCUSSION

5.1 Pinhole Experiment and Computer Simulation

When two waves propagate simultaneously in the same space, interference occurs. The interaction between the waves can either be constructive or destructive interference. The interference test conducted for this experiment used the notion that a two-pinhole mask was a method for physically illustrating the ability to cross correlate a signal by revealing the formation of regular interference patterns. Diffraction occurred as the pressure wave passed through the pinholes and produced spherical waves, similar to a Young’s double pinhole experiment. The phase difference of the waves at the observation plane was equal to the phase difference of the incident wave at the two pinholes plus the difference in distance that each pressure wave traveled from their respective pinhole to the observation plane. The pinhole mask experiment was designed to find the optimal size/spacing combination, which can separate the single scatter and multiple scatter components of the ultrasound using a two detector configuration following the Meyer et al. optical cross-correlation technique. It was demonstrated previously that single scattering speckle is inherently larger than multiple scattering speckle, so if one can find a spacing that is larger than the multiple scattering speckle but smaller than the single scattering speckle, then multiple scattering can be suppressed through cross-correlation.
The cross correlation technique was proposed with the understanding that the single scatter field would be correlated at the two pinholes and would result in interference, whereas the multiple scattering field would be uncorrelated and not result in any appreciable interference (it averages to zero). Consequently, any observed interference pattern could be solely attributed to the single scatter signal. As the source was rotated about a center point between the two pinholes, the signal intensity was predicted to display a sinusoidal variation with a period based on the wavelength and the spacing between the pinholes. Due to attenuation effects and the finite size of the pinholes, it was observed that the intensity of the output signal decayed in amplitude, not consistent with constant amplitude (i.e., it was a damped sinusoid). This concept was demonstrated as the fringe pattern intensities declined from initial to final position within the produced interference pattern.

It was observed that the quality of the fringe pattern increased as the pinhole size and spacing were increased. The experimental results showed that the percent error between the predicted first peak and the observed first peak were 37.77% and 76.54%, for pinhole masks 100/500 and 100/700 respectively. The percent error was reduced to 12.54% for the 300/700 mask. In addition, the percent error for the 300/700 mask was the lowest for the three masks for the computer simulation with the clean, noisy, and random noise signals. Given these results, it can be concluded that the optimal pinhole mask for this experiment was the 300/700 mask. The second research hypothesis stated that by using a predicted period equation, it was possible to determine the optimal pinhole size and spacing. With this, the second research hypothesis has been proven given that the predicted period equation was able to determine the optimal pinhole size and spacing of
the two-pinhole mask. In addition, the first research hypothesis stated that the pinhole mask cross-correlation method could determine field correlations. If it were possible to predict the fringe pattern periods as demonstrated, then it was shown that field correlations could be detected, thus verifying research hypothesis one.

The computer model was created to analyze the physical cross correlation method and help explain the experimental results, accounting for some of the effects not captured by the analytical model, mainly the breakdown of the theory for the smaller pinhole sizes. It was hypothesized that the computer model, if all physical factors were similar, would produce results resembling the pinhole experiment. The computer model confirmed that the signal magnitude degraded with rotation angle due to the finite pinhole size by showing the decay of the fringe pattern. In addition, the large number of reflections could be seen from the total pressure wave contour plots (Fig. 4.27, 4.28, and Appendix G). The reflections are most prevalent in Fig. 4.28 inside the pinhole conduit. The darker, more concentrated areas are regions of compression waves caused by the pressure wave’s interaction with the boundary. Within the pinhole conduit, several dark regions are shown on the top and bottom of each pinhole demonstrating a reflection of the pressure wave, which was calculated in the ray trace. However, the fringe patterns generated by the computer simulations resembled the experimental results for the 300/700 mask being within a 4% error of the predicted period, again confirming that the combination most accurately reflects the analytical (this screen) model and is the optimal pinhole size and spacing for the correlation measurements.

The simulations were conducted with not only a clean ultrasound signal, but also with a noisy ultrasound signal and a random noise signal. This demonstrated that the
added random noise would not affect the fringe pattern output, as it would be minimized by the cross-correlation technique. On the other hand, the random noise signal would produce a fringe pattern with no discernable pattern. The noisy ultrasound signal did produce a fringe pattern with peaks similar to the clean ultrasound signal and the experimental results while the random noise signal did not produce any discernable interference pattern. However, this phenomena was only observed for the 300/700 mask.

With the computer simulation being only a two-dimensional model, comparing the experimental results to the computer simulations had some limitations. The 2D computer model represented the apertures as infinite horizontal slits, and not finite sized pinholes as in the actual experiments. In addition, the 2D model did not take into account such factors as attenuation caused by interactions between the pressure wave and the pinhole mask or energy lost by three-dimensional interactions. Despite these limitations, the 2D model could accurately demonstrate the diffraction phenomenon similar to Young’s double slit experiments. However, since the predicted period equation was derived from Young’s double-slit experiment, which assumes that the light, or in this case sound, passes through a thin screen, the theoretical calculations for fringe spacing did not account for the depth of the slits, or pinholes.

A possible reason for the difference in the observed periods versus the predicted periods was that less signal light was transmitted through the smaller pinholes versus the larger ones. The 100μm pinholes allowed less than one percent (≈ 0.222%) of the transmitted energy to pass through the mask. On the other hand, the larger 300μm pinholes allowed ten times the amount of energy (≈ 2%) to pass through the pinholes.
Given this, the energy passing through the 100μm could be mostly due to residual radiation effects while most of the energy is reflected.

The interactions of the ultrasound inside the pinholes because of their finite depth can affect the output signal as well. The depth of the pinholes in this experiment was 500μm. This was three times the wavelength produced with the 10MHz transducer, 152μm. Because of this significant depth, multiple reflections occur in the pinholes, especially at higher angles. These reflections result in multiple scattering and to corresponding changes in the signal phase. The number of reflections can be found by performing a simple ray trace to follow the path of the pressure wave from the center of the transmitting transducer, through the pinholes, and to the receiving transducer assuming the reflections obey laws of geometric optics (Appendix H). The 100μm diameter pinhole has up to six reflections at higher angles while the larger ~300μm pinholes only reflect a maximum of twice. The ray trace does not take into account multiple interactions. Similarly, the 100μm pinhole is smaller than the 152MHz wavelength; this substantially inhibits the propagation of much of the signal, even at low relative incidence angles. As the angle of the transmitting transducer increases, the projected area of the pinhole with respect to the pressure wave decreases, while the effective distance that the pressure wave must travels to traverse the pinhole conduit increases. This increase in pressure wave path distance between the pinholes is the reason for the change in phase of the exiting signal.

Another possible explanation for the fringe pattern behavior and the failure of the cross-correlation technique for the smaller pinholes is evanescent wave coupling. When diffraction occurs at a screen, two types of waves are produced, evanescent and
homogeneous waves. The evanescent waves are formed from the diffraction by subwavelength structures (sharp edges and small pinholes) and do not propagate. However, evanescent waves can couple (along with their energy) into the screen, or pinhole mask, and propagate as body and surface waves to the second slit/pinhole where they can be converted back into propagating pressure waves and appear in the observation region [64, 65, 66]. Evanescent wave generation and the resulting coupling will be greater for narrower pinholes compared to wider pinholes. This effect can be verified by Fourier theory, which states that the spatial frequency content of the field diffracted by slit/pinhole is the Fourier-transform of the transmitted field. This means that the smaller the slit/pinhole, the wider the spatial frequency spectrum (the larger number of spatial frequency components). When the spatial frequency spectrum is wide, the higher frequency components, which represent the evanescent waves, are larger in magnitude (and greater in number) in comparison to the spectrum generated by narrow aperture. Thus, narrow apertures produce more evanescent waves, with the result that there is more coupling in the screen. Due to this higher-order correlation between the fields in the pinholes, the fringe patterns will have a much more complicated structure than the simple sinusoidal behavior attributed to the interference of two isolated pinholes [65, 66]. As a result, the theory resides better with the larger pinholes mask.

If evanescent wave coupling was the cause for the failure in the cross-correlation theory, the computer simulation would not have accurately demonstrated the effects due to the limitations in the boundary conditions. The boundary conditions of the pinhole mask that were defined as a hard boundary wall, or completely reflective, would be inaccurate and not allow evanescent coupling to occur. The most accurate boundary
conditions would have been an impedance boundary condition in which the material was set to copper. Other inconsistencies with the computer model as a result of the boundary conditions included the receiving transducer and the boundary between the ultrasonic gel and air. The boundary conditions on the receiving transducer, which were set to allow the pressure wave to pass out of the domain without any interactions. In actuality, reverberations would occur from the end of the transducer due to the pressure wave and cause the small interferences at the transducer face. In addition, the boundary between the gel and air was modeled at an impedance condition similar to the receiving transducer. The air/gel boundary, due to differences in speed of sound, would cause the pressure wave to be reflected back into the gel where it would interact with the initial pressure wave.

The convergence test revealed that the finite element approximation was converging to an acceptably accurate solution with respect to the exact solution. For this finite element computer simulation, the percent error converged to within two percent for the last four test cases, which included the number of mesh elements used for the computer simulation (~17,000 mesh elements). The mesh convergence lends credibility that the model is sufficiently accurate to allow reasonable observations and conclusions to be drawn from the results.

5.2 BMF Signal Characterization

The fluid flow experiment was designed to investigate the signal characteristics of the forward scattering Doppler ultrasound signal. The BMF experiments were conducted as a result of the previous experiments determining that the multiple scatter suppression
cross-correlation technique was feasible for ultrasound. The blood mimicking fluid contained scatterers that represented RBCs so the multiple scattering could be observed and the suppression method could be tested with ultrasound [60]. Multiple concentrations were used to demonstrate the insonation effects at multiple levels, similar to the variation in hematocrit.

The attenuation of energy and amplitude, if behaving in terms of previous studies, should have increased from lowest to highest concentration as the number of scatterers increased. However, the behavior of the BMF system did not resemble the predicted theory. This demonstrates that there might be some errors in the experimental setup. One possible error was the error in measurement of the particle concentrations. Since the particles are nearly neutrally buoyant, the particles did not settle and pack well enough to make an accurate measurement of the volume of particles. This could have lead to inaccuracies in the order of the concentrations. In addition, the packing factor of the particles changed with concentration, which was not well documented so the packing factor could not be estimated. This change in packing factor would also affect the characteristics of the received signals.

The signal characteristics of the blood mimicking fluid flow model were the first steps in determining the concentration of scatterers in the BMF based on attenuation. From this data and other tests, it will be possible to determine the optimal angle for insonation of the fluid and other signal properties for known concentrations. Additionally, a baseline can be set for future flow scattering experiments. The third research hypothesis stated that it was possible to suppression multiple scattering effects by a cross-correlation method. However, because neither the pinhole mask nor a multiple
transducer array was used with the blood mimicking fluid flow experiment to test
multiple scattering suppression techniques, multiple scatter suppression by a two-detector
cross-correlation method was not demonstrated, so the third research hypothesis was not
effectively modeled.
CHAPTER VI

FUTURE WORK AND CONCLUSION

6.1 Future Work

The overall aim of the project was to investigate concepts for the non-invasive detection of hematocrit. The cross-correlation technique was proposed as a possible method for minimizing multiple scattering speckle noise so that the single scattering speckle could be related to the input signal. To be used with hematocrit detection, the method would need multiple receiving transducers with their signals being correlated and related to the concentration of RBC’s. The multiple transducer array would be tested in an experiment similar to the setup for the BMF signal characterization. Varying the concentrations of the BMF would simulate the change in hematocrit and would allow the verification of the two-detector method for ultrasound. However, even though the optimal spacing would be determined for the scatterers in the BMF, the actual single scatter and multiple scatter speckle is determined by the scattering geometry, for blood this would be the RBCs. The RBCs have a much different shape than the BMF scatterers, bi-concave disc versus a sphere, along with a difference in reflectivity and viscosity. These differences will ultimately affect the spacing of the transducers. Human blood flow experiments will be necessary before the prototype device can be fully completed and verified for accuracy.
A continuation with the computer modeling would include modeling of the evanescent wave coupling and a computational flow dynamics (CFD) model. The effects of evanescent wave coupling could be tested for several different materials and pinhole masks configurations so that the true optimal pinhole size and spacing could be determined. The CFD model would include multiple scattering media so that the multiple scattering suppression method for ultrasound can be verified computationally. Overall, the computer modeling will be done before the experiments so that the experiments can be optimized for the best results.

6.2 Conclusion

A physical means to examine the viability of the Meyer cross-correlation method for minimizing multiple scattering speckle in ultrasound has been demonstrated. Interference fringe patterns due to correlated ultrasound fields were observed with periods predicted by the pinhole size, pinhole spacing, and frequency. The 300/700 mask configuration was shown to be the optimal mask for coherence detection. However, the results of the computer simulation demonstrated that there are other effects, such as multiple reflections inside the pinhole and evanescent wave coupling, which will influence the selection of the optimal pinhole size and spacing. Given these results, it could be concluded that the first research hypothesis was demonstrated because there was evidence of interference and a fringe pattern. The second research hypothesis was verified given that the predicted period equation determined the optimal pinhole size and spacing for this experiment. On the other hand, due to insufficient method for
determining the multiple scattering suppression, the third research hypothesis was not modeled and multiple scattering suppression was not demonstrated with ultrasound.
REFERENCES


[61] Standard for Models and Simulations (NASA-STD-7009)


APPENDICES
APPENDIX A

PINHOLE MASK EXPERIMENTAL EQUIPMENT.

Fig A.1: BCM Ultrasound System Modules and Mainframe.

Fig. A.2: Tektronix 3014B Oscilloscope.
APPENDIX B

HARVARD PULSATILE PUMP 1423 SPECIFICATIONS.

(Cat. No. 55-3321)

### Specifications

The specifications of all pumps are compared in the following chart.

<table>
<thead>
<tr>
<th>Harvard Pulsatile Blood Pump Comparison Chart</th>
<th>52-0652</th>
<th>55-1836</th>
<th>55-3321</th>
<th>55-3305</th>
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<tr>
<td>Catalog No.</td>
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<td>55-3321</td>
<td>55-3305</td>
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<td>Model No.</td>
<td>1407</td>
<td>1405</td>
<td>1421</td>
<td>1423</td>
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<tr>
<td>Stroke Volume</td>
<td>0.05 to 1.0 ml</td>
<td>0.5 to 10.0 ml</td>
<td>4 to 30 ml</td>
<td>15 to 100 ml</td>
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<tr>
<td>Stroke Rate (per min)</td>
<td>20 to 200</td>
<td>20 to 200</td>
<td>20 to 200</td>
<td>10 to 100</td>
</tr>
<tr>
<td>Minimum Volume (vol x rate)</td>
<td>1 to 200 ml</td>
<td>5 ml to 2.0 liters</td>
<td>80 ml to 6 liters</td>
<td>150 ml to 10 liters</td>
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<tr>
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<td>Fixed Phase</td>
<td>Adjustable Phase</td>
<td>Adjustable Phase</td>
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<td>50% systole</td>
<td>35 to 50%</td>
<td>35 to 50%</td>
<td></td>
</tr>
<tr>
<td>65% diastole</td>
<td>65% diastole</td>
<td>of cycle</td>
<td>of cycle</td>
<td></td>
</tr>
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<td>Tube Size (ID)</td>
<td>5/16 in</td>
<td>5/16 in</td>
<td>1/2 in</td>
<td>5/8 in</td>
</tr>
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<td>Piston Diameter</td>
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<td>1-1/16 in</td>
<td>2 in</td>
</tr>
<tr>
<td>Ball Valve Diameter</td>
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<td>5/16 in</td>
<td>1/2 in</td>
<td>5/8 in</td>
</tr>
<tr>
<td>Dimensions</td>
<td>31.2 x 150 x 250 mm</td>
<td>31.2 x 150 x 250 mm</td>
<td>(12.5 x 6.25 x 10 in)</td>
<td>(12.5 x 6.25 x 10 in)</td>
</tr>
<tr>
<td>Weight</td>
<td>7.9 kg (18 lb)</td>
<td>7.9 kg (18 lb)</td>
<td>13.6 kg (30 lb)</td>
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<td>50 W</td>
<td>50 W</td>
<td>50 W</td>
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<tr>
<td>Voltage</td>
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<td>115/230 V</td>
<td>115 V</td>
<td>115 V</td>
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<td>50-60 Hz</td>
<td>50-60 Hz</td>
<td>50-60 Hz</td>
<td>50-60 Hz</td>
</tr>
<tr>
<td>Application</td>
<td>Mice/Rats</td>
<td>Rabbits</td>
<td>Dogs/Monkeys</td>
<td>Large Animals; Hemodynamic Studies</td>
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</tbody>
</table>
APPENDIX C

PINHOLE SCENARIO DOMAINS.

Pinhole Scenario domains with mask of 300μm pinhole size and 700μm hole spacing; 16 models demonstrating transmitting transducer rotation from zero to forty-five degrees by increments of three degrees.

Figure C.1: Mask 300/700 at zero degrees.
Figure C.2: Mask 300/700 at three degrees.

Figure C.3: Mask 300/700 at six degrees.
Figure C.4: Mask 300/700 at nine degrees.

Figure C.5: Mask 300/700 at twelve degrees.
Figure C.6: Mask 300/700 at fifteen degrees.

Figure C.7: Mask 300/700 at eighteen degrees.
Figure C.8: Mask 300/700 at twenty-one degrees.

Figure C.9: Mask 300/700 at twenty-four degrees.
Figure C.10: Mask 300/700 at twenty-seven degrees.

Figure C.11: Mask 300/700 at thirty degrees.
Figure C.12: Mask 300/700 at thirty-three degrees.

Figure C.13: Mask 300/700 at thirty-six degrees.
Figure C.14: Mask 300/700 at thirty-nine degrees.

Figure C.15: Mask 300/700 at forty-two degrees.
Figure C.16: Mask 300/700 at forty-five degrees.
APPENDIX D

PINHOLE MASK EXPERIMENT ERROR ANALYSIS DATA.

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<th>Angle</th>
<th>+ 0.01 angle error</th>
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<td>0</td>
<td>-0.0050</td>
</tr>
<tr>
<td>2</td>
<td>0.02990</td>
</tr>
<tr>
<td>4</td>
<td>0.0648</td>
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<td>6</td>
<td>0.0997</td>
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<tr>
<td>8</td>
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<tr>
<td>10</td>
<td>0.1696</td>
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<tr>
<td>12</td>
<td>0.2045</td>
</tr>
<tr>
<td>14</td>
<td>0.2395</td>
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<tr>
<td>16</td>
<td>0.2744</td>
</tr>
<tr>
<td>18</td>
<td>0.3094</td>
</tr>
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<td>0.3444</td>
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<tr>
<td>46</td>
<td>0.7994</td>
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APPENDIX E

MESH IMAGES FROM CONVERGENCE STUDY.

Fig. E.1: Mesh #1 in convergence study (45).
Fig. E.2: Mesh #2 in the convergence study (60).

Fig. E.3: Mesh #3 in the convergence study (75).
Fig. E.4: Mesh #4 in the convergence study (90).

Fig. E.5: Mesh #5 in the convergence study (105).
Fig. E.6: Mesh #6 in the convergence study (120).

Fig. E.7: Mesh #7 in the convergence study (135).
Fig. E.8: Mesh #8 in the convergence study (150).
APPENDIX F

PINHOLE MASK EXPERIMENTAL DATA

Table F.1: Mask 100/500 experimental data.

<table>
<thead>
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<th>Angle (degrees)</th>
<th>Trial 1 (mV)</th>
<th>Trial 2 (mV)</th>
</tr>
</thead>
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<tr>
<td>0</td>
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<td>202</td>
</tr>
<tr>
<td>2</td>
<td>167</td>
<td>193</td>
</tr>
<tr>
<td>4</td>
<td>141</td>
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Table F.2: Mask 100/700 experimental data.

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Table F.3: Mask 300/700 experimental data.

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<th>Angle (degrees)</th>
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<th>Trial 2 (mV)</th>
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<td>10.5</td>
</tr>
</tbody>
</table>
APPENDIX G

TOTAL PRESSURE WAVE CONTOUR PLOTS.

Fig. G.1: Total pressure wave contour plot of mask 300/700 at time $0.7 \times 10^{-6}$ seconds.

Fig. G.2: Total pressure wave contour plot of mask 300/700 at time $1 \times 10^{-6}$ seconds.

Fig. G.3: Total pressure wave contour plot of mask 300/700 at time $1.5 \times 10^{-6}$ seconds.

Fig. G.4: Total pressure wave contour plot of mask 300/700 at time $2.0 \times 10^{-6}$ seconds.
Fig. G.5: Total pressure wave contour plot of mask 300/700 at time $2.3 \times 10^{-6}$ seconds.

Fig. G.6: Total pressure wave contour plot of mask 300/700 at time $2.6 \times 10^{-6}$ seconds.

Fig. G.7: Total pressure wave contour plot of mask 300/700 at time $3.0 \times 10^{-6}$ seconds.
APPENDIX H

RAY TRACE AND REFLECTIONS: CODE AND PLOTS

Fig. H.1: Ray trace number of reflections inside the pinhole mask for a mask with 100μm size pinholes.
Fig. H.2: Ray trace number of reflections inside the pinhole mask for a mask with 254μm size pinholes.

Fig. H.3: Ray trace number of reflections inside the pinhole mask for a mask with 300μm size pinholes.
Matlab code:

% determine distance traveled by pressure wave
clc

% all measurements are in microns

% pinhole diameter
pin_height = 100;
% pinhole depth
pin_depth = 500;
% number of reflections
reflect = zeros(1,52);
% check distance for angles 0 to 52 degrees
for n = 1:52;
    decide = 1;
    final = 0;
    % convert to radians
    angle = ((n-1))*(pi/180);
    linear_dist = 0;
    dist_travel = 0;
    % 1st reflection
    linear_dist = (pin_height/2)/tan(angle);
    dist_travel = (pin_height/2)/sin(angle);
    % other reflections
    while decide == 1
        linear_dist = linear_dist + pin_height/tan(angle);
        if linear_dist > pin_depth
            decide = 0;
        else
            dist_travel = dist_travel + pin_height/sin(angle);
        end
        reflect(n) = reflect(n) + 1;
    end

% distance to receiving transducer
final = ((500 - (linear_dist - pin_height/tan(angle))) + 1000)/cos(angle);
% length of ray path
ray_length(n) = 2000 + final + dist_travel;
% number of reflections
reflect
end
APPENDIX I

CONVERGENCE STUDY: MATLAB CODE

% data was loaded
load cs_45_t.txt
load cs_60_t.txt
load cs_75_t.txt
load cs_90_t.txt
load cs_105_t.txt
load cs_120_t.txt
load cs_135_t.txt
load cs_150_t.txt

% number of elements in mesh
elem = [6852,9424,11592,14056,16812,19604,21572,24172];

% number of mesh points in mesh
mesh_pts = [3647,4988,6122,7410,8839,10289,11321,12669];

% signals were integrated
%trapz(cs_45_t(:,1),cs_45_t(:,2));
t(1) = trapz(cs_45_t(:,1),cs_45_t(:,2));
t(2) = trapz(cs_60_t(:,1),cs_60_t(:,2));
t(3) = trapz(cs_75_t(:,1),cs_75_t(:,2));
t(4) = trapz(cs_90_t(:,1),cs_90_t(:,2));
t(5) = trapz(cs_105_t(:,1),cs_105_t(:,2));
t(6) = trapz(cs_120_t(:,1),cs_120_t(:,2));
t(7) = trapz(cs_135_t(:,1),cs_135_t(:,2));
t(8) = trapz(cs_150_t(:,1),cs_150_t(:,2));

%% percent error calculation
% percent error was calculated for all 13
for n = 1:8
    T(n) = (abs(t(n)-t(8))/t(8))*100;
end

figure(1)
a1 = plot(elem,t,'*-');
set(a1,'linewidth',2);
title('Total Transducer Face Signal integrated')
xlabel('Number of Mesh Elements')
ylabel('Magnitude (Pa*m)')
grid on

figure(2)
a1 = plot(elem,T,'*-');
set(a1,'linewidth',2);
title('Total Transducer Face Signal integrated')
xlabel('Number of Mesh Elements')
ylabel('Percent Error')
grid on
%% create ultrasound signal
Ac = 18;
ST = 2*10^6;
DT = 3*10^-7;
mu = 1;
f0 = 9*10^5;
w0 = f0*2*pi;
f0 = 1*10^7;
w0 = f0*2*pi;
GauS = 2.5*10^-7;
GauT = 1*10^-11;

%time lengths
hu = 0:.000000001:.0000009;
t = 0:.000000001:.000005;
US_sig = zeros(2,length(t));
US_sig(1,:) = t;
US_sig(2,1:length(tu)) = Ac *(1+mu*sin(w0.*(tu-DT)+pi/4)) .* sin(wc*(tu-DT)) .* exp(-100.*(tu-GauS).^2/(GauT));

%save data as text file
fid = fopen('US_sig.txt','wt');
fprintf(fid,'%12.10f %16.10f\n',US_sig);
fclose(fid)
load US_sig.txt
%plot data
figure(11)
plot(US_sig(:,1),US_sig(:,2)/100)
title('Computer Simulation Ultrasound Signal')
xlabel('Time (seconds)')
ylabel('Voltage (mV)')
axis([0,5*10^-6,-30/100,30/100])
grid on

%%% random noise signals

%length of noise is the same as ultrasound signal
s = length(t_u);
%initialize
noise = zeros(2,length(t));

%create random noise signal
noise(2,1:s) = randn(1,s)*(max(US_sig(2,:))*0.1); %10 percent noise
noise(1,1:length(t)) = t;
noise(2,1) = 0;
%save random noise as a text file
fid = fopen('rand_noise.txt','wt');
fprintf(fid,'%12.10f %16.10f\n',noise);
fclose(fid)

load rand_noise.txt %load new file

%% combination of signals with noise

% ultrasound signal + random noise
% initialize
us_no = zeros(2,length(t));
us_no(1,:) = t;
us_no(2,:) = US_sig(:,2);

% 10% random noise + US signal
us_no(2,1:s) = us_no(2,1:s) + randn(1,s)*(max(us_no(2,:))*0.1);
us_max = max(us_no(2,:));

% save random noise as a text file
fid = fopen('us_noise.txt','wt');
fprintf(fid,'%12.10f %16.10f
',us_no);
fclose(fid)

load us_noise.txt
APPENDIX K

PINHOLE MASK DATA ANALYSIS: MATLAB CODE

Example is of noisy ultrasound signal. All signal peak-to-peak voltage was calculated in the same method.

%load data
load UN_100400_0_out.txt
load UN_100400_3_out.txt
load UN_100400_6_out.txt
load UN_100400_9_out.txt
load UN_100400_12_out.txt
load UN_100400_15_out.txt
load UN_100400_18_out.txt
load UN_100400_21_out.txt
load UN_100400_24_out.txt
load UN_100400_27_out.txt
load UN_100400_30_out.txt
load UN_100400_33_out.txt
load UN_100400_36_out.txt
load UN_100400_39_out.txt
load UN_100400_42_out.txt
load UN_100400_45_out.txt

%determine peak-to-peak voltage
UN_fringe_100400(1) = abs(max(UN_100400_0_out(:,2))) + abs(min(UN_100400_0_out(:,2)));
UN_fringe_100400(2) = abs(max(UN_100400_3_out(:,2))) +
abs(min(UN_100400_3_out(:,2)));

UN_fringe_100400(3) = abs(max(UN_100400_6_out(:,2))) +
abs(min(UN_100400_6_out(:,2)));

UN_fringe_100400(4) = abs(max(UN_100400_9_out(:,2))) +
abs(min(UN_100400_9_out(:,2)));

UN_fringe_100400(5) = abs(max(UN_100400_12_out(:,2))) +
abs(min(UN_100400_12_out(:,2)));

UN_fringe_100400(6) = abs(max(UN_100400_15_out(:,2))) +
abs(min(UN_100400_15_out(:,2)));

UN_fringe_100400(7) = abs(max(UN_100400_18_out(:,2))) +
abs(min(UN_100400_18_out(:,2)));

UN_fringe_100400(8) = abs(max(UN_100400_21_out(:,2))) +
abs(min(UN_100400_21_out(:,2)));

UN_fringe_100400(9) = abs(max(UN_100400_24_out(:,2))) +
abs(min(UN_100400_24_out(:,2)));

UN_fringe_100400(10) = abs(max(UN_100400_27_out(:,2))) +
abs(min(UN_100400_27_out(:,2)));

UN_fringe_100400(11) = abs(max(UN_100400_30_out(:,2))) +
abs(min(UN_100400_30_out(:,2)));  

UN_fringe_100400(12) = abs(max(UN_100400_33_out(:,2))) +
abs(min(UN_100400_33_out(:,2)));

UN_fringe_100400(13) = abs(max(UN_100400_36_out(:,2))) +
abs(min(UN_100400_36_out(:,2)));

UN_fringe_100400(14) = abs(max(UN_100400_39_out(:,2))) +
abs(min(UN_100400_39_out(:,2)));

UN_fringe_100400(15) = abs(max(UN_100400_42_out(:,2))) +
abs(min(UN_100400_42_out(:,2)));

UN_fringe_100400(16) = abs(max(UN_100400_45_out(:,2))) +
abs(min(UN_100400_45_out(:,2)));