CHAPTER 1

Introduction

The purpose of this introduction is to set the stage for the rest of this dissertation part and the research presented herein. Here I will establish the merit and relevance of the presented work. The problems approached here apply to a variety of active areas of study and modern applications within the fields of acoustics and fluids, though the primary focus and motivation of this work, is better understand the physics related to specific biological effects of Diagnostic Ultrasound (DUS). Accordingly, I describe the driving physical mechanisms of interest to these problems, which are studied. The framework from which I approach these problems by modeling tissue as a compressible fluid system is also discussed. Finally, an overview of the goals and contributions of this thesis are presented.

1.1 A physical description of sound

Sounds are molecular-scale vibrations traveling through a medium. Atoms and molecules perturbed or displaced collide with neighboring atoms and molecules, which collide with their neighbors and so on. In this way, mechanical energy propagates as a wave, away from the initial perturbation location, through any gas, liquid, or solid medium. This is the basic mechanism by which sound moves through all matter whether it be the tissues in human body, the water in the oceans, or the plasma in the stars. Through years of study and experimentation, man has gained a deep understanding for the physical behavior of sound and has learned to harness it as a tool, leading to high-impact advancements throughout Science, Technology, Engineering, and Math (STEM) in

areas ranging from climate change to structural health monitoring and diagnostic and therapeutic medicine. While much of our basic understanding of sound has come from the theoretical study of sound propagating through a constant, infinite, homogeneous medium, there is no such medium in reality, and many of the interesting physical questions and real world applications of sound are concerned with the scenarios in which sound acts to physically alter the medium through which it is traveling.

The focus of this part of thesis is on problems in which sound travels between multiple media in such a way that the media themselves are physically changed or affected. Typically, when sound traveling in one medium encounters another medium, a portion of the acoustic energy is transmitted into the new medium, while the remainder is reflected and scattered back into medium from which the sound originated. In most cases, this results in little change in the media themselves, however, in some instances, acoustic energy can be converted into other forms of energy such as kinetic or thermal, resulting in bulk motion or heating of the media respectively. An example of this is a gas-vapor bubble within water or tissue driven by an acoustic wave. As a result of rising and falling acoustic pressure the bubble may oscillate or collapse, changing the temperature or pressure within the bubble and driving the motion of the surrounding medium. Another example is the dissipation of acoustic energy as heat through viscous mechanisms, resulting in a temperature rise in a viscous medium with an acoustic field. The resulting thermal or physical stresses associated with the heating or movement of the media may result in a physical change (eg., phase change) or chemical change (eg., denaturation of proteins in tissue). The ability of acoustic waves to physically alter a media is of particular interest to the field of medical ultrasound, in which it is relevant to both safety concerns in the context of diagnostic sonography and engineering concerns in the context of therapeutic Ultrasound (US).

1.2 Ultrasound in medicine and biological effects

The use of ultrasound in medicine dates back to the 1940s, when Austrian neurologist Dr. Karl Theodore Dussik attempted to use transmission ultrasound to outline the ventricles of the brain (Dussik, 1942; Singh & Goyal, 2007). Since then the abilities and use of US have expanded greatly and the technology has proven to be a powerful tool for noninvasive therapies and safe, real-time diagnostic imaging. Consequently, the use of US has become ubiquitous throughout modern medicine.

For context, I will explain the basic physical processes that occur during US procedures. In practice, high-frequency, typically MHz range, acoustic waves and pulses are created at the surface of the body using a piezoelectric US transducer. These vibrations, or acoustic waves, propagate via an impedance matching, acoustic coupling medium from the transducer into the tissue. Once in the tissue, a portion sound scatters at material interfaces within the body, where acoustic impedance changes, or more simply, some of the sound echoes whenever it moves from one tissue to another, or encounters a cavity in the body. This scattering of sound is the basic physical principle that makes the use of ultrasound for diagnostic imaging possible. In DUS, scattered echoes are picked up by a receiver, recorded, and processed. The strength and timing of these echoes are used to generate a real-time image of the scattering surface. This passage of acoustic waves through tissue does not typically directly alter or affect the tissues structures or processes and the use of ultrasound for imaging is typically considered safe and noninvasive. Despite this, this process is not entirely passive. When energy from ultrasound is converted to kinetic or thermal energy, within tissue, it can physically alter or damage that tissue through a variety of mechanisms. These effects to the body are referred to as US bioeffects. In therapeutic applications, US is used to intentionally cause desirable bioeffects that are beneficial to the patient. In the case of diagnostic ultrasound, bioeffects are generally undesirable side effects that are avoided if possible. Ultrasound bioeffects have motivated extensive research for use in the development of effective guidelines and regulations for the development and use of safe US technologies and procedures.

A large portion of past research into ultrasound bioeffects has focused on determining what types of US bioeffects exist, and under what circumstances they occur. This work has shown that bioeffects may take on a variety of different forms, depending on the US parameters and type of tissue exposed. Various kinds of hemorrhage and cell death are among the most common forms of US bioeffects. In gaseous tissues such the lung and intestines, ultrasonically induced hemorrhage has been observed. Lehmann & Herrick (1953) and Miller & Thomas (1994) observed abdominal petechial hemorrhage as a result of unfocused ultrasound in mice. And Child *et al.* (1990) found hemorrhage in mouse lungs after the animal was exposed to lithotripter pulses. Numerous other studies have been performed on the topic of US-induced lung hemorrhage and a much deeper review can be found in chapters 3 and 4. Pulsed ultrasound of the heart has been shown to be capable of inducing cardiac contractions in frogs and mice (Dalecki *et al.*, 1993; MacRobbie *et al.*, 1997). Cell death has been observed in liver, kidney, and heart as a result of Contrast-Enhanced Ultrasound (CEUS), which uses injections of contrast microbubbles as additional scattering surfaces Skyba *et al.* (1998); Miller *et al.* (2008a). In this thesis I will use computational models to investigate bioeffects resulting from CEUS and DUS-induced lung hemorrhage.

1.3 Tissue as a compressible fluid system

To investigate CEUS and DUS-induced lung hemorrhage, throughout this dissertation I will be modeling the relevant physical problems of ultrasound in human tissue as compressible, multiphase fluid systems. In this section I will attempt justify this general approach and explain some of the applicable assumptions and implications.

The underlying governing equations upon which each of our models are based are the general

conservation equations for mass, momentum, and energy for a fluid,

$$\frac{\partial \rho}{\partial t} + \nabla \cdot (\rho \boldsymbol{u}) = 0, \tag{1.1a}$$

$$\rho \frac{D\boldsymbol{u}}{Dt} = \nabla \cdot \boldsymbol{\tau} + \boldsymbol{g}, \tag{1.1b}$$

$$\frac{\partial E}{\partial t} + \nabla \cdot (E\boldsymbol{u}) = \rho (\boldsymbol{g} \cdot \boldsymbol{u}) + \nabla \cdot (\boldsymbol{\tau}\boldsymbol{u}) + \nabla \cdot \boldsymbol{q}, \tag{1.1c}$$

where ρ is density, $\boldsymbol{u}$ is the flow velocity vector, t is time, $\boldsymbol{\tau}$ is the stress tensor, which is a second order tensor. $\boldsymbol{g}$ is the body force vector, $E = \rho \left(e + \frac{1}{2} [\boldsymbol{u} \cdot \boldsymbol{u}]\right)$ is the total energy defined as the sum of the kinetic energy per unit mass $\frac{1}{2} (\boldsymbol{u} \cdot \boldsymbol{u})$ and the internal energy per unit mass e, and lastly $\boldsymbol{q}$ is the heat flux vector. To model ultrasound-tissue interactions, the general conservation equations (1.1) are simplified and manipulated based on the physics appropriate to the specific problem at hand. The closure of these equations is also treated differently depending on the particular problem and model. Details on the appropriate equations of state used to relate pressure and energy, constitutive equations used to relate stress and strain, and boundary conditions are described in greater detail in sections 2.3.2 and 3.3.3.

To consider what physical effects are at play during diagnostic ultrasound, both contrast-enhanced and of the lung, I consider the basic physical scenario of each of these problems. That is an acoustic wave travels through a multiphase medium consisting of soft tissue and gas. Soft tissues are viscoelastic materials, i.e., they exhibiting solid and fluid like behaviors, i.e, viscous and elastic effects may be simultaneously at play. These tissues include blood as well as lung, liver, and kidney tissue, which are relevant to the motivations of this thesis. The multiphase component of these problems suggests that gas-liquid/gas-viscoelastic interface phenomena such as surface tension may also be of some relevance. As fluid motion is expected, inertial effects will likely be of importance. Additionally, as ultrasonic heating is a known source of biological effects, I consider this possibility as well. And for completeness, since the vast majority of ultrasound procedures do not occur on the International Space Station, I consider the effects of gravity too. In the following two sessions, I introduce dimensional analysis to assess the relative importance of each of these

physical phenomena for the problems we approach in this part of the thesis.

1.3.1 Dimensional analysis and assumptions for Contrast Enhanced Ultrasound

CEUS-related bioeffects are generally attributed to a process called Inertial Cavitation (IC) in which a bubble or void within a fluid collapses rapidly. This can result in high temperatures, pressures, stresses, strains, and strain rates within the surrounding fluid. More details about this process and its relationship to US bioeffects will be provided in Section 1.4.1. In this work, I consider the problem of a single US pulse impinging upon a contrast agent microbubble, initially at rest within a viscoelastic soft tissue. For the sake of justification I consider a typical case here. In Chapter 2 a more in-depth analysis, specific to the work presented, is performed. Consider an ultrasound pulse of clinically relevant frequency $f = 3$ MHz and Peak Rarefaction Pressure Amplitude (PRPA)= $p_a = 1$ MPa. The soft tissue is treated as a Voigt type viscoelastic material as in (Yang & Church, 2005) and has a nominal density of $\rho = 1000$ kg/m^3, an elastic modulus ranging from $G = 10$ kPa to 1 MPa, and a viscosity of $\mu = 0.015$ Pa s. Surface tension will be based on water such that $S = 0.056$ N/m. Consider a characteristic velocity of $u = \sqrt{p_a/\rho} = 31.6$ m/s. Note that the physical properties of soft tissue vary widely and are poorly characterized, particularly at the strain rates associated with cavitation. As a characteristic length scale, I use a typical bubble size such that equilibrium radius is $R_0 = 1\mu$m.

Based on this setup I perform dimensional analysis to assess the relative importance of each of the potentially relevant physical mechanisms to the problem of acoustically-driven cavitation in soft tissue:

Viscosity: To access the relevance of viscosity I consider a Reynolds Number, which is defined as $Re = \rho u R_0/\mu = 2.1$ and is a measure ratio of inertial to viscous forces in a flow. A Reynolds number of order unity, suggests that viscous effects are non-negligible relative to inertia and cannot be neglected.

Heat transfer and thermal effects: In consideration of the role of heat transfer, I calculate a characteristic time scale for heat transfer $t_{thermal} = R_0^2/\alpha$, where α is the thermal diffusivity, which is $\alpha = 0.143 \times 10^{-6}$ m^2/s in water such that $t_{thermal} = 7\mu$s. This is compared to the approximate timescale for a spherical vapor bubble to collapse to its minimum radius, neglecting surface tension, which is approximately $t_{collapse} = 0.915\sqrt{\rho R_0^2/p_a} = 29$ ns (Brennen, 2003). Note that the form of the equation presented here is for the case where the vapor pressure in the bubble p_v is much smaller than the driving pressure p_a, which is true for ultrasonically driven cavitation. Here, $t_{collapse} << t_{thermal}$, suggesting that minimal heat transfer will occur during the collapse. This is perhaps unsurprising, as heat transfer is generally regarded as a much slower process than IC. In any case, heat transfer into and out of the bubble will be neglected in relevant analysis.

Surface Tension: The Weber number is defined as $We = \rho u^2 R_0/S = 17.9$ and represents the ratio of surface tension to inertial forces in the flow. The calculated We suggests that surface tension at the bubble wall is not negligibly small when the bubble is at its equilibrium radius. Additionally, I note that the effects of surface tension may have an even greater effect during collapse when the bubble radius may decrease by an order of magnitude or more. Hence surface tension will not be neglected.

Elasticity: The Cauchy number is defined as $Ca = \rho u^2/G = 1 - 100$ for the range of elastic moduli considered (i.e., 1000 - 5 kPa). Based on this the effects of elasticity are not expected to be particularly important to the bubble dynamics for the tissues of kPa order elasticity, though this is expected to change for stiffer tissues. Accordingly, elasticity will be included in the cavitation bubble model.

Gravity: The Froude number is defined as $Fr = u/\sqrt{gR_0} = 10^4$ and is a measure of the ratio of inertial to gravitational forces, or more generally, any applicable body forces. The calculated

Froude number suggests that gravitational and buoyancy effects are minimal relative to inertia and will be neglected for the sake of this analysis. This is of particular importance because it allows us to consider the case of a radially symmetric collapse, which greatly simplifies the problem.

In summary, based on the dimensional analysis performed, I will consider axially symmetric bubble dynamics in a Voigt-Viscoelastic medium with surface tension. The effects of gravity and heat transfer will be neglected.

1.3.2 Dimensional analysis and assumptions for acoustically driven alveolus

The work presented work is specifically interested in the problem of an ultrasound pulse impinging upon an alveolus within an adult human lung. To access the relevant physical mechanisms here in order to layout the logic for my assumptions and approach, I present a general case relevant to the motivating problem of lung ultrasound. A more comprehensive justification and analysis, specific to the work presented can be found in chapters 3 and 4. Consider an ultrasound pulse with central frequency $f = 3MHz$, and amplitude $p_a = 1$ MPa, which are within the expected parameter range based on past research (Miller *et al.*, 2015). I will use the mean diameter of a typical adult human alveolus as a characteristic length scale length scale $\ell_A = 200\mu$m (Ochs *et al.*, 2004). The alveolus is treated as being filled with air such that the sound speed is $c_A = 343$ m/s, the density is $\rho_A = 1.2$ kg/m^3, the kinematic viscosity is $\nu_A = 16.6\mu$ m^2/s, and no elasticity is present in the alveolar interior. The surrounding soft-tissue is treated as water-like, but with elasticity such that the sound speed is $c_T = 1500$ m/s, the density is $\rho_T = 1000$ kg/m^3, the viscosity is $\nu_T = 0.7\mu$m^2/s and the elastic modulus is $G = 5$ kPa (Cavalcante, 2005). I use a characteristic velocity $u_a = \sqrt{p_a/\rho_A}$. Based on the physical problem described here I use dimensional analysis to access the relative importance of potentially relevant physical mechanisms:

Viscosity: In consideration of effects of viscosity of the dynamics of the system during the ultrasonic interface, I calculate a viscous length scale on either side of the interface such that $\sigma_{vA} =$

$\sqrt{\nu_A/2\pi f} = 0.94\mu$m and $\sigma_{vT} = \sqrt{\nu_T/2\pi f} = 0.19\mu$m. On either side of the interface $\sigma_v << \ell$ such that the viscous layer is small compared to the flow geometry during the ultrasonic interactions. In recognition that the viscous layer may grow in time, after the passage of the acoustic wave, according to $\sigma_v(t) \sim \sqrt{\nu t}$ we calculate that for a 1 kHz Pulse Repetition Frequency (PRF), the viscous layer may grow between subsequent pulses to $\mathcal{O}(\ell)$ in the alveolar airspace and $\mathcal{O}(0.1\ell)$ in the surrounding tissue. Hence viscosity can be neglected for sufficiently early times, and I will do so in the model for simplicity. I will not consider times later than $\approx 300\mu$s to maintain reasonable accuracy of our inviscid assumption. The applicability of this assumption in practical lung ultrasound is aided by the fact that even higher frequencies are sometimes used in clinical application (e.g., typical frequencies may be $f = 5$ MHz in adults and 12 MHz in newborns) Lichtenstein (2009).

Heat transfer and thermal effects: I use similar arguments to those used for viscous effects in consideration of thermal effects. The thermal length scale is defined as $\sigma_\kappa = \sqrt{\kappa/\pi f \rho C_p}$, where the C_p is the specific heat and κ is the thermal conductivity. In air $C_{pA} = 1005$ J/Kg K and $\kappa_A = 0.027$ W/m K and in Water $C_{pT} = 1005$ J/Kg K and $\kappa_T = 0.49$ W/m K. Hence $\sigma_{\kappa A} = 0.3\mu$m and $\sigma_{\kappa T} = 1.5\mu$m. On either side of the interface, $\sigma_\kappa << \ell$ such that the thermal boundary layer is small relative to the characteristic length of the flow. Hence I will neglect heat transfer in my approach to this problem moving forward.

Surface Tension: The role of surface tension in the alveoli is critical to healthy respiratory function. Alveoli secrete pulmonary surfactant, which lowers the surface tension at the alveolar surface, helping prevent airway collapse and easing the re-inflation of alveoli during breathing. As a result of this surfactant, alveolar surface tension is far below that of water and has been reported as $S_A = 9$ mN/m (Schürch *et al.*, 1976). Hence I define an acoustic Weber number as $We = p_a\ell/S_A = 22222$. This suggests that forces due to surface tension are small relative to the acoustic pressure at the interface. Based on this, I will neglect surface tension in my analysis as

well.

Elasticity: To assess the expected impact of elasticity on the system I define an acoustic Cauchy number $Ca = \rho_T u_a^2/G$ which becomes the ratio of the acoustic pressure to the elasticity $p_a/G = 200$. This suggests that the effects of elastic effects will be dominated by the acoustic pressure during the wave-interface interaction within the tissue. Within the alveolar air space, there is no elasticity and the Cauchy number is infinite. Based on this, I will neglect elasticity in my model. Additional calculations considering the relevance of this assumption at later times, after the passage of the wave will be provided in Chapter 4.

Gravity: The importance of gravity is assessed based on a Froude number calculation $Fr = u_a/\sqrt{g\ell} = \sqrt{p_a/\rho g\ell} = 714$. This suggests that gravitational forces are small relative to inertia, and will be neglected. Another reasonable justification for neglecting gravity is that the orientation of the model problem in space is arbitrary and as a 2D model I treat the flow as existing in a plane that is orthogonal to gravitational forces and thus not unaffected by gravity.

1.3.3 Limitations

Before proceeding I would like to acknowledge that the simplifications and assumptions made in the previous sections, while justified in the specified regimes, do deviate from the true physical systems. The purpose of these simplifications is to make the relevant problems tractable with the available resources (computational, intellectual, financial, temporal, etc...). There are many limitations to described model systems that result in aspects of the true physics that are not captured. In both CEUS and in ultrasound-alveoli interactions, the presented dimensional analysis is based on tissue properties such as viscosity and elasticity and behavior that are poorly characterized in both nature and quantity. Additionally the analysis performed here is for reference cases within the relevant range, and certain dependencies, such as the frequency dependence of sound speed in bulk lung tissue, are not captured here. Furthermore, actual tissues are highly heterogeneous and may

be characterized by a wide range of physical length scales. Despite these limitations, the purpose of this work is to gain insight into the approximate physics applicable to these problems, which hopefully this approach achieves.

1.4 Physical mechanisms of ultrasound bioeffects

Depending on the type of physical damage mechanism responsible, US bioeffects are classified into two groups, thermal and non-thermal. The first group, thermal bioeffects are characterized by deposition of acoustic energy into tissue as heat and are often a result of therapeutic, rather than diagnostic, ultrasound. This heating can lead to a variety of deleterious effects including the release of highly reactive free radicals and protein denaturation at the molecular level and protein denaturation and death at the cellular level, ultimately causing tissue damage or death. As an example, one class of therapeutic US, know as High-Intensity Focused Ultrasound (HIFU) uses of strong, concentrated acoustic fields, to intentionally convert acoustic energy to heat through viscous dissipation. This is used to raise the temperature of unwanted tissues such as fat or cancer to destroy it. Little else will be said about thermal bioeffects, as the bioeffects problems of interest to this work fall into the non-thermal category. Non-thermal bioeffects are attributed to a variety of physical phenomena including acoustic radiation force, radiation torque, and acoustic streaming though the bulk of non-thermal bioeffects are commonly associated with acoustical cavitation, which is the most widely studied non-thermal mechanisms (Dalecki, 2004). For certain bioeffects, such as DUS-induced lung hemorrhage, the physical mechanisms is largely unknown.

The bioeffects that are of motivation and interest to this thesis are those that can result from DUS, which are unintentional and a represent a potential safety concern. DUS bioeffects tend to be a result of mechanical processes and typically take the form of hemorrhage, tissue damage or cell death.

1.4.1 Cavitation of ultrasound contrast agent microbubbles

Acoustic cavitation is the phenomenon by which gas nano and microbubbles, called cavitation nuclei, are cyclically grown by low pressures within the US field and collapsed high pressures within the field. When the bubble dynamics during collapse are dominated by the inertia of the surrounding fluid, it is called Inertial Cavitation IC. IC is typically violent and results in the bubble collapsing to a fraction of its original size. There are several possible damage mechanisms associated with IC that may be responsible for observed US bioeffects. Upon collapse, the pressure and temperature within the bubbles spike, often reaching billions of pascals and thousands of Kelvin respectively. Due to the pressure difference between the vapor/gas mixture within the bubble at collapse and the surrounding media, the collapsed bubble can emit a powerful shock wave which can be damaging to the bubbles surroundings. When cavitation is triggered near a rigid surface, the bubble can collapse in a radially asymmetric fashion causing a high speed "re-entrant" jet of liquid to impinge upon the surface, effectively striking the surface with a liquid hammer. If cavitation occurs at an appropriate distance from a non-rigid surface, such as soft tissue boundaries and blood vessel walls, the jet can impinge away from the surface, potentially invaginating the surface (Brujan, 2011). Figure 1.1 schematically illustrates potential cavitation damage mechanisms within a blood vessel.

As a result of the potential for cavitation-related US bioeffects the United States Food and Drug Administration called for a metric to predict likely cavitation damage from ultrasound. As bioeffects are typically attributed to IC, efforts to predict cavitation damage considered the likelihood of IC based on theoretical calculations of free gas bubbles in water. In the case of acoustic cavitation, this depends on the duration of peak negative pressure experienced by a cavitation nucleus, with longer interactions depositing more energy into the nucleus, and thus having a greater likelihood inducing IC. The duration of the PRPA is inversely related to the US frequency. **?** demonstrated that the threshold PRPA needed to trigger IC, defined based on a maximum bubble temperature $\geq$ 5000K, depended on the size of the cavitation nucleus. Smaller cavitation nucleii, must over-

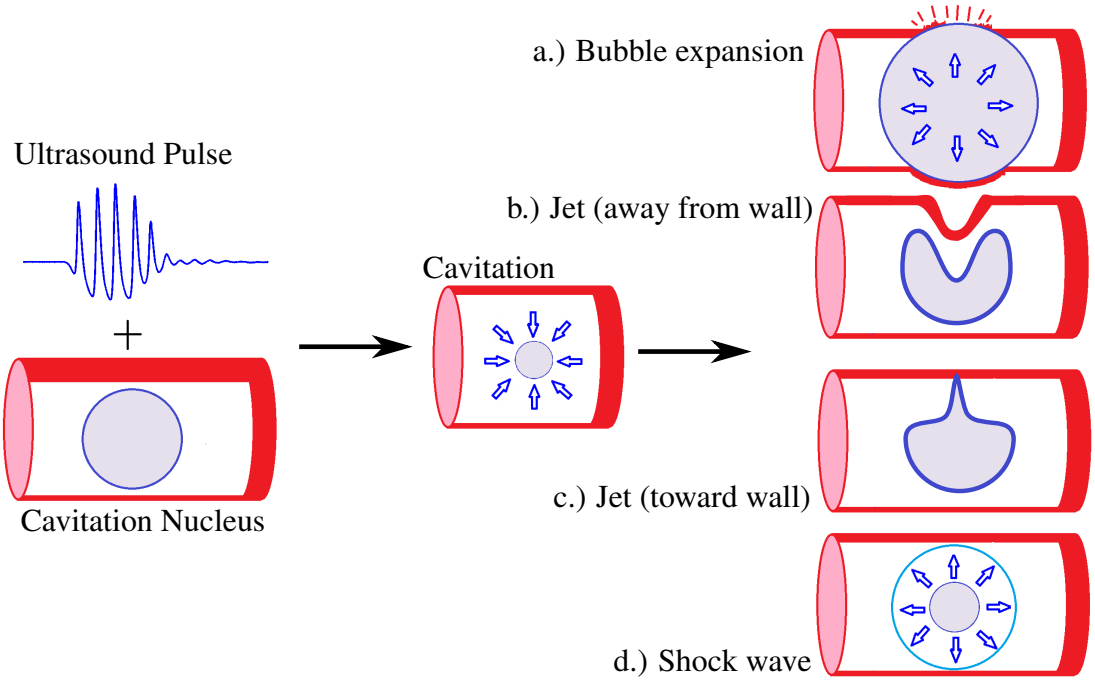

Figure 1.1: A schematic illustration of ultrasound induced cavitation and potential bioeffects damage mechanisms (from top to bottom): a). Bubble expansion beyond the radius of a surrounding blood vessel. b.) A cavitation jet away from the wall of a surrounding blood vessel or tissue surface causes the surface to invaginate. c.) A cavitation jet of high speed liquid strikes a vessel or tissue wall. d.) A shock wave created by the bubble collapse encounters nearby tissue.

come greater surface tension effects in order to cavitate, with the Laplace pressure scaling inversely with the radius of the nucleus. Furthermore, as initial radius a nucleus increases, the inertia of the surrounding fluid that must be overcome also increasesAiu (2000). Thus **?** illustrated that for a given frequency their is an optimal nucleus size for triggering IC. Based on these calculations and corrections for heat dissipation in tissue the Mechanical Index (MI) was created as a measure of ultrasound induced cavitation related bioeffects and defined as

$$MI = \frac{P_{r.3}}{\sqrt{f_c}}, \tag{1.2}$$

where $P_{r.3}$ is the PRPA derated by 0.3 dB/MHz-cm and f_c is the center frequency Apfel & Holland (1991). The United States Food and Drug Administration (FDA) mandates that $MI \leq 1.9$ for diagnostic imaging, though US bioeffects have been observed at MI below this in case of DUS of mammalian lungs.

While IC does not typically occur during non-contrast DUS, it is of concern during CEUS, which uses contrast-agent microbubbles injected into patients bloodstream to act as additional scattering surfaces. This allows for high contrast imaging and can be used to ultrasonically image blood flow, which is useful for diagnosing heart valve problems, liver lesions, and more (Claudon *et al.*, 2012; Rognin *et al.*, 2008). However, the use of contrast agent microbubbles can also have potential deleterious side effects. These microbubbles can act as cavitation nuclei and the resulting cavitation has been associated with a variety of different forms of cellular death and damage. The precise ultrasonic thresholds for which cavitation and bioeffects occur have been a topic of intense study and are not completely physically described. Furthermore, the exact physical mechanisms through which cavitation causes bioeffects are also not clearly understood (Barnett *et al.*, 1994).

1.4.2 Ultrasound-induced lung hemorrhage

The second US bioeffects topic of interest to this thesis is DUS-induced Lung hemorrhage (LH). In the relevant literature this is also sometimes referred to more specifically as Pulmonary Capil-

lary Hemorrhage (PCH). This phenomenon was first discovered in mice over twenty years ago by Child *et al.* (1990) and has since been shown to occur in a variety of other mammals including rats, pigs, rabbits, and monkeys O'Brien & Zachary (1997); Miller (2012); Tarantal & Canfield (1994). Research into this phenomena has been in three main areas: (1) Determining the physical mechanism of the hemorrhage; (2) Understanding how the occurrence and severity of the hemorrhage on the ultrasonic properties (frequency, amplitude, waveform, etc...); and (3) Understanding how the occurrence and severity of the hemorrhage depend on the characteristics of ultrasound subject (species, age, anesthesia, etc...). The work in this thesis pertains primarily to the first of these three areas.

Despite extensive previous research into DUS-induced LH, the underlying physical mechanisms are still not well understood. Furthermore, past work has shown that common US bioeffects mechanisms do not explain the observed injuries. Thermal damage mechanisms appear unlikely to be the primary source of damage as DUS-induced lung lesions do not appear similar to those induced by heat (Zachary *et al.*, 2006). Furthermore, cavitation mechanisms do not appear to be responsible, as the severity of DUS-induced LH in mice increased under raised hydrostatic pressure (O'Brien *et al.*, 2000) and was unaffected by the introduction of US contrast agents into subjects. Both of these results are inconsistent with what is expected of IC-induced bioeffects. More recent work by Miller (2016) investigating acoustical radiation surface pressure as a potential damage mechanism found that the pressures expected in pulsed ultrasound were likely too low to completely explain the observed hemorrhage on their own. Simon *et al.* (2012) found that atomization and fountaining occurred at tissue-air interfaces subjected to HIFU and suggested that this could potentially happen at diagnostic levels as well. Similarly, works by Tjan & Phillips (2007, 2008) model the evolution of an inviscid, free surface subjected to a Gaussian velocity potential and find that this can lead to the ejection of liquid droplets. They go on to say that DUS of the lung may similarly lead to the ejected of droplets capable of puncturing the air-filled sacs within the lung. The problem of US-lung interaction is the central motivation of chapters 3 and 4. As such, a far more in-depth literature review will be provided in these chapters.

1.4.2.1 Driven fluid-fluid interfaces

The physical problem underlying interactions between ultrasound waves and the various tissue and fluid layers of the body is that of a mechanical wave traveling in one fluid encountering a second fluid of differing physical properties. As was previously explained, this can result in acoustic energy being converted into motion or heat. In the case of the bubble, the relevant manifestation of this was cavitation. Another manifestation of this is the growth of perturbations at fluid-fluid interfaces as a result of non-uniform velocity gradients that occur at the driven interface. Another way of thinking of this is in terms of baroclinic vorticity, or localized fluid rotation, generated by the misalignment of interface density gradients and mechanical wave pressure gradients. In this dissertation I propose baroclinic vorticity-driven strain as a potential physical mechanism for ultrasound induced alveolar hemorrhage. In the remaining portion of section I discuss in greater detail the underlying physics at play here and some of the past work that has been done to understand it.

There has been extensive past research into the physics that underlies interactions between mechanical waves, acceleration, and fluid-fluid interfaces. Much of this research is motivated by applications in fusion energy and astrophysics and accordingly has sought to investigate regimes outside of those of acoustic interests. Taylor (1950) predicted that for an interface between two fluids of different density, if the fluid was accelerated normal to the interface in the heavy-to-light direction, perturbations at the interface would grow. That is to say that a "bubble" of light fluid penetrates the heavy fluid, and a "spike" of heavy fluid penetrates the light fluid. This is known as the Rayleigh-Taylor Instability (RTI). A similar topic of past study is the Richtmyer-Meshkov Instability (RMI), which occurs when a perturbed fluid-fluid interface is instantaneously accelerated by a shock, causing the interface perturbation to grow (Brouillette, 2002; Drake, 2006). This growth is driven by a sheet of baroclinic vorticity deposited along the interface as a result of misalignment between the pressure gradient across the shock and the density gradient across the perturbed interface. This physical mechanism by which these misaligned gradients create a torque on fluid particles and generate vorticity can be thought of in terms of a hydrostatic balance upon a particle. Pressure gradients result in acceleration of the flow that is inversely proportional to

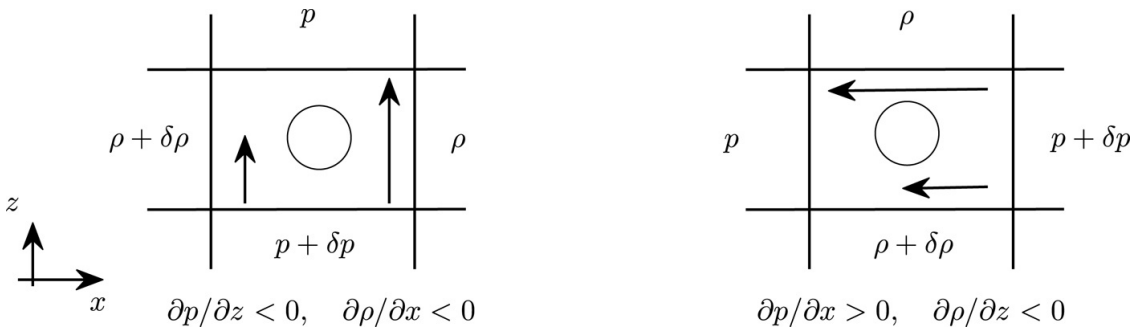

Figure 1.2: From Heifetz & Mak (2015). A hydrostatic force balance upon a particle subject to perpendicular pressure and density gradients illustrates baroclinic torque on a fluid particle.

density. When these two gradients are misaligned, the result is a shearing effect on the fluid and vorticity is generated (Heifetz & Mak, 2015). A graphical explanations of baroclinic vorticity generation is shown in Figure 1.2, which has been adapted from (Heifetz & Mak, 2015). Analytically, baroclinic vorticity generation can be shown by taking the curl of the conservation of momentum equation for a compressible fluid. It is worth noting that it is a nonlinear effect and cannot be explained by traditional linear acoustics.

The physics of the classic RMI are fairly well understood. For the classical RMI setup a planar shock impinges normally upon the peaks and troughs of a sinusoidal interface. The interface is accelerated non-uniformly counter-rotating vorticies are generated across the interface. This drives peaks and troughs of the interface to accelerate in the opposite direction. Much like in the case of the RTI, this too results in light fluid penetrating the heavy fluid and vice versa. For the case of a wave moving from a light fluid into a heavy one, the peaks and troughs of the interface accelerate away from one another, growing the interface perturbation perturbation. For the case of a wave moving from a heavy fluid to a lighter fluid, the peaks and troughs interface initially accelerate toward one another. They then pass each other, inverting the phase of the interface perturbation, and continue moving in opposite directions, growing the perturbation amplitude. This process is illustrated in Figure 1.3, which has been adapted from Brouillette (2002). This work proposes that similar physics occur at ultrasonically driven air-tissue interfaces within the lungs.

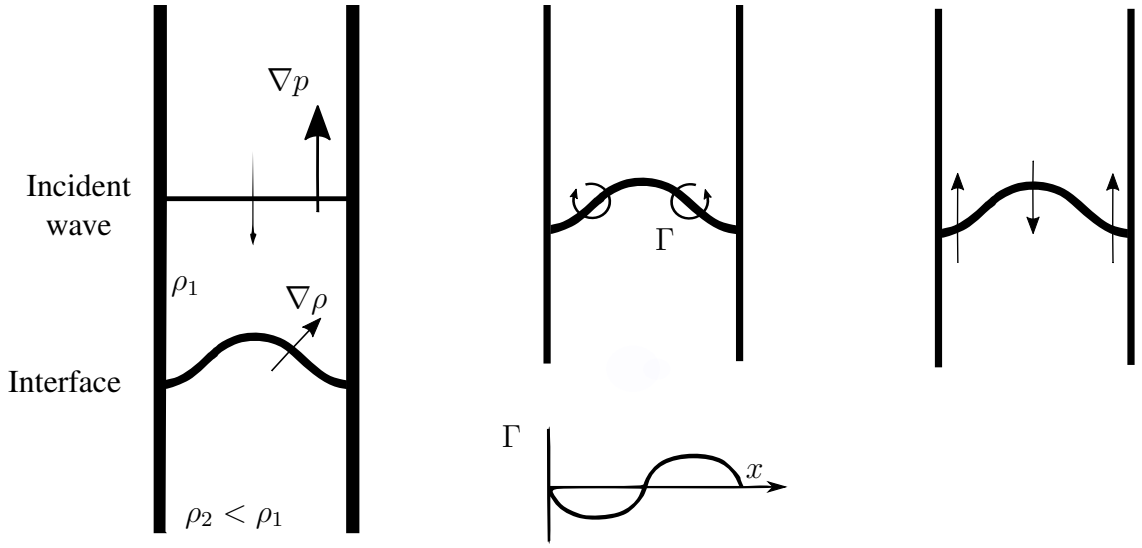

Figure 1.3: Adapted from Brouillette (2002). The RMI for a heavy-light interface is illustrated. The initial condition (left), circulation post wave-interface interaction (center), and perturbation growth (right) are shown.

1.5 Thesis overview

This part of the thesis presents work studying the physics of two problems relevant to ultrasound bioeffects: 1) Cavitation of ultrasound contrast agents microbubbles in human tissue, and 2) DUS of the lung. For each problem, a computational model is developed and used to simulate the relevant dynamics in order to make conclusions about the physics that may be relevant to the observed biological effect.

In Chapter 2, I simulate the cavitation bubble dynamics of contrast agent microbubbles in soft tissue (Patterson *et al.*, 2012a). Experimentally measured US waves with known bioeffects occurrence and thresholds are used Miller *et al.* (2008b). A parametric study is performed, relating ultrasound and tissue parameters to calculated cavitation bubble dynamics. The soft tissue is modeled as a Voigt viscoelastic medium based on the work of Yang & Church (2005). The calculated cavitation dynamics and theoretical inertial cavitation thresholds (Flynn, 1982; Apfel, 1982) are compared with bioeffects thresholds associated with each US pulse, as defined by the observation of kidney hemorrhage in rats after exposure to CEUS by Miller *et al.* (2008b). While the results were generally dependent on US, gas, and tissue properties, it was found that the theoretical in-

ertial cavitation thresholds were lower than observed bioeffects thresholds. It is shown that these thresholds correlate strongly to calculated metrics of cavitation, such as dimensionless maximum radius $R_{max}/R_{equilibrium}$ and that this correlation is lost when simply looking at the dimensional maximum bubble size R_{max}, which is not a cavitation metric.

In Chapter 3, I develop a model of an ultrasonically-driven alveolus as a compressible, multi-phase fluid system. This model is used to study the fundamental problem of an acoustically-driven perturbed liquid-air interface. I demonstrate that under the assumptions presented in Section 1.3.2, strong acoustic waves of appropriate waveform are capable of generating sufficient baroclinic vorticity to appreciably deform the interface. The dependence of this deformation on the amplitude and temporal characteristics of the wave is studied. It is demonstrated that the deformation rate scales with the amount of circulation per unit arc length of the interface. It is also shown that the amount of circulation deposited by the wave is heavily dependent on the deformation that occurs during the wave-interface interaction, and therefore depends on the transient properties of the wave.

In Chapter 4, the work of the previous chapter is extended to increase its relevance to clinical US. The model used in the previous chapter is used to calculate the stresses and strains induced byUS pulses on perturbed liquid-gas, similar to those of the alveolus. These calculated stresses and strains are compared to accepted failure criteria. It is shown that viscous stresses are small compared to expected failure thresholds. However it is also shown that strains at gas-liquid interfaces such as those of the lungs, driven by acoustically-generated vorticity, may be sufficient to drive hemorrhage for sufficiently strong ultrasound pulses. This work concludes that while vorticity may be a possible mechanism for driving DUS-introduced lung hemorrhage, additional work will need to be completed that accounts for multiple pulses as well as physical effects of elasticity and viscosity in order fully understand the role of vorticity in this problem.

In the final chapter 5 of Part I of this dissertation, I summarize the main conclusions takeaways and accomplishments of this work. I Also make recommendations for future work to overcome the limitations of the presented research and extend this work to address relevant problems within the

field.