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ACOUSTO-OPTIC IMAGING IN DIFFUSE MEDIA USING PULSED ULTRASOUND AND THE PHOTOREFRACTIVE EFFECT

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COLLEGE OF ENGINEERING

Dissertation

ACOUSTO-OPTIC IMAGING IN DIFFUSE MEDIA USING PULSED ULTRASOUND AND THE PHOTOREFRACTIVE EFFECT

by

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Submitted in partial fulfillment of the requirements for the degree of
Doctor of Philosophy
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Dedication

This work is dedicated to
my wife Li Liu,
my son David L. Sui,
my sister Xin Sui,
and my mom and dad.

Thank you all for your love, understanding, and support throughout my life and my academic career.
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The past four years that I spent working on this dissertation have been the most rewarding experience in my career, during which I believe that I learned and grew both intellectually and personally. It is with great pleasure that I acknowledge the many people who made this experience possible and enjoyable.

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Lei Sui

Boston, MA

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ABSTRACT

Acousto-optic imaging (AOI) in optically diffuse media is a hybrid imaging modality in which a focused ultrasound beam is used to locally phase modulate light inside of turbid media. The modulated optical field carries with it information about the optical properties in the region where the light and sound interact. The motivation for the development of AOI systems is to measure optical properties at large depths within biological tissue with high spatial resolution.

A photorefractive crystal (PRC) based interferometry system is developed for the detection of phase modulated light in AOI applications. Two-wave mixing in the PRC creates a reference beam that is wavefront matched to the modulated optical field collected from the specimen. The phase modulation is converted to an intensity modulation at the optical detector when these two fields interfere. The interferometer has
a high optical etendue, making it well suited for AOI where the scattered light levels are typically low. A theoretical model for the detection of acoustically induced phase modulation in turbid media using PRC based interferometry is detailed.

An AOI system, using a single element focused ultrasound transducer to pump the AO interaction and the PRC based detection system, is fabricated and tested on tissue mimicking phantoms. It is found that the system has sufficient sensitivity to detect broadband AO signals generated using pulsed ultrasound, allowing for AOI at low time averaged ultrasound output levels. The spatial resolution of the AO imaging system is studied as a function of the ultrasound pulse parameters. A theoretical model of light propagation in turbid media is used to explore the dependence of the AO response on the experimental geometry, light collection aperture, and target optical properties.

Finally, a multimodal imaging system combining pulsed AOI and conventional B-mode ultrasound imaging is developed. B-mode ultrasound and AO images of targets embedded in both highly diffuse phantoms and biological tissue \textit{ex vivo} are obtained, and millimeter resolution is demonstrated in three dimensions. The AO images are intrinsically co-registered with the B-mode ultrasound images. The results suggest that AOI can be used to supplement conventional B-mode ultrasound imaging with optical information.
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Chapter 1

Introduction

1.1. Current Medical Imaging Modalities

A number of imaging techniques have been developed for medical applications over the last century [1, 2]. It is unquestionable that these imaging modalities are central to the entire medical community, in terms of both diagnosing and monitoring diseases. To date, the most successful examples, which have seen widespread use in clinical practice, include conventional X-rays, computed tomography (CT), diagnostic ultrasound, and magnetic resonance imaging (MRI). Additionally, new imaging techniques are still coming out or are under investigation, such as electrical impedance tomography (EIT) [3, 4], terahertz imaging [5, 6] and various forms of optical imaging [7]. This raises a series of challenging questions: why are there so many imaging modalities, do we need all of them, and do we still need new ones? The answers to the above questions will become clear as the characteristics of new and existing medical imaging techniques are briefly reviewed.
First of all, in spite of their considerable success, none of the current imaging modalities are “perfect” or ideally applicable to all kinds of biomedical applications. To illustrate this, a general comparison of the current imaging techniques is summarized in Table 1.1. Detailed descriptions of the relevant physical principles governing each technique can be found in literature [1, 2, 8]. As can be seen, each modality has its own advantages and limitations, as measured by contrast, spatial resolution, imaging depth, cost, speed, safety and portability. Based on their individual strengths, specific applications have been assigned to them.

<table>
<thead>
<tr>
<th>Modality</th>
<th>X-Ray</th>
<th>CT</th>
<th>Ultrasound</th>
<th>MRI</th>
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<td>Image Contrast</td>
<td>Tissue Absorption</td>
<td>Tissue Absorption</td>
<td>Mechanical Properties</td>
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<td>Spatial Resolution</td>
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<td>~1 mm</td>
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<tr>
<td>Imaging Depth</td>
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<td>3-25 cm (Frequency dependent)</td>
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<td>Bone, Lung, Breast</td>
<td>Brain, Bone, Lung</td>
<td>Fetus monitoring, Cardiovascular, Breast, Abdomen</td>
<td>Brain, Functional imaging</td>
</tr>
</tbody>
</table>

Table 1.1: Comparison of existing medical imaging modalities and their typical medical applications, reproduced from [8] with slight modifications.

Secondly, almost without exception, as they gain acceptance, new imaging techniques have come to be regarded as complementary to existing methods, rather than completely replacing established techniques. Different imaging modalities are typically based on different physical mechanisms for contrast, and thus reveal unique features of
the human body and yield different sets of diagnostic information. For example, X-rays imaging, diagnostic ultrasound, MRI, and optical imaging are sensitive to four different physical attributes: X-ray absorption, acoustic impedance, biochemical related relaxation constants, and optical absorption and scattering, respectively. Biological tissues that appear identical or similar in one physical characteristic might differ widely in another. This differentiation can be extremely valuable depending on the nature of the illness and the requisite diagnostic markers. In this way, new imaging techniques can supplement existing techniques, yielding “multi-mode” images that offer additional information about the sample in question.

Thirdly, the limitations of existing medical imaging modalities for some particular applications make new imaging techniques highly desirable. Among the many examples, breast cancer detection will be used to underscore this fact. Breast cancer is the most common malignant neoplasm and is a leading cause of cancer-related deaths of women in the United States [9]. Even though breast cancer cannot be completely prevented yet, its early detection can effectively improve cure rate, reduce the extent of treatment and save lives. At present, X-ray mammography is the “gold standard” for breast cancer imaging, with diagnostic ultrasound as the preferred supplement. However, X-ray mammography utilizes ionizing radiation, and imaging of radiographically dense breasts is difficult. Since a significant fraction (35-40%) of women has dense breasts, X-ray mammography runs the risk of false diagnoses in this subpopulation of women. In addition, breast cancer detectable with either X-ray mammogram or diagnostic ultrasound is usually physically large and biologically advanced, most likely, reaching the lethal range [10].
Consequently, it is imperative to develop new imaging modalities, such as optical imaging, to fill in the gaps of current methods, especially for (but not limited to) applications like the (early) detection of breast cancers.

1.2. Optical Biomedical Imaging

It is well known that, in the visible and near-infrared (NIR) wavelength regime, light can travel through centimeters of tissue and still be detectable; a fact that is effectively demonstrated by shining a flashlight onto one’s hand. Such phenomenon motivated people to “look” inside the body using light. The incoherent light imaging of human body was explored as early as 1929 [11]. However, it was not until recently (1990s) that coherent laser-based optical imaging for biomedical applications, known as Optical Biomedical Imaging, gained broad interest and acceptance. This is primarily due to advances in the understanding of light propagation inside biological tissue and improvements of laser related instrumentation. Optical imaging of biological tissue is very attractive not only because it is inexpensive, non-invasive and non-ionizing as opposed to X-rays, but also because it can provide valuable imaging contrasts and physiologically relevant functional information.

Optical imaging contrast in tissue consists mainly of spatially dependent variations in optical absorption and scattering, which are the two most important optical properties of a biological sample. Both of these parameters are intrinsically sensitive to abnormal tissue activities, e.g., the development of tumors and diseases. Macroscopically speaking, such activities will alter the components between normal and abnormal tissues, and the differences in tissue types will be manifested by differences in optical absorption.
and/or scattering properties. For instance, rapidly growing tumorous tissue typically requires a significant supply of blood-borne nutrients, and is thus highly vascularized. Blood is a major chromophore (optical absorber) in tissue and is about two orders (100 times) more absorbing than normal tissue in the visible and near-infrared (NIR) spectral range [12] (see Chapter 2 for details). Overall, this yields a 2-5 fold increase in optical contrast between tumors and normal tissues [13], while in conventional diagnostic ultrasound the primary imaging contrast (acoustic impedance) varies by only a few percent for most soft tissues.

Microscopically speaking, different molecules in tissue have different absorption spectra and scattering characteristics. In the visible and near-infrared (NIR) band of the electromagnetic spectrum, both the optical scattering and absorption properties are associated with the molecular constituents and their microstructures. The chemical composition of the tissue is directly linked to the optical absorption, which thus can be used to assess angiogenesis and hyper-metabolism. The morphology and refractive-index distribution of tissue is closely connected to the optical scattering coefficient, which consequently reflects microstructural changes in biological tissues at the cellular and sub-cellular levels. Therefore, it is not difficult to imagine that the differences in optical properties could occur far earlier than other macro-indicators, such as bulk mechanical properties. This makes detection of cancer at the very early stages possible. It is important to mention that functional parameters, such as oxygen saturation of hemoglobin in regional blood and the concentration of hemoglobin in blood flow, can also be inferred from measurements of optical properties. These parameters are important
for functional imaging, diagnosis, and therapeutic monitoring. For example, malignant
tumors are often associated with hypoxia (deficiency of oxygen content in hemoglobin),
and thus have higher concentrations of deoxyhemoglobin than benign tumors [14]. This
information could potentially be used to differentiate tumors.

Until now, several optical imaging techniques have been proposed and have shown good success [7]. Based on their imaging depths, optical imaging techniques can be classified into two general categories. The first category is called near-surface tissue imaging. Time-gated optical imaging [15, 16], optical microscopy and optical coherence tomography (OCT) [17-19] belong in this category. In near-surface tissue imaging, ballistic photons, which experience no scattering in tissue and travel straight paths (like X-rays), are employed and the imaging resolution is extremely high due to the relatively short optical wavelength. For example, 1 µm imaging resolution is currently achievable in OCT [20]. However, since the number of ballistic photons decay exponentially with the tissue thickness due to the high tissue scattering coefficient, the imaging depth of these imaging techniques is very limited, typically less than a few millimeters. Therefore, these imaging techniques are clearly not sufficient for such applications as cancer detection in breast, which typically has a clinical thickness of 5-10 cm.

The second category is called deep tissue imaging, in which diffuse photons that undergo multiple scattering events and thus possess wandering trajectories are used in order to penetrate deeper into tissue (several centimeters). Diffuse optical tomography (DOT) is a case in point in this category [21]. Subsurface images are obtained through the use of various sophisticated image reconstruction algorithms based on the diffusion
equation. The image quality is usually algorithm dependent and the spatial resolution is rather poor (5-10 mm). Presently, the trade-off between imaging resolution and imaging depth for pure optical imaging techniques is one of the main challenges in biomedical optics.

The poor resolution of pure optical techniques for deep tissue imaging arises from the fact that light propagation inside biological tissue is dominated by multiple scattering and light transport is characterized by diffusion rather than wave propagation. This is especially true inside the so-called “therapeutic window” (750-950 nm) where the overall optical absorption coefficient of biological tissues ($\mu_a \sim 0.1 \text{ cm}^{-1}$) is minimal compared to optical scattering coefficient ($\mu_s \sim 100 \text{ cm}^{-1}$). This overwhelming multiple-scattering effect blurs the optical images, preventing light from yielding good spatial resolution. In an attempt to overcome this limitation, ultrasonic techniques are “combined” with pure optical imaging techniques, as ultrasonic waves scatter much less readily in biological tissue and offer sub-millimeter resolution even at depth. Such combined imaging techniques mainly include photoacoustic imaging/tomography (also called optoacoustic imaging) [22-27], sonoluminescent tomography [28], and acousto-optic imaging (AOI) [22-27]. The latter of these three techniques, AOI, is the subject of this dissertation.

1.3. **Acousto-optic Imaging**

1.3.1. **General Review**
Acousto-optic imaging (AOI) in diffuse media\(^1\), including biological tissue, is a new dual-wave sensing technique in which a focused ultrasound beam is used to locally modulate, or “tag”, multiply scattered light (see Fig. 1.1). As a result of the ultrasonic perturbation, the phase and/or the amplitude of the diffuse light that pass through the column of the ultrasound beam are modulated (the detailed mechanisms are discussed below). By employing appropriate light detection and signal processing techniques, these “tagged” photons can be distinguished from the background photons that do not traverse the volume occupied by the ultrasound beam. The extent of this modulation depends on the amplitude and spatial extent of the sound field and the optical properties of the diffuse sample (primarily the reduced scattering and absorption coefficients). By quantifying the modulation strength, local optical information can be extracted. Since the modulated/tagged photons are generated within the ultrasound beam, the imaging resolution of this technique is determined by the spatial distribution of ultrasound which, for short acoustic pulses and a tightly focused ultrasound source, can reside within a sub-millimeter volume.

This general technique is referred to in the literature as a number of different names, depending on the background and perspective of the investigator: “ultrasound tagging of light” (UTL; Marks \textit{et al.} [29], Mahan \textit{et al.} [30]), “acousto-optic tomography” (AOT; Kempe \textit{et al.} [31] and Forget \textit{et al.} [32]), “acousto-optic(al) imaging” (AOI; Leveque \textit{et al.} [33, 34], and Selb \textit{et al.} [35]), “acousto-photonic imaging”\(^1\) Acousto-optic imaging can also be implemented in clear media, but this is not particularly relevant to biomedical applications. Throughout this dissertation, unless otherwise noted, the term of “acousto-optic imaging” is only limited to the work done in diffuse media.
(API, DiMarzio et al. [36]) and “ultrasound-modulated optical tomography” (UMOT; Wang and Zhao [37]). Regardless of the differences in these descriptive terms, the goal behind all these techniques is the same: to reveal the optically relevant physiological information while maintaining ultrasonic spatial resolution.

Since AOI is still in its early stages of development, its potential clinical applications have not been well explored. However, based on the potential for good optical imaging contrast at relatively large imaging depths and the unique hybrid nature of AOI, several possible applications can be envisioned, including the detection and diagnosis of breast cancer, neuroscience [38], and imaging brain\(^2\) for the detection of stroke, hemorrhage and brain function [21]. Thanks to the “virtual light source” (modulated photons) created by the ultrasound inside the diffuse media, AOI can also be used to non-invasively characterize the optical properties of diffuse media [34, 39] and map the photon distribution inside it [40, 41]. In addition, AOI can be combined with existing imaging modalities, such as diagnostic ultrasound, thus supplementing the conventional imaging techniques with additional information. The fusion of AOI and B-mode diagnostic ultrasound will be discussed in detail in Chapter 5 of this dissertation.

### 1.3.2. Principle of AOI—Overview of Theoretical Work

The principle of AOI is based on acousto-optic (AO) interaction in turbid media, i.e., the ultrasonic modulation of diffuse light. Although the AO effect in clear media has been

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2 Although it is well known that human skull can seriously attenuate and distort ultrasound waves, the development of new signal processing technologies, such as the time-reversal technique, might help to effectively focus ultrasound into the human brain.
known for a long time [42], its counterpart, AO interaction in diffuse media is quite complex and has only been studied recently. The complexity comes from the random walk of light inside the optically inhomogenous media. So far, three possible mechanisms have been identified for ultrasonic modulation of light in scattering media. All of these three mechanisms are associated with the perturbation of optical descriptors (absorption, scattering, and refractive index) of the turbid media caused by the ultrasound beam.

The first mechanism relies on ultrasound-induced local variations of the optical properties of the media, including absorption, scattering, and index of refraction. To conceptualize this, consider a small volume of an insonified diffuse sample with a characteristic length of several acoustic wavelengths as shown in Fig. 1.1. As the focused sound beam traverses this small volume, it will compress and rarify the media within this volume, resulting in a time and space dependent perturbation of the bulk density. This leads to a perturbation of the number density of optical absorbers and scatterers, which influences the local optical absorption coefficient and scattering coefficient, respectively. Since the local refractive index also varies with the bulk density, attenuation due to the scattering/reflection also results (analogous to the reflection due to the acoustic impedance mismatch in the field of acoustics [43-45]). Thus, when light is traveling through this volume, its amplitude is modulated, and the time scale for the periodic changes is given by the ultrasound frequency. Mahan et al. [30] modeled the ultrasonic modulation of light amplitude, which does not require a coherent light source. However, the amplitude modulation of incoherent light has not been observed experimentally [37].
Therefore, this mechanism is not considered to be the dominant mechanism for the AO effect in diffuse media.

The second mechanism is directly related to the ultrasound-induced displacement of optical scatterers. When coherent light passes through turbid media, light traversing different path lengths (i.e., possessing different phases) interferes at the aperture of a detector, resulting in a light field consisting of bright and dark regions corresponding to constructive and destructive interference, respectively. This is known as speckle [46].

The existence of the ultrasound beam will generate a periodic motion of the optical scatterers residing within the ultrasound beam. Since the ultrasound beam is not spatially uniform (i.e., both the phase and amplitude of the ultrasonic waves vary with the spatial location), the motion of the scatterers is not expected to be coherent (uniform). As a result, the optical path lengths accumulated from the multiple scattering events are
modulated at the ultrasonic frequency. The net result is a modulation in the phase of the multiply scattered light, and this modulation occurs at the ultrasound frequency. Interference of un-modulated and modulated light results in intensity variation. Leutz and Maret [47] modeled the ultrasonic modulation of multiple-scattering speckles in the weakly scattering regime (i.e., the scattering mean free path is much greater than the acoustic wavelength), and showed good agreement between their model and experimental results.

The third mechanism is caused by variations of the optical phases of multiply scattered light in response to the ultrasonic modulation of the index of refraction\(^3\). As mentioned above, the pressure wave induces a periodic density perturbation in compressible media, and subsequently a perturbation of the index of refraction as well. It is well known that the phase shift that light undergoes along a path is proportional to the optical path length, which is an integration of the refractive index over the distance in a medium with varying refractive index. As a result of the ultrasonic modulation of the index of refraction, the optical phase along a multiple scattering path is also modulated. As was the case in the second mechanism, the contribution to speckle from light traversing the ultrasound beam is similarly modulated. This mechanism was recently incorporated into a theory developed by Wang [48, 49], who combined the last two mechanisms and applied them to the case of isotropic scattering. Later on, Sakadzic and Wang [50] extended this model to the case of anisotropic scattering.

\(^3\)It should be clarified that refractive index plays two different roles in the first and third mechanisms, which contribute to the amplitude and phase modulations, respectively.
It should be mentioned that both the second and the third mechanisms are phase-modulation related, and require coherent laser light. Since the modulation of incoherent light has not been observed experimentally yet, the last two mechanisms are currently considered to be the primary mechanisms for ultrasonic modulation of multiple scattered light—the AO effect in diffuse media. The relative importance of the last two mechanisms is dependent on the optical scattering mean free path relative to the acoustic wavelength [48, 49].

1.3.3. Implementation of AOI—Overview of Experimental Work

Although the idea of generating images based on AO interaction is promising, AOI has proven difficult to realize experimentally. The biggest technical barrier to AOI is low sensitivity, which is due to a couple of factors. Firstly, the flux of tagged photons in biological tissue is very small because of the relatively high effective attenuation coefficient of biological tissue, $\mu_{\text{eff}} \approx \sqrt{3\mu_a\mu_s'}$, where $\mu_a$ and $\mu_s'$ are the absorption and reduced scattering coefficient, respectively (see details in Chapter 2). Based on diffusion theory [51], the effective attenuation coefficient determines how fast diffuse photons are attenuated, and is relatively high ($\sim 2 \text{ cm}^{-1}$) inside biological tissue despite a relatively low absorption coefficient ($\mu_a \sim 0.1 \text{ cm}^{-1}$). Therefore, the flux of ultrasound-modulated light is expected to be very small deep inside the biological sample.

Secondly, the spatial incoherence of the ultrasound modulated speckle pattern reduces the detected modulation depth when using sensors possessing apertures large enough to encompass several speckles. Light, after traveling through turbid media, forms
speckles, whose individual grains are modulated at the ultrasonic frequency as discussed above. In highly diffuse media, light travels over multiple paths from the optical source to the detection system, and the modulation of these individual grains induced by the ultrasound depends on the spatial position that the AO interaction takes place. Deep inside biological samples, viable light paths normally encompass a region with characteristic dimensions larger than an acoustic wavelength, and thus the modulation of these individual speckle grains is not expected to be coherent. Therefore, the modulation depth will be reduced when multiple speckles grains are summed.

A great deal of experimental work has been done since Dolfi and Micheron [52] patented the concept of photon frequency marking using ultrasound in 1989. Most of the current effort is focusing on developing new detection schemes to enhance the sensitivity and balancing the trade-off between axial resolution and detection sensitivity; short acoustic pulses achieve better resolution along the axis of sound propagation, but the reduced AO interaction volume and the broad detection bandwidth also reduce the detection sensitivity. Marks et al. [29] first reported the modulation of diffuse laser light with pulsed focused ultrasound in a homogeneous scattering media in 1993. This was followed by the work of Wang et al. [53] and Kempe et al. [31], who demonstrated the utility of ultrasound tagging of diffuse photons for imaging purposes. In order to enhance the signal-to-noise ratio (SNR), the former group employed a continuous-wave (CW) ultrasound source, and the modulated optical field was detected using a photomultiplier tube (PMT).
A key issue is the spatial decorrelation of the speckle field. Conventional single-detector techniques result in extremely low light levels when the detection aperture is limited to single speckle detection, and reduced modulation depth when the detection aperture is increased to encompass multiple speckles. To overcome the limitations of single detector techniques, Leveque et al. [54] employed a multiple detector system based on a CCD array, where each element on the array sensed light from a single speckle grain. By summing the individual modulation amplitudes from all of the pixels, they improved the SNR by a factor of $\sim N^{1/2}$, where $N$ is the number of coherence areas detected, corresponding to the number of pixels on the CCD. With this improved detection sensitivity, they, for the first time, obtained a one-dimensional (1-D) AO image in an ex vivo biological sample. Unfortunately, the CCD approach that has been employed is not suitable for pulsed ultrasound measurements due to the relatively long time required for image acquisition. In addition, the system is sensitive to speckle decorrelation during the measurement time. More recently, Gross et al. [55] improved the sensitivity of this parallel detection scheme by using a heterodyne technique, and proposed to filter out the speckle decorrelation noise using a spatial filter system. Additional work in the field includes the study of AOI in the reflectance geometry [34, 56, 57], the investigation of AOI using the second harmonics of the generated AO signals (to improve the spatial resolution) [35], and the employment of tomographic reconstruction in this technique [58].

In the majority of AOI systems, CW ultrasound sources are employed, which allow for greatly enhanced sensitivity and noise immunity through a reduction in
detection bandwidth and an increase in the AO interaction volume (more tagged photons). However, the use of CW sources has several drawbacks. First, CW ultrasound based AOI affords very limited axial resolution since the entire length of the ultrasound beam is active, making it difficult to distinguish photons emanating from different portions of the insonified volume. In addition, the use of CW ultrasound increases the potential for deleterious bio-effects, such as excessive tissue heating, that can result from the continuous high-intensity ultrasound exposure. In contrast, pulsed ultrasound permits significantly greater peak acoustic pressures while staying within the Food and Drug Administration (FDA) exposure guidelines [59]. Finally, narrow-band CW processing techniques are not compatible with conventional diagnostic ultrasound imaging machines, which typically employ short-pulse ultrasound.

To achieve axial resolution for CW exposures, Wang and Ku [60] introduced a technique in which a single optical detector is used and the CW ultrasound source is chirped at a rate fast enough to ensure that, at a given instant in time, different locations along the axis of propagation are exposed to different frequency ultrasound. By synchronizing data acquisition with the start time of the chirp, a particular frequency is assigned to each location along the ultrasonic axis. A 1-D axial scan could then be produced from the time-dependent frequency-domain information of the ultrasound-modulated signals. Due to the relative low sensitivity associated with the single-detector detection, this technique was originally demonstrated in less diffuse media using ballistic light. Later on, Yao et al. [61] and Forget et al. [32] combined this technique with the parallel detection system to achieve the axial resolution with enhanced sensitivity, and
obtained 2-D AO images in highly diffuse media, including biological tissue \textit{ex vivo}. Alternatively, in the time domain, Lev and Sfez [40] used ultrasonic pulses to construct CW signals by devising a reshaping algorithm to synchronize the ultrasonic pulses. By using short ultrasound pulses, they improved the spatial resolution and demonstrated the 3-D mapping of photon density in a homogeneous diffuse phantom.

1.4. \textbf{Motivation and Focus of the Work}

Challenges always come before motivation. Therefore, it is appropriate to reiterate and summarize the main technical difficulties of AOI discussed thus far. AOI, as with most new technologies, faces many problems, especially in terms of optical detection techniques and axial resolution (which is dependant on the ultrasound operational mode). Currently, the most critical technical barrier to AOI is the low detection sensitivity, i.e., $\text{SNR}$. Conventional single detector techniques yield extremely low signal (light) levels when a single speckle is received, and reduced modulation depth when multiple speckles are collected. CCD-based multiple detector techniques do not suffer from the reduction of modulation depth associated with the spatial incoherence of the speckle pattern, and thus dramatically improves the $\text{SNR}$. However, the CCD detector is a relatively slow device, is not suitable for pulsed ultrasound measurements due to the relatively long time required for image acquisition, and is sensitive to speckle decorrelation during the measurement time. With regards to the ultrasound operational modes, CW ultrasound is typically used to improve the sensitivity by narrowing the detection bandwidth and increasing the AO interaction volume, but it gives limited axial resolution and could induce deleterious
thermal bio-effects. If SNR issues could be resolved, pulsed ultrasound is highly desirable because it is safer, yields good axial resolution, and is compatible with conventional diagnostic ultrasound systems currently in use in clinics. In short, the “ideal” AOI setup is characterized by fast response, high detected photon flux (a large sensing aperture collecting multiple speckles), coherent summation (without reducing the modulation depth), and good axial resolution (typically requires pulsed ultrasound). The solution has proven to be elusive.

Motivated by this challenge, we report on a novel photorefractive-crystal (PRC) based interferometry system for the detection of ultrasound-modulated light in diffuse media [62-64]. The PRC-based interferometer is a “smart” device that can dynamically compensate for the complex speckle pattern and makes the collection of multiple speckles without reducing the modulation depth possible. (The detailed discussion on this subject will follow up in Chapter 3.) The detection system designed employs a large aperture, high speed, single-element detector, and is shown to have sufficient sensitivity to detect the transiently modulated optical signals generated by a pulsed ultrasound source employing output levels and pulse durations currently employed by clinical ultrasound imaging machines. In other words, we achieve good axial resolution with reasonably good sensitivity.

This single-detector, PRC-based detection system is used to image optically absorbing targets embedded inside highly diffusive tissue-mimicking phantoms and \textit{ex vivo} biological tissue. By using short pulses of focused ultrasound, 1-D images along the ultrasonic propagation axis are derived from the time-domain AO signals [64, 65]. To
generate such a 1-D “line scan”, time is converted to distance by multiplying the elapsed
time by the known speed of sound in the sample. The use of short ultrasound pulses
makes this technique adaptive to conventional diagnostic ultrasound, and further
motivates a direct fusion of AOI with diagnostic ultrasound. In this work, the
combination of conventional diagnostic ultrasound and AOI is investigated using a
commercial medical scanner (Analogic, AN2300) [66, 67]. The AN2300 was used to
both generate B-mode ultrasound images and excite AO signals, resulting in color coded
AO images that are co-registered to B-mode images of the same sample. Results confirm
that AO signals can be excited using a commercial scanner, and that it is possible to
combine AOI and diagnostic ultrasound to form three-dimensional (3-D) images sensitive
to both optical and acoustical contrasts of the sample.

In order to qualitatively explain the experimental results, the diffusion
approximation is used to study the light transport in diffuse media, revealing the photon
distribution inside a given sample. For simple experimental geometries, analytical
solutions to the diffusion equation are given. In addition, the concept of detection
sensitivity map, i.e., the dependence of sensitivity on the location where AO interaction
takes places, is developed for given detection schemes.

1.5.  Road Map of the Dissertation

The present Chapter provides the background and motivation material, and outlines the
primary focus of the work. A concise literature review is also included, from both
theoretical and experimental perspectives. The background of light interaction with
tissue, light propagation in tissue (primarily based on the diffusion approximation), and the concept of detection sensitivity map are discussed in Chapter 2. Chapter 3 documents the design and setup of the PRC-based interferometry system for the detection of AO signals. Also included in Chapter 3 is a discussion of the detection difficulties of conventional AOI systems. In Chapter 4, the experimental results using a single-element ultrasound transducer are discussed, including proof-of-principle results obtained using the PRC-based system, the imaging capability of the system and the spatial resolution of the system. The fusion of AOI and conventional B-mode ultrasound imaging is reported in Chapter 5. Finally, several appendices are included which contain supporting information and the work concludes with the bibliography.
References:


Chapter 2

Theoretical Background and Modeling

2.0 Overview

In order to interpret acousto-optic signals in turbid media, including biological tissue, the nature of light transport in such media should be well understood. The transport of light in turbid media is primarily determined by two types of interaction between light and the media: optical absorption and optical scattering. In Section 2.1, both optical absorption and scattering in tissue, a complex turbid medium, are reviewed. Parameters used to quantify optical absorption and scattering are introduced. Section 2.2 overviews the current approaches for the modeling of light propagation in tissue, with the focus on the diffusion approximation (DA), which leads to a relatively simple governing equation called the diffusion equation (DE). The analytical solutions to the DE are given for infinite, semi-infinite and slab geometries. Section 2.3 introduces and investigates the concept of a detection sensitivity map in AOI.
2.1 Light Interaction with Tissue

When a photon is sent into a tissue sample, two things may happen along its path: the photon is either absorbed or redirected. These two phenomena are called optical absorption and optical scattering, respectively, both of which will be discussed in this section. A number of physical parameters are also given to quantify optical absorption and scattering, providing some background information for the subsequent section on light propagation in tissue. In the context of AOI, a detailed understanding of light-tissue interaction will help us to appreciate the image contrast mechanisms, to identify the imaging parameters, and to realize the imaging limitations.

2.1.1 Optical Absorption

Absorption is important in the interaction of light with tissue, from both therapeutic and diagnostic perspectives. On one hand, the absorption of laser or other light sources can potentially damage tissue through mechanisms such as the photochemical effect (the basis of Photodynamic Therapy (PDT)) and the photothermal effect (commonly used for laser surgery). On the other hand, the absorption of light provides an important diagnostic role—offering a clue to the chemical composition of a tissue and providing metabolic information.

The mechanism of optical absorption by tissue is related to the molecular structure of tissue constituents. Photons are packets or quanta of light with a particular frequency, and possess a specific energy determined by $E = h \nu$, where $E$ is the photon energy, $\nu$ is the photon frequency, and $h$ is Planck's constant. A molecule typically
consists of multiple atoms (which are composed of electrons, protons and neutrons) joined by shared pairs of electrons. The molecular charge state can change in a quantized fashion by “absorbing” the energy of a photon. The energy of an incident photon must match the energy required for the molecule’s state transition in order for absorption to occur. In other words, photon absorption occurs as a quantum event. The energy absorbed from the incident field is most often dissipated as heat within the medium, primarily due to the internal collisions of molecules. A more detailed discussion on the subject of absorption of electromagnetic radiation can be found in literature [1] and it is beyond the scope of this dissertation.

The overall effect of absorption is a reduction in the intensity of the light beam traversing the medium. In a homogeneous, uniformly absorbing medium, the relationship between the absorption of light and the thickness of the medium is governed by the Lambert-Bouguer Law:

\[
\frac{dI}{I} = \mu_a dl, \quad (2.1)
\]

which states that the fraction \(dI/I\) of the incident intensity \(I\) absorbed in a thin layer \(dl\) is proportional to the thickness of the layer. The proportionality constant \(\mu_a\), is identified as the absorption coefficient. The subscript “a” is used for parameters describing absorption and the subscript “s” will be used in the following sections to describe scattering.
Integration of Eq. (2.1) over a finite thickness $l$, for a constant incident intensity $I_0$, yields:

$$I = I_0 e^{-\mu_l}.$$  \hspace{1cm} (2.2)

As for compounds, the absorption coefficient was determined to be linearly related to the concentration of the compound diluted in a non-absorbing medium by Beer in 1852. Following that, the absorption coefficient can be expressed in terms of the volume density $\rho_a$ (cm$^3$) and the absorption cross-section $\sigma_a$ (cm$^2$) of the absorbers as

$$\mu_a = \rho_a \sigma_a,$$  \hspace{1cm} (2.3)

giving the following form of the Beer-Lambert Law:

$$I = I_0 e^{-\rho_a \sigma_a l}.$$  \hspace{1cm} (2.4)

In homogeneous, absorbing media composed of several components, the total absorption coefficient is equal to the sum of their individual absorption coefficients, weighted by their relative concentrations. In general, the absorption coefficient $\mu_a$ can be interpreted as the probability that a photon will be absorbed by the medium per unit length. The reciprocal of the absorption coefficient, called the absorption length, can be conceptualized as the mean free path a photon travels between consecutive absorption events.
Biological tissue is a turbid medium, and has many different components. Tissue components that absorb light are collectively called *chromophores*. Different chromophores have their own unique absorption characteristics or spectra. As a result, the absorption spectra of biological tissues vary with tissue types, locations, and constituents. The primary spectra of several tissue types and tissue constituents are shown in Fig. 2.1, along with the absorption coefficients at some typical laser wavelengths [2]. Several things need to be pointed out: (1) For ultraviolet (UV) wavelengths, the primary absorbers in biological tissue are protein, DNA, and water. The absorption typically increases with the decrease of optical wavelength. (2) In the infrared (IR) wavelength regime, water is the dominant absorbing chromophore. (3) In the red to near-infrared (NIR) electromagnetic spectrum, the absorption of biological tissues is the smallest, and the penetration of light is consequently the largest (several centimeters). This region is ideally suited for biomedical applications, and thus is called the “*diagnostic and therapeutic window*” (750-950 nm).

![Figure 2.1: Primary absorption spectra of several tissue types and tissue constituents, along with the absorption coefficients at some typical laser wavelengths. It is noted that the absorption spectra of water has been scaled down by 75% to mimic a typical tissue with 75% water content. From Jacques [2].](image-url)
Within the therapeutic window, some of the most important absorbing constituents in biological tissues are water and blood. Water mainly affects the average/effective absorption coefficient of tissues, which globally governs the light transport and determines the spatial distribution of light intensity in tissues. Blood content in tissue and oxygen saturation in blood are important physiological parameters in diagnostic imaging. Water is the most abundant substance in the human body, accounting 60%-80% of the total body mass. Therefore, the absorption of water is significant in tissues, especially in soft tissues (such as skin and breast), despite its relatively low absorption within the therapeutic window. The spectrum of water is given in Fig. 2.1, which is scaled down by 75% to mimic a tissue with 75% water content and is similar to that of skin. It is also noticed in Fig. 2.1 that blood and melanosomes are both strong optical absorbers, however, their volume fractions in most soft tissues are only a few percent (or even less). As a result, blood and melanosomes primarily affect local light absorption and spatially averaged absorption coefficients are only modestly impacted by them. Blood is important in that its absorbing characteristic changes uniquely according to function and metabolism of biological tissues. The dominant contributor to optical absorption in blood is red blood cells, which are mainly composed of hemoglobin (95%). Hemoglobin is responsible for delivering oxygen to the peripheral tissues and returning waste gases, such as carbon dioxide, to the lungs to be exhaled. In the oxygenated state, hemoglobin is referred to as oxyhemoglobin (HbO₂), and in the reduced state, it is called deoxyhemoglobin (Hb). Each hemoglobin molecule can carry a total of four molecules of oxygen (O₂), in which case it is said to be 100% saturated. If
blood is not fully saturated, some of the hemoglobin molecules have less than four oxygen molecules bound. The statistical average of all oxygen bound to hemoglobin molecules relative to the total amount that can be bound is called oxygen saturation (SO₂). Both the oxygen saturation in regional blood and the total concentration of blood flow in biological tissues are key functional parameters, based on which optical techniques have been widely employed [3, 4].

The specific absorption spectra of oxy- and deoxyhemoglobin are shown in Fig. 2.2, based on the data given by Prahl [5]. While both Hb and HbO₂ absorb strongly in the blue and green regions of the visible spectrum, the absorption of deoxyhemoglobin (Hb) is slightly stronger beyond 590 nm. Hence venous blood, which is about 75% saturated, appears in a darker red than the arterial blood, which is about 98% saturated in adults. Note the isobestic point is around 800 nm. This suggests that the functional parameters (blood volume and oxygen saturation) can be obtained if the tissue absorption coefficients at two nearby different wavelengths, towards either side of this isobestic point, can be determined. The information may be useful, for example, for differentiating tumors.

There are a number of other chromophores, such as lipids, cytochrome and myoglobin, which are not covered in this section due to the limited space. More details about them can be found in literature [2].
2.1.2 Optical Scattering

Scattering, the dominant effect for light propagation in turbid media (including biological tissues), complicates photon paths and blurs optical images. Scattering also plays a diagnostic role, and there are some indications that scattering properties differ between tumorigenic cells and nontumorigenic cells [6]. In addition, optical scattering, along with optical absorption, determines the photon distribution inside biological tissues.

Scattering of light arises from the spatial fluctuations in the refractive index, $n$, inside a medium. Such fluctuations can be either discrete particles or more continuous variations in $n$. Depending on the frequency of the scattered photons compared to that of the incident light, scattering mainly falls into two categories: Elastic scattering and Raman scattering (inelastic scattering). Elastic scattering occurs when charged particles in a medium are set into oscillatory motion by the electric field of the incident wave, and

![Figure 2.2: The absorption spectra of deoxyhemoglobin (Hb) and oxyhemoglobin (HbO$_2$) in the wavelength range of 250 nm-1000 nm. From Prahl [5].](image)
re-emit light of the same frequency as the primary wave (there is no energy change between the incident photons and the re-emitted photons). In Raman scattering, the incident photons interact with the scatterers in such a way that energy is either gained or lost so that the scattered photons are shifted in frequency. In the work reported herein, the term “scattering” refers only to elastic scattering.

The parameter that is used to quantify the scattering effect in optically turbid media is called the scattering coefficient, $\mu_s$. The scattering of light can be defined in the same manner as absorption for a collimated source, and is given by:

$$I = I_0 e^{-\mu_s l},$$

(2.5)

where $I$ is the non-scattered component of light remaining after traversing a non-absorbing sample of thickness $l$. The normalized transmission, $I/I_0 = e^{-\mu_s l}$, can be interpreted as the probability of transmission of the photon without redirection by scattering after a path length $l$. In terms of volume/particle density $\rho$, and scattering cross-section $\sigma_s$, one can express the scattering coefficient as the scattering cross-sectional area per unit volume, i.e.,

$$\mu_s = \rho \sigma_s.$$  

(2.6)

The reciprocal of the scattering coefficient, $1/\mu_s$, known as the scattering mean free path, is the average distance that a photon travels between consecutive scattering events and is schematically illustrated in Fig. 2.3(a).

The characteristics of optical scattering by individual particles (or other structures) in turbid media strongly depend on the size of the particles. Based on the
dimensions of the particles compared to the incident wavelengths, scattering of light can be classified into two categories: Rayleigh scattering and Mie scattering. Rayleigh scattering (also called the Rayleigh limit of Mie scattering) refers to the scattering of light off particles whose dimensions are much smaller than the optical wavelength, typically less than a tenth of the incident wavelength. The most important feature of Rayleigh scattering is its wavelength-dependence (or frequency-dependence). Lord Rayleigh is the first scientist to quantitatively study this, and found that the scattered field intensity $I$ varies with the inverse fourth power of the incident wavelength $\lambda$, i.e., $I \propto 1/\lambda^4$.\(^1\) Mie scattering, described by Mie theory, is referred to as the light scattering caused by particles whose dimensions are on the order of the photon wavelength or larger. Photons are most strongly scattered by those structures whose size matches the photon wavelength. Therefore, in turbid media, including biological tissues, Mie scattering dominates.

Scattering can be isotropic or anisotropic. However, both Rayleigh scattering and Mie scattering by a complex structure or a sphere are typically anisotropic, that is, the intensity of the scattered light field is angularly dependent with respect to the direction of the incident light. Typical patterns exhibited by Rayleigh scattering and Mie scattering are given in Fig. 2.3(b). Physical parameters used to describe this behavior include the phase function and anisotropy, which will be reviewed in the following paragraphs.

When a photon is incident along a direction described by the unit vector $\hat{s}$ and experiences a scattering event, the angular probability of its being scattered into

\(^1\) The strong wavelength dependence of Rayleigh scattering enhances the shorter wavelengths, giving us the blue sky.
direction \( \hat{s}' \) is given by the normalized phase function \( f(\hat{s}, \hat{s}') \), which has units of \( \text{sr}^{-1} \). If the probability distribution is independent on the incident angle, the phase function can be further simplified and expressed as a function of the cosine of the scattering angle \( \hat{s} \cdot \hat{s}' = \cos \theta \):

\[
f(\hat{s}, \hat{s}') = f(\cos \theta).
\]

(2.7)

In Fig. 2.3(b-c), the relative lengths of the “scattered” arrows are related to the phase function.

---

**Figure 2.3**: Schematic illustration of some physical parameters related to optical scattering.

- **(a)**: Mean free path—scattering and transport
  - Scattering mean free path \( = \langle l_s \rangle = 1/\mu_s \)
  - Transport mean free path \( = \langle l_t/(1-g) \rangle = 1/\mu_s' \)

- **(b)**: Typical Rayleigh and Mie Scattering Patterns
  - Rayleigh Scattering
  - Mie Scattering
  - Mie Scattering, larger particles

- **(c)**: Anisotropy factor
  - \( g = 0 \)
  - \( g = 0.9 \)
Anisotropy is expressed in terms of the mean value of the cosine of the scattering angle, termed the anisotropy factor, $g$:

$$g = \langle \cos \theta \rangle = \int_{-1}^{1} \cos \theta f(\cos \theta) d\cos \theta. \quad (2.8)$$

It should be noted that $g$ is dimensionless and is a measure of the amount of forward direction retained after a single scattering event. The limiting cases are $g=0$ for perfectly isotropic scattering, and $g=1$ for forward scattering. To give a physical interpretation of anisotropy, two different cases for $g=0$ and $g=0.9$ in a single scattering event, are schematically illustrated in Fig. 2.3(c). In biological tissues, light scattering is highly forward-directed, thus resulting in a relative high value of $g$. Although $g$ is tissue and wavelength dependent, 0.9 is a typical value for soft tissues within the therapeutic window [7].

The transport (or reduced) scattering coefficient, $\mu_s'$, is defined as

$$\mu_s' = \mu_s (1 - g). \quad (2.9)$$

The reduced scattering coefficient is a lumped parameter that incorporates both the scattering coefficient and the anisotropy. The purpose of $\mu_s'$ is to describe the diffusion of photons in terms of a random walk of step size $1/\mu_s'$, where each step involves an isotropic scattering interaction (referring to Fig. 2.3(a)). In other words, $\mu_s'$ expresses scattering from an anisotropic medium in terms of an effective isotropic scattering coefficient. The reduced scattering coefficient is a fundamental parameter in the diffusion theory of light propagation through random media, which will be discussed in the following section. The mean free path traveled by a collimated beam of light before it
becomes effectively isotropic is given by $1/\mu_s'$, which is normally called reduced (transport) mean free path. The reduced mean free path is an effective length for multiple scattering (e.g., in biological tissues), after which the original anisotropic scattering becomes isotropic, i.e., the photon has lost all memory of its initial direction.

The total attenuation coefficient is defined by summing both scattering and absorption coefficients, i.e.,

$$\mu_t = \mu_s + \mu_a,$$  \hspace{1cm} (2.10)

where $1/\mu_t$ is commonly referred to as the mean free path between either a scattering or absorption event. By analogy, the transport attenuation coefficient $\mu_t'$ is defined as

$$\mu_t' = \mu_s' + \mu_a'.$$  \hspace{1cm} (2.11)

Having discussed the general features of optical scattering and its physical descriptors in turbid media, we will have a close look at optical scattering inside biological tissues. The light scattered by a tissue has interacted with the ultrastructure of the tissue. Tissue ultrastructure ranges from membranes to membrane aggregates to collagen fibers to nuclei to cells. Some of the tissue ultrastructure that affects visible and infrared light is given in Fig. 2.4. As mentioned above, Mie scattering dominates in such turbid media as tissues, where photons are most strongly scattered by those structures whose size is on the order of the photon wavelength.

In soft tissues, two components—lipids and collagen fibers are especially responsible for the scattering of light within the therapeutic window. Lipids are composed of cellular membranes, membrane folds, and membranous structures such as
mitochondria. While other objects such as protein aggregates and cell nuclei are also sources of scattering, the lipid/water interface of membranes presents a strong refractive index mismatch and thus plays a major role in scattering. Lipid content in soft tissues varies within a large range [2], but in general, soft tissues with higher (or lower) lipid content will show increased (or decreased) scattering. In addition to lipids, collagen fibers are strongly scattering tissue components. For example, the dermis of skin and the sclera of the eye are tissues with high collagen fiber content. Collagen fibers vary from 0.1 µm-diameter fibrils to 8 µm-diameter fiber bundles. Both the contributions from lipids and collagen fibers can be predicted by Mie theory.

![Hierarchy of ultrastructure](image)

Figure 2.4: The size range of tissue ultrastructure which affects visible and infrared light by Mie and Rayleigh scattering. From [2].

### 2.2 Light Propagation in Tissue—The Diffusion Approximation

To utilize light for both therapeutic and diagnostic purposes, one must understand the details of light propagation in turbid media. In AOI, regardless of the detection technique
employed, ultrasound-modulated optical signals are directly related to the number of tagged photons. It is therefore important that we understand how the photon density (or the light intensity) is distributed within a turbid medium, such as tissue. To do so, the diffusion approximation (DA) is chosen following a general overview of the current modeling methods. Based on the DA, the diffusion equation (DE) can be derived, which has a relatively simple form and governs light propagation in tissue in the diffusion regime. The analytical solutions to the DE for some particular geometries are introduced, and these solutions will be helpful in understanding the AO signals to be presented in the following Chapters.

2.2.1 Current Modeling Approaches of Light Propagation in Tissue

Currently, there are several approaches to modeling light propagation in optically turbid media. Some of the most successful models will be concisely reviewed in this section; a more indepth discussion of the subject can be found in the review papers by Arridge [8, 9].

In principle, the propagation of light in turbid media, where multiple scattering dominates, can be rigorously described using Maxwell’s electromagnetic theory. However, the full solution to the multiple-scattering problem is often too complex to be useful in many real applications. More suitably, the problem can be simplified by ignoring the wave characteristics of light, such as polarization and interference, and only considering the flow of energy through the media. This is essentially the idea of radiative transfer theory [10]. This theory proposes that light transport in turbid media is governed
by a Radiative Transfer Equation (RTE), and the solutions to the RTE may be obtained either stochastically or deterministically.

Although the RTE is a deterministic equation, no general analytical solution exists except for very simple cases, such as in purely absorbing media (and simple geometries). This is clearly not the case for biological tissues. A commonly used simplification of the RTE is called the diffusion approximation (DA), leading to the diffusion equation (DE), from which analytical solutions can be derived for certain geometries. The main disadvantage of the DA is that it is not very accurate under certain circumstances, such as near the sources, detectors, boundaries or strong optical absorbers.

Besides the DA, stochastic approaches to implement the RTE can also be employed. One such technique, the Monte Carlo (MC) method, has seen widespread use in the simulations of laser-tissue interactions [11]. In the MC method, light is modeled as a stream of particles/photons that are injected into the medium and move in straight lines through tissue between successive absorption and scattering events. By shooting enough photons, the statistical nature of the photon paths can be resolved. The advantages of the MC method include simple implementation, the ability to handle complex geometries and inhomogeneities, and accuracy (even near the sources, detectors, boundaries and strong absorbers). The main disadvantage of the MC method is that it is computationally costly and time-consuming because enough photons have to be used in the simulation to reduce statistical noise.

2.2.2 The Diffusion Equation
Based on the DA to the RTE, the DE can be derived. The DE is one of the most useful models for the light-tissue interaction as it can be solved analytically for simple geometries. Currently, the DE has been used extensively in photon propagation modeling in both the time and frequency domains [12, 13]. The complete derivation of the DE has been documented in a number of sources [8, 10, 14, 15]. Below, we briefly summarized the theoretical development with a focus on the procedure employed, assumptions made, and the inherent limitations in the model.

The RTE ignores the wave and particle characteristics of light, and can be used to accurately model the distribution of energy (light intensity) in a highly diffuse medium. In general, the RTE has the following integro-differential form [10]:

\[
\frac{1}{c} \frac{\partial I(\vec{r}, t, \hat{s})}{\partial t} + \hat{s} \cdot \nabla I(\vec{r}, t, \hat{s}) + \mu_s I(\vec{r}, t, \hat{s}) = \mu_s \int_{4\pi} f(\hat{s}, \hat{s}') I(\vec{r}, t, \hat{s}') d\Omega' + S(\vec{r}, t, \hat{s}), \tag{2.12}
\]

where \(c\) is the speed of light in the turbid medium, \(I(\vec{r}, t, \hat{s})\) is the radiance\(^2\) (also called specific intensity) at point \(r\) at time \(t\) in the direction defined by a vector \(\hat{s}\), and \(S(\vec{r}, t, \hat{s})\) is the source term, which describes the power injected into a unit solid angle centered on \(\hat{s}\) in a unit volume centered at position \(r\) at time \(t\), and has units of \(\text{W} \cdot \text{m}^{-3} \cdot \text{sr}^{-1}\) (the remaining parameters are as defined in Section 2.1). Physically, the RTE is derived from conservation of energy: energy lost (temporal variation—the first term on the left-hand-side of the RTE, spatial gradient—the second term, and losses due to the scattering and absorption—the third term) is equal to energy gained (photons re-scattered to direction \(\hat{s}\)

---

\(^2\)Radiance is a physical quantity that represents the intensity of a light beam. It is defined as power per unit solid angle per unit projected area (the area normal to the direction of the light beam). The SI unit of radiance is watt per steradian per square metre (W·m\(^{-2}\)·sr\(^{-1}\)).
from all directions—the first term on the right-hand-side of the RTE, and the source—the second term).

Due to the complexity of the RTE, it is nearly impossible to obtain analytical solutions with a degree of generality useful for real problems. Therefore, the solution of the RTE typically requires numerical simulations, which are often computationally expensive. To simplify the RTE, a commonly used method is the $P_N$ approximation, which expands the radiance $I$ and source term $S$ as a sum of spherical harmonic functions to the $N^{th}$ order, i.e. [8],

$$I(\vec{r}, t, \hat{s}) = \sum_{l=0}^{N} \sum_{m=-l}^{l} \left( \frac{2l+1}{4\pi} \right)^{\frac{1}{2}} Y_{l,m}(\vec{r}, t) Y_{l,m}(\hat{s});$$

(2.13)

$$S(\vec{r}, t, \hat{s}) = \sum_{l=0}^{N} \sum_{m=-l}^{l} \left( \frac{2l+1}{4\pi} \right)^{\frac{1}{2}} q_{l,m}(\vec{r}, t) Y_{l,m}(\hat{s});$$

(2.14)

where $Y_{l,m}$ are spherical harmonics. In the $P_1$ approximation, $Y_{l,m}$ is truncated after the first order, and thus has only four terms which are: $Y_{0,0} = \sqrt{1/4\pi}$, $Y_{1,0} = \sqrt{3/4\pi} \cos \theta$, $Y_{1,1} = -\sqrt{3/8\pi} e^{i\phi} \sin \theta$, and $Y_{1,-1} = \sqrt{3/8\pi} e^{-i\phi} \sin \theta$. It is observed that $Y_{0,0}$ is a scalar and that the other 3 terms represent the three components of a vector. Therefore, the radiance and the source can be approximated using the vector format [10, 14, 15] as follows:

$$I(\vec{r}, t, \hat{s}) \quad \text{or} \quad S(\vec{r}, t, \hat{s}) \approx U(\vec{r}, t) + \hat{F}(\vec{r}, t) \cdot \hat{s}. \quad (2.15)$$

Thus, both the radiance and source terms can be expressed in terms of an isotropic intensity distribution $U(\vec{r}, t)$ and a small directional flux $\hat{F}(\vec{r}, t)$. The isotropic distribution is dominant (otherwise, higher orders of $N$ have to be kept), which requires that scattering be much stronger than absorption in a diffuse medium. The above
$U(\vec{r}, t)$ and $\vec{F}(\vec{r}, t)$ can be determined by integrating Eq. (2.15) over the entire solid angle $\Omega$ and first multiplying Eq. (2.15) by $\hat{s}$ and then integrating over the entire solid angle $\Omega$, respectively. Finally, the radiance and source terms can be rewritten in the following form [14, 15]:

$$
I(\vec{r}, t, \hat{s}) = \frac{1}{4\pi} \phi(\vec{r}, t) + \frac{3}{4\pi} \vec{J}(\vec{r}, t) \cdot \hat{s}; \\
S(\vec{r}, t, \hat{s}) = \frac{1}{4\pi} S_0(\vec{r}, t) + \frac{3}{4\pi} \vec{S}_1(\vec{r}, t) \cdot \hat{s},
$$

(2.16)

where $\phi(\vec{r}, t) = \int \frac{I(\vec{r}, t, \hat{s})}{4\pi} d\Omega$; $S_0(\vec{r}, t) = \int \frac{S(\vec{r}, t, \hat{s})}{4\pi} d\Omega$; $\vec{J}(\vec{r}, t) = \int \frac{I(\vec{r}, t, \hat{s})}{4\pi} \hat{s} d\Omega$; $\vec{S}_1(\vec{r}, t) = \int \frac{S(\vec{r}, t, \hat{s})}{4\pi} \hat{s} d\Omega$.

(2.17)

(2.18)

Physically, $\phi(\vec{r}, t)$ is interpreted as the fluence rate (or photon density)$^3$, and $\vec{J}(\vec{r}, t)$ is the photon current/flux.

After introducing these expressions and substituting them into the RTE (Eq. 2.12), the algebra consists of two steps: (i) integrating the RTE on $\hat{s}$ over $4\pi$, and (ii) multiplying the RTE by $\hat{s}$ then integrating over $4\pi$. Accordingly, these two steps lead to two new equations (step (i) leads to Eq. (2.19) and step (ii) leads to Eq. (2.20)):

$$
\frac{1}{c} \frac{\partial \phi(\vec{r}, t)}{\partial t} + \nabla \cdot \vec{J}(\vec{r}, t) + \mu_a \phi(\vec{r}, t) = S_0(\vec{r}, t),
$$

(2.19)

$$
\frac{1}{c} \frac{\partial \vec{J}(\vec{r}, t)}{\partial t} + \frac{1}{3} \nabla \phi(\vec{r}, t) + (\mu_a + \mu_r) \vec{J}(\vec{r}, t) = \vec{S}_1(\vec{r}, t).
$$

(2.20)

$^3$ Fluence rate (with units of W/m$^2$) at a given point in space is typically defined in the following way: The radiant power incident (from all directions) on an infinitesimal imaginary spherical volume containing this point divided by the cross-sectional area of the imaginary sphere. Fluence rate is directly related to the photon density $\phi(\vec{r}, t)$ (with units of 1/m$^3$) by three constant parameters: $\phi(\vec{r}, t) = \frac{ch\nu}{\pi h c} \nu(\vec{r}, t)$, where $c$, $h$, and $\nu$ are as defined in the text. In this sense, there is no difference between fluence rate and photon density.
The DA further assumes: (1) the source is isotropic or isotropic dominant so that \( S_1(\vec{r}, t) \rightarrow 0 \) in Eq. (2.20); and (2) \(|1/c_\mu ' \partial \vec{J}(\vec{r}, t)/\partial t| << |\vec{J}(\vec{r}, t)|\), which means that the time variation of the diffuse photon flux vector \( J \) over a period of \( 1/c_\mu ' \) is assumed to be negligible with respect to the vector itself and thus leads to \( \partial \vec{J}/\partial t \rightarrow 0 \) in Eq. (2.20)\(^4\).

Incorporating the above assumptions into Eqs. (2.19) and (2.20), we obtain:

\[
\frac{1}{c} \frac{\partial}{\partial t} \phi(\vec{r}, t) - \nabla \cdot D \nabla \phi(\vec{r}, t) + \mu_a \phi(\vec{r}, t) = S_0(\vec{r}, t),
\]

(2.21)

\[
\vec{J} = -D \nabla \phi,
\]

(2.22)

where

\[
D = \frac{1}{3} \left[ \mu_a + (1 - g) \mu_r \right].
\]

(2.23)

Here, \( D \) is referred to as the diffusion coefficient/constant. Note that \( D \) is a function of space for an inhomogenous medium. Eq. (2.22) is Fick’s Law in the general formulism of diffusion, which states that the flux/current is proportional to the negative gradient of concentration. For a homogeneous medium where \( D \) is a constant, the above equation becomes the diffusion equation (DE):

\[
\frac{1}{c} \frac{\partial}{\partial t} \phi(\vec{r}, t) - D \nabla^2 \phi(\vec{r}, t) + \mu_a \phi(\vec{r}, t) = S_0(\vec{r}, t)
\]

(2.24)

\(^4\) This clearly holds for steady state photon distribution, say, generated from a CW laser. If the source is amplitude modulated (which could be the case in diffuse optical tomography), this generally requires that the modulated frequency is relatively “low”. This becomes clearer if \( \vec{J} \) is written down in the following form: \( \vec{J} \sim e^{i \omega t} \), where \( \omega \) is the source modulated frequency. In this case, the above assumption becomes \( \omega << c_\mu ' \). Since, for a typical biological sample, \( c_\mu ' \) corresponds to a frequency equal to or greater than about 1 GHz, this assumption should be valid as long as the source is modulated at frequencies lower than about 1 GHz.
The derivation leading from the RTE to the DE is based on several assumptions, all of which impose some limitations to the applicability of the DE [8, 16]. The DA is only valid in the diffusion regime where \( \mu_a << \mu_s' = \mu_s(1 - g) \). This guarantees that the photons are scattered multiple times and behave diffusely before they are absorbed. Fortunately, this condition is true for most of biological tissues in the visible and the near-infrared wavelength regimes.\(^5\) In addition, this condition implies that the DA predicts the distribution of light intensity deep inside the turbid medium better than near boundaries or near where dramatic changes in optical properties occur. This arises from the fact that the photons near boundaries or strong absorbers can be far from diffuse.

### 2.2.3 Boundary Conditions of the Diffusion Equation

Boundary conditions are needed to solve the DE. Three common boundary conditions:

1. The partial-current boundary condition (also called the radiation boundary condition),
2. The extrapolated-boundary condition, and
3. The zero-boundary condition, have been widely investigated and employed for solving the DE [14, 15, 17]. However, none of

\(^5\) It should be aware, though, that there are regions of the body where the diffusion approximation does not strictly hold, such as cerebrospinal clear layer of the head where \( \mu_s' \) is small.
these boundary conditions are exact due to the approximate nature of the DE itself. For a diffuse medium bounded by a convex surface $\Sigma$ (see Fig. 2.5), the exact boundary condition for the RTE (not for the DE) in terms of the radiance $I$, assuming no mismatch in the refractive index between the diffuse medium 1 and the surrounding non-diffuse medium 2 (i.e., $n_1=n_2$), is that at the surface there should be no diffuse light entering medium 1 [10]:

$$I(\vec{r},t,\hat{s}) = 0 \text{ for } \hat{s} \text{ pointed inward and for } \vec{r} \text{ on } \Sigma. \quad (2.25)$$

While Eq. (2.25) is the exact boundary condition for the RTE, the DE itself involves the fluence rate $\phi(\vec{r},t)$. Therefore, for the DE, a boundary condition expressed in terms of fluence rate (rather than in terms of radiance) should be adopted. With the simple angular distribution assumed for $I$ (Eq. 2.16 in which $I$ is truncated after the first-order spherical harmonics, i.e., $P_1$ approximation), the condition described by Eq. (2.25) cannot be satisfied and some approximations must be considered in terms of fluence rate. One such approximation is the condition that at the surface $\Sigma$, the total diffuse flux directed inward must be zero [10]:

$$\int_{2 \pi} I(\vec{r},t,\hat{s})(\hat{s} \cdot \hat{n}) d\Omega = 0, \quad (2.26)$$

where $\hat{n}$ is a unit vector directed inward normal to the surface, and the integration is performed over $2\pi$ in the hemisphere $\hat{s} \cdot \hat{n} > 0$. Equation (2.26) is attractive in that it can be expressed in terms of fluence rate alone. After substituting $I(\vec{r},t,\hat{s})$ with $I(\vec{r},t,\hat{s}) = \left(\frac{1}{4\pi}\right)\phi(\vec{r},t) - D\left(\frac{3}{4\pi}\right)\nabla \cdot \hat{s}$ (combing Eqs. (2.16) and (2.22)) in the above Equation, one obtains [10]:

48
\[
\phi(\vec{r}, t) - 2D\hat{n} \cdot \nabla \phi(\vec{r}, t) = 0 \quad \text{for } \vec{r} \text{ on } \Sigma.
\] (2.27)

Equation (2.27) is the so-called “partial-current boundary condition”. It should be noted that the above boundary condition is only valid for \(n_1 = n_2\). If there is a mismatch in the refractive index across the surface, the total diffuse flux at the boundary directed into the medium is not equal to zero, instead, it is equal to the outwardly directed flux reflected by the surface [14, 18]. In this case, the boundary condition can be derived by taking into account Fresnel reflection [14, 15]:

\[
\phi(\vec{r}, t) - 2AD\hat{n} \cdot \nabla \phi(\vec{r}, t) = 0 \quad \text{for } \vec{r} \text{ on } \Sigma,
\] (2.28)

where \(A\) is a function of the relative index of refraction between medium 1 and medium 2. For \(n_1 = n_2\) where \(A = 1\) [14, 17], Eq. (2.28) reduces to Eq. (2.27).

To solve the DE for certain geometries, e.g., semi-infinite and slab geometries, two additional *simple but more approximate* boundary conditions are commonly used (instead of the partial-current boundary condition): the extrapolated-boundary condition and the zero-boundary condition. The extrapolated-boundary condition assumes that the fluence rate is equal to zero at an extrapolated boundary outside the turbid medium positioned at a distance \(z_e\) given by

\[
z_e = 2AD.
\] (2.29)

This condition is an approximation to the partial-current boundary condition and assumes a linear behavior of the fluence rate around the geometrical boundaries [19]; note that under this assumption Eq. (2.28) leads directly to \(\phi(\vec{r}, t) = 0\) at \(z_e = 2AD\). The zero-boundary condition assumes that the fluence rate is equal to zero at the physical boundary [12]. This is typically only used if the observations are made at a large distance compared
with the extrapolated boundary given in Eq. (2.29). It is not possible to take into account the effect of reflection at the boundary using the zero-boundary condition.

As we move from boundary conditions (1) through (3), the degree of approximation is increasing and the accuracy is generally reducing. The choice of the boundary conditions is a trade-off, and often depends on the particular problem that one is addressing. It should be emphasized that even the most “accurate” boundary condition—the partial-current boundary condition, is approximate. A detailed discussion of these boundary conditions and their accuracies can be found in the literature [14, 15].

### 2.2.4 Analytical Solutions to the DE for Certain Geometries

For a homogeneous diffuse medium, analytical solutions to the DE for infinite, semi-infinite and slab geometries can be obtained. These geometries are particularly interesting because of their relevance to clinical configurations. For instance, the semi-infinite geometry can be used to model a typical backward-detection problem [12] over a large tissue volume, and a slab geometry is relevant when simulating transmission and reflection problems [14, 17]. In the context of AOI, these solutions will be helpful in interpreting the observed AO signals.

The time-dependent DE for a homogenous medium is given in Eq. (2.24). However, since typical AOI systems employ CW lasers, only the solution to the steady-state DE will be discussed here. In the steady state, Eq. (2.24) reduces to:

\[
[\nabla^2 - \mu_{\text{eff}}^2] \phi(\vec{r}) = -S_0(\vec{r}) / D
\]

(2.30)
where the quantity \( \mu_{\text{eff}} = \sqrt{\frac{\mu_a}{D}} = \sqrt{\frac{3}{2} \mu_a (\mu_a + \mu_s')} \) is referred to as the effective attenuation coefficient. Analogous to the scattering mean free path, the inverse of \( \mu_{\text{eff}} \) is the effective attenuation length. Equation (2.30) is very similar to the Helmholtz Equation, with the only sign difference before \( \mu_{\text{eff}}^2 \) due to the photon attenuation from scattering and absorption in turbid media.

### 2.2.4.1 Infinite Medium

The analytical solution to Eq. (2.30) is available for a point source in an infinite medium [20]. In cylindrical coordinates, the steady-state solution for the fluence rate at a detection point \((r, \theta, z)\) from an isotropic point source at \((r', \theta', z')\) in an infinite turbid medium has the following Green’s function form [17]:

\[
\phi_x(r, \theta, z; r', \theta', z') = \frac{1}{4\pi D} \frac{1}{\rho_i} \exp(-\mu_{\text{eff}} \rho_i),
\]

where \(\rho_i\) is the distance between the source and the detection point which can be easily derived from the geometrical relationship as:

\[
\rho_i = \sqrt{r^2 + r'^2 - 2rr' \cos(\theta - \theta') + (z - z')^2}.
\]

The Green’s function solution given above can also be used to solve the two practical problems shown schematically in Fig. 2.6: a collimated laser beam incident on (a) a semi-infinite space, and (b) a slab geometry. In the DA, the light source is required to be isotropic, which is clearly not the case for a collimated laser beam incident onto a turbid medium. However, this issue can be conveniently resolved by representing a collimated beam at the surface as an isotropic point source at a depth
$z_0 = [(1-g)\mu_s]^{-1} = \mu_s^{-1}$ below the surface [12, 14, 15, 20]. The rationale behind this approach is that all the incident photons are initially scattered (isotropically) at a depth $z_0 = 1/\mu_s$ below the surface. This approach has been widely adopted for the modeling of the diffuse light distribution resulting from a collimated light source due to its simplicity (see the detailed discussion about this in Contini’s paper [14]).

2.2.4.2 Semi-infinite Geometry

In a semi-infinite turbid medium (see Fig. 2.6 (a)), the boundary condition at the surface of the medium becomes important. The extrapolated-boundary condition can be applied, and states that the fluence rate at the extrapolated boundary (see Eq. (2.29)) is equal to

![Figure 2.6: (a) Geometry for the calculation of $\phi(r, \theta, z)$ for a semi-infinite homogeneous medium. The collimated incident beam (pencil beam) is assumed to create an isotropic light source at depth $z_0$, indicated by the filled circle. The extrapolated boundary condition for $\phi(r, \theta, z = -z_e) = 0$ can be met by adding an image source indicated by the open circle. (b) Geometry for the calculation of $\phi(r, \theta, z)$ for a slab homogeneous medium. The boundary conditions for $\phi(r, \theta, z = 0)$ and $\phi(r, \theta, z = d)$ can be met by adding an infinite series of dipole sources. The first three are shown in this illustration.](image)
zero. This condition can be satisfied using the method of images [12, 21], where a virtual source is placed at a distance \( z_0 \) before the extrapolated plane, i.e., at a distance \( z_e + z_0 \) in front of the physical boundary of the medium. By summing the contributions from both the original source and its image, the solution for the semi-infinite geometry can be obtained:

\[
\phi_1 (r, \theta, z; r', \theta', z' = z_0) = \frac{1}{4\pi D} \left( \frac{\exp(-\mu_{\text{eff}} \rho_1)}{\rho_1} - \frac{\exp(-\mu_{\text{eff}} \rho_2)}{\rho_2} \right),
\]

(2.33)

where \( \rho_1 = \rho_1 |_{z = z_0} \) as defined in Eq. (2.32) and \( \rho_2 \) is the distance from the mirror image source to position \((r, \theta, z)\), i.e.,

\[
\rho_2 = \sqrt{r^2 + r'^2 - 2rr'\cos(\theta - \theta') + (z + z' + 2z_e)^2} \bigg|_{z' = z_0}.
\]

(2.34)

The semi-infinite geometry can be used to model a typical backward-detection problem over a large tissue volume whose dimensions are much larger than the effective attenuation length. The photon distribution in a typical semi-infinite biological sample with \( \mu_a = 0.1 \text{ cm}^{-1} \) and \( \mu_s' = 10 \text{ cm}^{-1} \), is given in Fig. 2.7. A collimated laser beam is incident along \( z \) direction at \( r = 0 \) and is approximated as a point source at \( z = 0.1 \text{ cm}^{-1} \) with unit power (1W). In addition, it is assumed that there is no mismatch in the refractive index (i.e., \( A = 1 \)). In this case, the photon distribution is axially-symmetric and only the photon distribution in the \( rz \) plane is shown. It can be seen that the photon density is exponentially (determined by the effective attenuation coefficient) decreasing along the \( z \) direction and has a Gaussian-like distribution along the \( r \) direction. It should be noted that (1) the above solutions are more accurate far away from the source and the
boundary of the biological sample; and (2) the peak seen in Fig. 2.7 (b) at \( z = 0.1 \text{ cm}^{-1} \) is due to the singularity of Eq. (2.33) at \( z = 0.1 \text{ cm} \).

Figure 2.7: Photon distribution inside a typical semi-infinite biological sample ($\mu_a = 0.1 \text{ cm}^{-1}$, $\mu_s = 100 \text{ cm}^{-1}$ and $g = 0.9$) when a collimated laser beam is incident along $z$ direction at $r = 0$. (a) Photon distribution inside $rz$ plane (log-scale), (b) photon distribution along $z$ at $r = 0$, and (c) photon distribution along $r$ at $z = 3 \text{ cm}$. Note that the solution is only valid far away from the source and the boundary.
2.2.4.3 Slab Geometry

For a slab geometry (see Fig. 2.6(b)), and again using the extrapolated-boundary condition, the fluence rates are equal to zero at two virtual boundaries located at \( z = -z_e \) and \( z = d+z_e \), where \( d \) is the thickness of the slab. At \( z = -z_e \), this condition can be satisfied by introducing a mirror source at \( z = -ze-z_0 \). On the other hand, at \( z = d+z_e \), the zero-fluence rate can be met by adding another dipole source (positioned at \( z = 2d+3z_e \)) which is symmetric to the previous dipole source (positioned at \( z = -z_e \)) along the virtual boundary located at \( z = d+z_e \). However, by doing this, the boundary condition at \( z = -z_e \) is violated. Both the extrapolated-boundary conditions at \( z = -z_e \) and \( z = d+z_e \) can be met only by adding an infinite number of dipole sources [12, 15, 17]. The \( z \) coordinates of the \( ith \) dipole (pairs of original and image sources) can be generalized as [14, 17]:

\[
\begin{align*}
  z_{i,+} &= -z_e + 2i(d + 2z_e) + (z_0 + z_e), \quad \text{for positive sources denoted as filled circles,} \\
  z_{i,-} &= -z_e + 2i(d + 2z_e) - (z_0 + z_e), \quad \text{for negative sources denoted as open circles,}
\end{align*}
\]

where \( i=0, \pm1, \pm2, \ldots \) is the index of the dipoles. The dipoles are numbered in such a way that the \( 0^{th} \) dipole corresponds to the source pair that straddles the front boundary of the slab, the \( 1^{st} \) dipole denotes the image of the \( 0^{th} \) pair about the back extrapolated boundary and the \(-1^{st}\) dipole indicates the image of the first pair about the front extrapolated boundary.

By introducing all of these image sources, the extrapolated-boundary conditions at \( z=-z_e \) and \( z=d+z_e \) can be met, and the solution to the slab geometry for a collimated laser beam can be obtained by adding all the contributions from these image source pairs [17]:
\[
\phi_i(r, \theta, z; \theta', z' = z_0) = \sum_{i=\infty}^{\infty} \left[ \phi_\infty(r, \theta, z; \theta', \theta'_i, z_i) - \phi_\infty(r, \theta, z; \theta', \theta'_i, z_i) \right].
\] (2.35)

Although the number of image sources is infinite, the series may be truncated after the first several source pairs as the higher-order dipoles have less impact on the final solution due to the increasing distance from the slab. In practice, a finite number of source pairs is sufficient for most applications. The solutions to the slab geometry of a biological tissue with a thickness of 1 cm at \(A=1\) are given in Fig. 2.8, where, again, the incident collimated beam is represented as a point source with unit power (1W) at \(z = 0.1\) cm. By comparing the results from the slab geometry (Eq. 2.35) with that from the semi-infinite geometry (the results are also plotted in Fig. 2.8), one can see that the finite thickness of the slab starts to play a role.

Figure 2.8: Photon distribution inside a typical biological slab (\(\mu_a = 0.1 \text{ cm}^{-1}, \mu_s = 100 \text{ cm}^{-1}\) and \(g = 0.9\)) with a thickness of 1 cm when a collimated laser beam is incident along the \(z\) direction at \(r = 0\). (a) Photon distribution inside \(r-z\) plane (log-scale), (b) photon distribution along \(z\) at \(r = 0\), and (c) photon distribution along \(r\) at \(z = 0.5\) cm. For the purpose of comparison, the solutions to the semi-infinite geometry (Eq. 2.33) are also plotted. Note that the photon distribution is axially-symmetric in this case, and three dipole sources are used in this calculation as shown in Fig. 2.6(b).
2.3 The Detection Sensitivity Map

2.3.1 Introduction

A typical AOI setup is shown in Fig. 2.9. Ultrasound is used to locally “tag” (or modulate) the diffuse photons/light, which will then be frequency shifted or phase modulated. As the ultrasound waves propagate into the turbid medium, they create “virtual” sources of tagged photons inside the medium through the acousto-optic interaction as discussed in Chapter 1. These tagged photons will then propagate through the turbid medium to a boundary and are detected. AOI systems typically fall into two categories: forward/transmission detection [22-25] (Scenario 1 in Fig. 2.9) and backward/reflection detection [26, 27] (Scenario 2 in Fig. 2.9). Consider two identical virtual point sources of tagged light with the same strength (imagine the case where one photon at two different locations possess the same phase shift induced by the ultrasound), denoted by VS1 and VS2 in Fig. 2.9. The detection probability (or the measured strength) of these two identical virtual sources by an optical detector, either in the forward detection or in the backward detection, is not expected to be the same. The Green’s function solution of a point source in an infinite medium (see Eq. 2.31), states that the photon density decreases with the distance between the source and the observation point. In addition, the acceptance solid angles formed between the optical detector (with a fixed detection/sensing aperture) and the sources also decrease with the distance. In the transmission configuration (Scenario 1), for example, it is reasonable to expect that the signal detected from VS2 will be stronger than that from VS1, although both of the sources have the same strength.
AOI typically involves the spatial scanning of the ultrasound beam (either electronically or mechanically), and this means that if the transducer is moved from Position 1 to Position 2, a stronger signal could be detected even though the photon density inside the diffuse sample was uniformly distributed (which is typically not the case, as we know from the previous section). This “artifact” is a consequence of the experimental geometry, i.e., the relative positions of the detector and the virtual sources.

For a given setup in which the laser beam and the optical detector are fixed in space, we refer to the relationship between the likelihood of detecting light from a given virtual source and its spatial location as the “Detection Sensitivity Map”. In order to extract quantitative physical parameters from the measured acousto-optic signals, the problem of the detection sensitivity map should be studied. In addition, an understanding of this problem could lead to a possible optimization of the experimental configurations in AOI.
2.3.2 General Formulation of the Problem

Consider diffuse photons inside a turbid medium that are tagged by ultrasound at some position \( \hat{r}_s \) as illustrated in Fig. 2.10. The tagged photons are assumed to emanate from a point source of light with unit strength. The measured strength of this point source depends on the sensing aperture \( A_d \) and position \( \hat{r}_d \) of the optical detector. The optical detector is a device that measures the photon flux or optical power (the number of photons reaching the surface of the detector per unit time) [1]. The photon flux at the surface of the diffuse sample can be calculated from Fick’s law (see Eq. 22):

\[
\phi \nabla - D \frac{\partial \phi}{\partial r} = J_s(\hat{r}_s) \text{ for } \hat{r}_s \text{ at the boundary } \Sigma.
\]

(2.36)

where \( \phi \) is the fluence rate, subject to the DE and its corresponding boundary conditions, as discussed above. If the optical detector is placed close to or on the sample boundary \( \Sigma \), then the measured strength \( M_s \) of this unit virtual point source from the optical detector will be:

\[
M_s(\hat{r}_d; \hat{r}_s) = C_0 \int_{A_d} [-\hat{n}_d \cdot J(\hat{r}; \hat{r}_s)] \bigg|_{\hat{r}=\hat{r}_d} dA_d,
\]

(2.37)

where \( C_0 \) is related to the conversion efficiency of the detector and is a constant for a given optical detector, \( \hat{n}_d \) is a unit vector normal to the surface of the detector pointing outward, and the whole integration is performed over the surface of the detector.

The above formulation has been used extensively to describe the transmittance and reflectance of light in optically diffuse media [14, 15, 17]. It has also been

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6 The vector of the photon flux can be decomposed into two components: one is normal to the surface of the optical detector and the other is in parallel with the surface. Only the component of the photon flux normal to the surface of the optical detector will be sensed.
demonstrated in the literature that the diffusion approximation shows good agreement with experimental measurements and Monte Carlo simulation [12, 14]. It is therefore reasonable to assume that the diffusion approximation will be useful in investigating the light distribution and detection sensitivity map in AOI, although ultimately the diffusion-approximation results should be compared to experimental measurements and Monte Carlo simulation for validation.

2.3.3 Detection Sensitivity Map for Certain Geometries

Generally speaking, for a complex geometry, the detection sensitivity map described by Eq. (2.37) is difficult to obtain. However, for semi-infinite and slab geometries, relatively simple solutions could be found. These solutions are interesting because these experimental geometries are often used in AOI.

2.3.3.1 Semi-infinite Geometry

In a cylindrical coordinate system, consider an optical detector located at \((r = 0, \theta, z = 0)\) for the semi-infinite geometry shown in Fig. 2.6(a). It is assumed that the flat sensing
surface of the optical detector is normal to the z axis, i.e., \( \hat{n}_d = \hat{z} \). The spatial distribution of the fluence rate for a point source located at \( \hat{r}_s = (r_s, \theta_s, z_s) \) has been given in Eq. (2.33). Based on this, Eq. (2.37) becomes:

\[
M_s(\hat{r}_d; \hat{r}_s) = C_0 \int_{A_d} D \frac{\partial \phi}{\partial z} \bigg|_{z=0, r=0} dA_d
\]

\[
= C_0 \int_{A_d} \left[ R_\infty(r, \theta, z = 0; r_s, \theta_s, z_s) - R_\infty(r, \theta, z = 0; r_s, \theta_s, -z_s - 2z_c) \right] \bigg|_{r=0} dA_d
\]

in which \( R_\infty \) is given by [17]:

\[
R_\infty(r, \theta, z = 0; r', \theta', z') = D \frac{\partial \phi_{\infty}}{\partial z} \bigg|_{z=0} = \frac{z'(1 + \mu_{\text{eff}} \rho) \exp(-\mu_{\text{eff}} \rho)}{4\pi \rho^3},
\]

where

\[
\rho = \rho(r, \theta, z; r', \theta', z') = \sqrt{r^2 + r'^2 - 2rr' \cos(\theta - \theta') + (z + z' + 2z_c)^2}.
\]

### 2.3.3.1.1 Point Detector

If the detector size is small, then the variation of the integrand in Eq. (2.38) is negligible and the integrand itself can be treated as a constant over the detector sensing aperture. This approximation is reasonable, for example, if a single mode optical fiber is utilized to collect the scattered light. In this case, Eq. (2.38) simplifies to:

\[
M_s(\hat{r}_d; \hat{r}_s) = C_0 A_d \left[ R_\infty(r, \theta, z = 0; r_s, \theta_s, z_s) - R_\infty(r, \theta, z = 0; r_s, \theta_s, -z_s - 2z_c) \right]_{r=0}
\]

\[
= \frac{z_s(1 + \mu_{\text{eff}} \rho_1) \exp(-\mu_{\text{eff}} \rho_1)}{4\pi \rho_1^3} - \frac{(z_s + 2z_c)(1 + \mu_{\text{eff}} \rho_2) \exp(-\mu_{\text{eff}} \rho_2)}{4\pi \rho_2^3}
\]

where \( \rho_1 = \sqrt{r_s^2 + z_s^2} \) and \( \rho_2 = \sqrt{r_s^2 + (z_s + 2z_c)^2} \).

The detection sensitivity of the virtual sources generated at different locations and detected by a point detector at \( r = 0, z = 0 \) is plotted in Fig. 2.11 for a typical biological
sample with \( \mu_a = 0.1 \text{ cm}^{-1} \) and \( \mu_s' = 10 \text{ cm}^{-1} \). The farther away the tagged photons are generated from the point detector, the less chance there is for these photons to be detected. This leads to a weaker detected signal, which is in agreement with our initial prediction. The solution given here is different from the fluence-rate calculation shown in Fig. 2.7, although they do look similar\(^7\). Figure 2.7 shows how the photon density is spatially distributed for a given incident laser beam, while Fig. 2.11 is independent on where the laser beam is located and strongly depends on where the detector is located. For instance, if the optical detector is moved to another different \( r \) location at \( z = 0 \), the origin of the plot shown in Fig. 2.11(a) will shift along with the optical detector.

### 2.3.3.1.2 Finite-Aperture Detector

When the detector has a finite aperture, the equation for the sensitivity map has to be integrated over the aperture of the detector. Here we consider the detection sensitivity map along \( z \) axis for an optical detector which has a disk surface sensing area with a radius of \( a \), with the center of the disk located at \( r = 0 \) and \( z = 0 \). This makes the problem axially symmetric and the above integration can be written as:

\[
M_s(\vec{r}_d; \vec{r}_s) = C_0 \int_0^t \left[ \frac{z_s (1 + \mu_{\text{eff}} \rho_1) \exp(-\mu_{\text{eff}} \rho_1)}{4\pi \rho_1^3} + \frac{(z_s + 2z_e)(1 + \mu_{\text{eff}} \rho_2) \exp(-\mu_{\text{eff}} \rho_2)}{4\pi \rho_2^3} \right] 2\pi r dr
\]

(2.43)

where \( \rho_1 = \sqrt{r^2 + z_s^2} \) and \( \rho_2 = \sqrt{r^2 + (z_s + 2z_e)^2} \).

\(^7\) Mathematically, this similarity can be understood by the following simple 1-D analysis: For a 1-D Green’s function solution (see Eq. 2.31—the fluence-rate in an infinite medium) is given by \( e^{-\mu_{\text{eff}} x} / x \). The spatial derivative (see Eq. 2.37 for the detection sensitivity) of this function is equal to \( (e^{-\mu_{\text{eff}} x} / x)(-\mu_{\text{eff}} - 1/x) \), which is directly related to the Green’s function itself. In particular, in the far field where \( \mu_{\text{eff}} \gg 1/x \), the spatial derivative (or the detection sensitivity) is proportional to the fluence rate.
Figure 2.11: For a point detector located at \((r = 0, \theta = 0, z = 0)\), the normalized detection sensitivity of the virtual sources generated at different \(r\) and \(z\) locations for a semi-infinite geometry (a) log-scale \(r\)-\(z\)-plane sensitivity map, (b) the detection sensitivity along \(z\) and (c) the detection sensitivity along \(r\) at \(z = 1.5\) cm.
Equation (2.43) is numerically integrated and the sensitivity map along the \( z \) axis is plotted in Fig. 2.12 for several different detection apertures. The calculation is performed for a sample with \( \mu_a = 0.1 \text{ cm}^{-1} \) and \( \mu_s' = 10 \text{ cm}^{-1} \). The detection probability of the virtual sources generated along the \( z \) axis is decreasing with the distance from the detector for all detection aperture sizes. However, the slope of the curve is a function of aperture size. Larger apertures have a slower decay with depth and thus allow for a higher probability of detecting a photon emitted from deep inside the sample. This behavior can be partly explained by the larger solid angle formed between the source and the finite aperture. As the aperture size is reduced, the solution approaches that given for the point detector. Figure 2.13 plots how the sensitivity map changes with the absorption coefficient (or the effective attenuation coefficient) of the sample. As expected, higher absorption of the sample leads to a lower detection probability of the virtual sources emitted at the same \( z \) location, thus limiting the imaging depth. It can also be seen that
the slopes of the curves along the $z$ axis decrease with the effective attenuation coefficient, which can be explained by the term $\exp(-\mu_{\text{eff}} \rho)$ in Eq. (2.43).

2.3.3.2 Slab Geometry

The other geometry of interest for AOI applications is the slab geometry. In the cylindrical coordinate system, consider an optical detector located at $(r = 0, \theta, z = 0)$ for a slab geometry as shown in Fig. 2.6(b). Again, it is assumed that the flat surface of the optical detector is perpendicular to the $z$ axis, i.e., $\hat{n}_d = \pm \hat{z}$. The spatial distribution of the fluence rate for a point source located at $\vec{r}_s = (r_s, \theta_s, z_s)$ has been given in Eq. (2.35). Based on this, Eq. (2.37) can be solved, yielding:
\begin{align*}
M_s (\vec{r}_d ; \vec{r}_s) &= C_0 \int_{A_d} \frac{\partial \phi}{\partial z} \bigg|_{z=0, r=0} dA_d \\
&= C_0 \sum_{i=-\infty}^{\infty} [R_\infty (r, \theta_\infty, z = 0; r_s, \theta_s, z_{i_\infty}) - R_\infty (r, \theta, z = 0; r_s, \theta_s, z_{i_\infty})] \bigg|_{r=0} dA_d
\end{align*}

(2.44)

where $R_\infty$ and $z_{i_d}$ are defined as above.

### 2.3.3.2.1 Point Detector

For a point detector, as discussed in 2.3.3.1.1, Eq. (2.44) can be simplified to:

\begin{align*}
M_s (\vec{r}_d ; \vec{r}_s) &= C_0 \sum_{i=-\infty}^{\infty} [R_\infty (r, \theta_\infty, z = 0; r_s, \theta_s, z_{i_\infty}) - R_\infty (r, \theta, z = 0; r_s, \theta_s, z_{i_\infty})] \bigg|_{z=0} .
\end{align*}

(2.45)

For a biological sample ($\mu_a = 0.1 \text{ cm}^{-1}$ and $\mu_s' = 10 \text{ cm}^{-1}$) with a thickness of 1 cm, Eq. (2.45) is numerically calculated and the results are shown in Fig. 2.14, where three pairs of dipoles ($i = -1, 0, +1$) have been used.

It is important to point out that the detection sensitivity map could play different roles in the forward and backward detection modes (see Fig. 2.15). From Section 2.2, we know that the photon density decreases with the distance away from the optical source. This decrease is balanced by the increase in detection sensitivity towards the optical detector in the forward detection mode (assuming that the optical source and detector are co-axial as shown in Fig. 2.15). While in the backward detection mode, this decrease could be amplified by the decrease in detection sensitivity away from the detector. In AOI, both the detection sensitivity map and the photon distribution affect the AO signals detected at different locations.
Figure 2.14: For a point detector located at \((r, \theta, z) = (0, 0, 0)\), the normalized detection sensitivity of the virtual sources generated at different \(r\) and \(z\) locations for a slab geometry with a thickness of 1 cm: (a) log-scale \(rz\)-plane sensitivity map, (b) the detection sensitivity changing along \(z\), (c) the detection sensitivity changing along \(r\) at \(z = 0.5\) cm.
Figure 2.15 shows a product (multiplication) of the detection sensitivity map (see Fig. 2.14) and the photon distribution (see Fig. 2.8) for a typical biological sample ($\mu_a = 0.1 \text{ cm}^{-1}$ and $\mu_s' = 10 \text{ cm}^{-1}$) with a thickness of 1 cm. Figure 2.15(a) corresponds to the backward detection and Fig. 2.15(b) corresponds to the forward detection. In both cases, the collimated laser beam is incident from the top of the sample at $r = 0$, and the optical point detector is co-axial with the laser beam. As expected, the results show that the combination of the photon density and the detection sensitivity map in the forward detection leads to a relatively uniform AO signal strength distribution along the $z$ axis. In contrast, in the backward detection mode, the AO signal strength along the $z$ axis dramatically decreases deep inside the biological sample, making it difficult to image at larger depths.

2.3.3.2.2 Finite-Aperture Detector
In this case we consider the detection sensitivity map along the \( z \) axis for an optical detector with a flat circular sensing area of radius \( a \), with the center of the disk-like sensor located at \( r = 0 \) and \( z = 0 \). The problem is axially symmetric and the above integration can be written as:

\[
M_z(\bar{r}_d; \bar{r}_s) = C_0 \int_0^a \sum_{l=-\infty}^{\infty} \left[ R_\infty(r, \theta, z = 0; r_s, \theta_s, z_{l,+}) - R_\infty(r, \theta, z = 0; r_s, \theta_s, z_{l,-}) \right] \bigg|_{r=0} 2\pi r dr
\]

(2.46)

where \( \rho_1 = \sqrt{r^2 + z_s^2} \) and \( \rho_2 = \sqrt{r^2 + (z_s + 2z_e)^2} \).

Equation (2.46) is numerically integrated and the sensitivity map along the \( z \) axis is plotted (Fig. 2.16) for several different detection apertures. It is noted that the detection probability of a tagged photon originating from a given \( z \) location does not increase linearly with the aperture size. For instance, at \( z = 0.5 \), as the detector’s radius increases from 0.1 cm to 0.5 cm, the detection probability of the virtual source is increased by a factor of \( \sim 10 \). In contrast, the same increase ratio in the detection aperture size (from 1 cm to 5 cm) only leads to an increase in the detection probability by a factor of \( \sim 0.1 \). This can be explained by the fact that the virtual source is located along the detector axis and the contribution far away from its axis is negligible at the sample surface.

Figure 2.17 plots the sensitivity map as a function of the absorption coefficient (or the effective attenuation coefficient) of the sample. The results shown here for the slab geometry are qualitatively similar to that for a semi-infinite geometry (see Fig. 2.12 and Fig. 13). The presence of the second boundary, however, modifies the sensitivity map in the vicinity of the boundary.
Figure 2.16: The detection sensitivity map along the $z$ axis for a finite-aperture detector located at $r = 0$ and $z = 0$ in the slab geometry with a thickness of 1 cm (see Fig. 2.6(b)). For a typical biological sample with $\mu_a = 0.1$ cm$^{-1}$ and $\mu_s' = 10$ cm$^{-1}$, the detection sensitivity maps changes with the size of the detection aperture.

Figure 2.17: The detection sensitivity map along the $z$ axis for a finite-aperture detector located at $r = 0$ and $z = 0$ in the slab geometry (see Fig. 2.6(b)). For a given detector with a radius of 1 cm, the detection sensitivity maps changes with the absorption coefficient provided the reduced scattering coefficient of the sample is kept constant at 10 cm$^{-1}$. 

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2.3.4 Discussion of the Results

What we have learned from the study of the detection sensitivity map can be summarized as follows:

(1) The positions of the source and the receiver need to be considered in an AOI system. The position of the source determines the initial photon distribution, and thus determines how many photons are available for the local ultrasound tagging. The sensitivity map, on the other hand, determines how these photons are detected. It is then necessary to scale AO signals by these factors to ensure that the amplitude of the AO signals gives a proper measure of AO interaction, from which the local opto-mechanical properties can be properly interpreted/extracted.

(2) The size of the detection aperture is important. Large detection apertures allow for a high probability of detecting ultrasound-tagged photons, and thus lead to larger $SNR$. This suggests that an optical detector with larger apertures is helpful in potentially improving the $SNR$ by collecting photons emitted from a large area of the sample surface. However, it should be noted that the larger the detector aperture is, the larger the amount of noise (from, say, the background untagged photons). Therefore, in practice, the choice of detector aperture dimensions might constitute a trade-off.

(3) Consideration of the interplay between the photon distribution and the detection sensitivity map reveals a potential limitation to the backward detection configuration. In this case, the AO signal amplitude decreases very rapidly with distance between the detector and source locations (see Fig. 2.15), therefore limiting the imaging depth.
(4) Finally, it is important to recognize that the detection sensitivity map is not the only factor that determines the $SNR$ in an AOI system. Another important factor is the ratio of the flux of modulated/tagged photons to background photons. Indeed, depending on where one chooses to position the detector, the $SNR$ could be dominated by the flux background (untagged) photons incident on the detector. This could be the case, say, when the sensor is positioned near the laser source.
References:


Chapter 3

Experimental Design and Setup

3.0 Overview

The photorefractive-crystal (PRC) based interferometry system developed for the detection of ultrasound-modulated optical signals is described in this Chapter. In order to appreciate the experimental approach, a brief introduction to the challenges associated with detecting AO signals is provided in Section 3.1. Section 3.2 describes the design of the PRC-based interferometer for AO sensing, including some basic background information on the photorefractive effect. Following that, the overall experimental setup is described in detail in Section 3.3, along with a description of the test samples used in our AOI experiments. These samples include both tissue-mimicking phantoms and \textit{ex vivo} biological tissues.
3.1 Technical Challenges Associated with AO Signal Detection

In AOI, as explained in Chapter 1, a focused acoustic field interacts with multiply-scattered laser light in turbid media. The acoustic field causes a phase modulation in the optical field emanating from the interaction region, and the phase-modulated optical field carries with it information about the local optical and mechanical properties of the media. The implementation of AOI relies on the detection of this phase-modulated optical signal, that is, the ultrasound-tagged photons.

Despite years of effort, low sensitivity continues to be the major technical barrier to effective AOI. The detection difficulty mainly arises from the statistical nature of the output field—speckle, formed by coherent laser light after passing through a turbid medium. As a result, the output field of the scattered/diffuse light has a very complex wave-front associated with the speckle pattern, in which the ultrasound-modulated optical signals are embedded (see Fig. 3.1).

![Figure 3.1: Schematic illustration of the AOI configuration and two possible detection apertures.](image)
Heterodyning schemes are typically suitable for the detection of the phase-modulated optical signals [1-3]. A traditional heterodyning detection system employs a coherent optical field possessing stable phase, called the local oscillator (LO). By mixing the phase-modulated optical field (i.e., the signal beam) with the LO, one can convert the phase modulation to an intensity modulation, which can be directly measured by a photodetector. In a common realization of a heterodyning AO sensing system, the portion of the diffuse light that passes through the column of the ultrasound beam is phase modulated and acts as the signal beam, while the remaining coherent light that does not traverse the ultrasound beam remains un-modulated and functions as the LO (the reference beam). This simplest heterodyning scheme in AOI employs a single optical detector and constitutes the first generation of AOI detection systems [4-6].

Although a single optical detector for AO sensing, as mentioned above, can be easily implemented, certain detection challenges have been identified [4, 7, 8]. To illustrate these challenges, consider the following simple analysis. At the surface of a single optical detector, different photons or “light rays” that traverse different path lengths through the turbid medium will interfere with each other and thus form a speckle pattern. In the case of the AOI experiments, the speckle pattern contains the ultrasound-modulated optical information, and can be “discretized” into many speckle grains (small bright or dark areas/patches). The intensity of one speckle grain, numbered as $i$, can be written as the sum of two terms—a background intensity $I_{0i}$ and a modulated intensity at the ultrasound frequency $\omega$, characterized by the modulation depth $m_i$, as follows:

$$I_i = I_{0i} + m_i I_{0i} \cos(\omega t + \alpha_i),$$

(3.1)
in which $\alpha_i$ is the corresponding phase associated with this speckle grain. In a thick, highly diffuse medium where the typical photon path length is much larger than the acoustic wavelength\(^1\), $\alpha_i$ is expected to be randomly distributed between 0 and $2\pi$ from one speckle grain to the next—the speckle field is spatially decorrelated. This expectation is validated by experimental measurements [7]. When the detection aperture of the single optical detector is limited to a single speckle grain, an extremely low light level is present at the detector and the signal-to-noise ratio ($SNR$) is poor. On the other hand, if multiple speckle grains are gathered, the signal detected at the photodetector is a result of a summation over all the collected speckle grains. The random phase of each individual speckle grain leads to an incoherent summation over multiple speckles, and the ultrasound-modulated component of the signal cancels out. The end result is a very small modulation depth (inversely proportional to the square root of the collected number of speckle grains [4]) and the $SNR$ problem persists.

In order to overcome the limitations of single optical detector techniques, Leveque et al. [7] presented a new approach to detect the ultrasound-modulated optical signals in parallel using a CCD array. In their technique, the size of a speckle grain is adjusted to approximately match the size of a single element of the CCD array. The beauty of the parallel detection scheme is that it can independently measure the phase $\alpha_i$ and amplitude $m_i I_{o_i}$ of each individual speckle grain. By summing the (measured)

\[^1\text{For instance, across a 3-cm thick biological tissue sample with } \mu_s' = 10 \text{ cm}^{-1}, \text{ the averaged photon path length is on the order of 30 cm. While for a MHz ultrasound transducer, the acoustic wavelength is only on the order of mm.}\]
individual modulation amplitudes $m_i I_{0i}$ (discarding the phase information) from all of the pixels, the $SNR$ can be improved by a factor of $\sqrt{N}$, where $N$ is the total number of speckle grains collected. However, this parallel detection scheme employs continuous-wave (CW) ultrasound, which gives very limited axial resolution and is not compatible with conventional diagnostic ultrasound.

Bearing in mind these technological challenges, we propose in this work a new detection scheme—the PRC-based interferometer—for the detection of ultrasound-modulated optical signals. Thanks to the dynamic holographic nature of the PRC-based interferometry system, it can compensate for the complex wave-front of the output diffuse light field, which prevents the conventional signal-detector techniques from doing the coherent summation as discussed above. The PRC-based interferometry system and its particular application to AOI will be described in detail in the following section.

3.2 The PRC-Based Interferometry System for AOI

In order to better understand the PRC-based interferometer, some basic background about the photorefractive effect is given in Section 3.2.1. Following that, Section 3.2.2 details the operating principle of a conventional PRC-based interferometer, and Section 3.2.3 explains how it helps to detect the ultrasound-modulated optical signals in the particular case of AOI.

3.2.1 The Photorefractive Crystal

The photorefractive crystal (PRC) is material in which the index of refraction varies according to the spatial distribution of the incident light intensity. The PRC exhibits both
photoconductive and electro-optic behavior [1, 9, 10]. Photo-induced charges create a space-charge distribution that produces an internal electric field, which, in turn, alters the refractive index by means of the electro-optic effect\(^2\). To further understand the physical basis of the photorefractive behavior, a brief description of the photorefractive process is given in this section, where a simple case of two plane waves interfering inside the crystal is considered\(^3\).

\(\text{Incident Waves} \)

\[ \text{Incident Light Intensity} \]

\[ \text{Free-carriers (Electrons)} \]

\[ \text{Generation and Diffusion} \]

\[ \text{Free-carriers (Electrons)} \]

\[ \text{Trapping} \]

\[ \text{Electrical Field} \]

\[ \text{Refractive Index Grating} \]

Figure 3.2: The processes that mediate the photorefractive effect in which the spatial distribution of incident light intensity alters the index of refraction of the crystal. Slightly modified from [1].

\(^2\) The electro-optic effect is defined as the change in the dielectric constant (or refractive index) of a material in response to an applied electric field. This effect can be grouped into two classes: Pockels effect (linear electro-optic effect) and Kerr effect (quadratic electro-optic effect) [1]. The crystal used in this work falls into the category of linear electro-optic (Pockels) effect.

\(^3\) Since the study of the photorefractive effect itself is a vast field, only the basic background information is given here. Readers who want to learn more about this subject are referred to [1, 9-11].
When two plane waves mix inside the PRC (see Fig. 3.2), a sinusoidal intensity pattern is produced as a result of light interference. Light is absorbed inside the crystal and free carriers (electrons or holes) are generated in the bright regions of the intensity pattern. These carriers diffuse and/or drift from the bright regions\(^4\), leaving fixed charges behind. The carriers are trapped at deep levels in the dark regions resulting in a non-uniform (periodic) space-charge distribution. The periodic space-charge field alters the refractive index of the crystal through the electro-optic effect and forms a refractive-index grating inside the crystal. The processes described above are schematically shown in Fig. 3.2. The key point here is that the periodic intensity pattern leads to a periodic space charge distribution and finally to a periodic refractive index distribution inside the photorefractive crystal.

A simplified 1-D steady-state expression for the position-dependent change of the refractive index as a function of the light intensity \(I(x)\), in the absence of the application of an external electric field can be written as \([1]\):

\[
\Delta n(x) = -\frac{1}{2} n_0^3 r \frac{k_B T}{e} \frac{1}{I(x)} \frac{dI}{dx}, (3.2)
\]

where \(n_0\) is the nominal refractive index of the crystal, \(r\) is the Pockels coefficient or linear electro-optic coefficient, \(k_B\) is Boltzmann’s constant, \(T\) is the temperature and \(e\) is the electron charge. From Eq. (3.2), it can be readily seen that (1) the change in the photorefractive index of the PRC is proportional to both the spatial intensity gradient and

\(^4\) This process can be enhanced by the application of an external electric field, which will enhance the formation of the photorefractive grating. Without the application of the external field the movement of electrons is assisted only by diffusion and that state of electrons is called diffusion regime, whereas the state of electrons where they are forced to drift using an external field is called drift regime \([11]\).
the linear electro-optic coefficient; and (2) the photorefractive grating will be spatially shifted by a quarter “wavelength” with respect to the space intensity distribution, due to the spatial derivative of the intensity in Eq. (3.2). This spatial shift of a quarter wavelength is important (more specifically, optimal) to the so-called two-wave mixing (TWM) process, where the two incident beams travel together in the PRC and exchange energy via reflection from the created grating [11, 12].

Although the plane-wave model presented above is simplified, it reflects the essential behavior of photorefractive materials. Its relevance can be appreciated by noting that any arbitrary wave-front can be treated as a superposition of plane waves. Therefore, it can be deduced that if either of the incident beams has an arbitrary/complex wave-front, a complicated spatial intensity pattern will be formed inside the PRC and a complex refractive index distribution will be subsequently created. Regardless of the complexity of the incident wave-front, the photorefractive grating formed inside the crystal “stores” both the structural and amplitude information of the incident beam. In this sense, the PRC behaves as a hologram\(^5\) [1]. The stored information in the form of the change of the refractive index inside the crystal can be “read out” (or reconstructed) by diffracting a third beam or the incident beam itself, depending on the polarization of the writing beams, crystal orientation, and spatial phase of the grating [11].

Many applications have been developed based on the unique features of the PRC, including coherent signal detection (i.e., adaptive interferometers), optical image

\(^5\) A traditional hologram is a thin transparency on which the interference pattern between the original wave and a reference wave is recorded. Due to the finite thickness, strictly speaking, the PRC acts as a volume hologram [1].
processing, real-time holography, and others [1, 9-11]. In this work, we are particularly motivated by the PRC-based interferometer, which can compensate for the complex wave-front of the incident signal beam, the main impediment to AO signal detection as discussed previously. The following section will describe the principles of the PRC-based interferometer.

3.2.2 Operating Principle of Conventional PRC-based Interferometers

![Diagram of PRC-based interferometer](image)

Figure 3.3: Depiction of the operating principle of a PRC-based interferometer.

PRC-based interferometers have seen widespread use in the optical detection of ultrasound in nondestructive evaluation and materials characterization applications [13-15]. These systems are ideally suited for detecting high frequency vibrations from optically rough surfaces, which typically result in signal beams with complex wavefronts. In such a system (see Fig. 3.3), an incident laser beam is reflected off of the target material acquiring a phase modulation in the presence of motion. The scattered signal
beam is then sent to the PRC where it is mixed with a reference beam (or pump beam) which is derived from the same incident illumination beam (using a beam splitter). As described in Section 3.2.1, an interference pattern is formed in the crystal exciting free carriers in the bright regions, which drift or diffuse to the dark regions leading to a space charge field formation. The index of refraction is modulated through the electro-optic effect, and the reference beam is diffracted off of this grating into the signal beam direction in the two-wave mixing (TWM) process. An external electric field\(^6\) can be applied to the crystal, which serves to enhance the TWM gain and hence the detection sensitivity [11, 16]. The diffracted reference beam’s phase (wave) front replicates that of the signal beam, providing a local oscillator (LO).

When the signal and reference beams are continuously on, the writing of the index grating in the PRC and the subsequent reconstruction are done simultaneously, yielding a transmitted signal beam and diffracted reference beam propagating in the same direction. The index grating adapts itself to low frequency variations of the signal beam, which it passes on to the reference beam. On the other hand, high frequency perturbations in the signal beam (from, say, ultrasound induced phase modulation) are not written into the grating because the PRC cannot respond rapidly enough. The diffracted reference beam (static LO) and the transmitted (dynamically changing) signal beam interfere at the photodetector where any dynamic phase modulation encoded on the signal beam is converted to an intensity modulation. It should be emphasized that the PRC is adaptive in

\(^6\) Two types of electric field can be applied: AC field and DC field. Both of the electric fields can help to increase the magnitude of the space charge field in the photorefractive processes as described in Section 3.2.1, and thus to enhance the TWM gain. The detailed discussion about this subject can be found in the literature [11, 16, 17].
that the index grating is continually “rewritten” on the time scale of the PRC response time, while high frequency modulation produced by the ultrasonic source is not compensated for, producing a relative phase shift between the signal and reference beams and an intensity change at the detector. The PRC response time represents the time required for space charge field to form, and it is controlled by both the material parameters of the PRC and the intensity of the incident beams [11]. For a given crystal, the response time typically varies inversely with the power density incident on the crystal. The ability to adapt to low frequency disturbances is key to the application of AOI in vivo, for we expect that physiological motions and environmental vibrations could induce phase shifts in the signal beam that are significantly greater than those produced by the ultrasound beam itself. Indeed, speckle de-correlation is currently one of the main challenges in the field of AOI.

Figure 3.4: The output intensity of an interferometer as a function of path-length (phase) difference between the signal beam and the reference beam.
Although the operation principle of the PRC-based interferometer described above seems complicated, the idea behind it is straightforward. Simply put, the PRC-based interferometry scheme is similar to classical interferometers (e.g., Michelson’s interferometer [1, 2, 18]) with the main difference being that the reference beam matches with the complex wave-front of the signal beam, a fact that allows for coherent signal detection. When implementing optical interferometers for the detection of ultrasound (described in detail elsewhere [2, 3]), the detection sensitivity of the interferometer depends strongly on the phase (path-length) difference between the signal beam and the reference beam (see Fig. 3.4). In the linear detection of small amplitude signals, photorefractive interferometers are typically designed such that the diffracted reference beam and transmitted signal beam are placed in quadrature. This scenario corresponds to point A in Fig. 3.4, where the slope of the curve is maximum so that it is most sensitive to the small phase variation in the optical signal beam induced by ultrasound. Moreover, at this point (in quadrature) the relationship between relative intensity change and phase shift is approximately linear.

### 3.2.3 PRC-based Interferometer for the Detection of AO Signals

The concept of the conventional PRC-based interferometer discussed above cannot be directly applied to the detection of ultrasound-modulated optical signals in AOI. This is due to the fact that the application of a conventional PRC-based interferometer to the detection of high-frequency out-of-plane surface displacements pre-assumes that the local rough surface will move uniformly (i.e., there is no, or negligible, relative displacement among the points on the rough surface). In these cases, the shape of the phase front of the
signal beam is constant over the time, which is clearly not the case in AO sensing as discussed in Section 3.1. In AOI, the complex wave-front of the collected diffuse light field is spatially modulated/perturbed, somewhat randomly, by the ultrasound beam, which prevents the ultrasound-modulated optical signals from being coherently detected. Although the PRC-based interferometer can provide a wave-front-matched LO, it has to be modified for use in an AO sensing system. In order to do that, we need to re-analyze the operation of the conventional PRC based interferometer by taking into account the new circumstances imposed by AOI.

Here we again consider the simple case of two plane waves interfering within a photorefractive crystal as illustrated in Fig. 3.5. The signal beam intensity is represented by $I_{SO}$ at the entrance to the PRC and $I_{SE}$ at the exit of a PRC with length $L$. The signal beam is phase modulated through an interaction with a pulsed ultrasound beam\(^7\), where the phase modulation has the form:

$$\phi = \phi_a f(t) \sin(\omega_a t + \chi_r). \quad (3.3)$$

Here $\phi_a$ and $\omega_a$ are the amplitude and the angular frequency of the phase modulation, respectively, $f(t)$ is the normalized envelope of the phase modulation (corresponding to the envelope of the ultrasonic tone burst in this plane-wave case), and $\chi_r$ is a constant that depends on the optical path. It is assumed that the signal beam is phase modulated at a frequency sufficiently high so that the PRC response time is long with respect to the oscillation period. Furthermore, it is assumed that the length of the ultrasonic tone burst,

\(^7\) Pulsed ultrasound is considered here due to the fact that part of the goal of this work is to develop a pulsed ultrasound based AOI system, which allows for enhanced axial resolution (over CW ultrasound based AOI).
as defined by the envelope function \( f(t) \), is also short with respect to the crystal response time such that the index grating remains static over the measurement period. In our experiments, the response time of the \( \text{Bi}_{12}\text{SiO}_{20} \) (BSO) PRC is measured to be approximately 150 ms, the acoustic period is 1 \( \mu \)s, and the duration of the acoustic pulse is typically less than 10 \( \mu \)s; these conditions support the assumptions listed above.

The signal beam is amplified as it propagates through the crystal with a TWM gain of \( \gamma \) as the reference beam is diffracted into the signal beam direction, as discussed above. The diffracted reference beam has the same phase front as the transmitted signal beam, but does not acquire the high frequency phase modulation. Note that the gain coefficient is complex and that the diffracted reference beam may be uniformly shifted in phase with respect to the signal beam. The gain coefficient is given by \( \gamma = \gamma' + i\gamma'' \), where \( \gamma' \) is the real part of the gain and \( \gamma'' \) is the imaginary part. The optical absorption coefficient in the crystal is given by \( \alpha \). In the undepleted pump approximation where the intensity of the reference beam, denoted by \( I_R \) in Fig. 3.5, is large compared to that of the
signal beam, the intensity of the transmitted signal beam at the exit of the crystal, \( I_{SE} \), is given by [19]:

\[
I_{SE} = \exp(-\alpha L) I_{SO} \left\{ e^{\gamma L} - 1 \right\}^2 + 1 + 2 \Re[(e^{\gamma L} - 1) * \exp(i \phi_a f(t) \sin(\omega_a t + \chi))] \right\} . \quad (3.4)
\]

Expanding Equation (3.4) using a Bessel series expansion and retaining only the lowest order terms we find:

\[
I_{SE}^{AC} = 4 \exp(-\alpha L) I_{SO} e^{\gamma L} \sin(\gamma L) J_1(\phi_a f(t)) \sin(\omega_a t + \chi) \quad (3.5)
\]

and

\[
I_{SE}^{DC} = \exp(-\alpha L) I_{SO} \left\{ e^{\gamma L} - 1 \right\}^2 + 1 + 2(e^{\gamma L} \cos(\gamma L) - 1) J_0(\phi_a f(t)) \right\} . \quad (3.6)
\]

Equation (3.5) gives the intensity of the signal beam modulation at the ultrasound frequency, \( \omega_a \). Equation (3.6) shows that, in addition to the modulation at the ultrasound frequency, a “DC-shifted” signal is expected which depends only on the amplitude of the phase modulation and the envelope of the ultrasound pulse train. The resulting signal at the detector, found by summing Eq. (3.5) and Eq. (3.6), is a sinusoidal pulse train of duration \( f(t) \) riding on top of a DC offset.

Now consider the case of an ultrasonic pulse propagating in optically diffuse media. Photons travel over multiple paths from the optical source to the detection system, and the phase modulation induced by the ultrasound depends on the spatial location where the acousto-optic interaction takes place. This is taken into account in Eq. (3.3) through the variable \( \chi_r \), which is path dependent. At a given instant (in time), viable photon paths encompass a region with characteristic dimensions larger than an acoustic wavelength. Thus, when collecting light from multiple optical paths in highly diffuse
media, as mentioned above, $\chi_r$ are expected to be distributed randomly between 0 and $2\pi$ and the signals observed at the ultrasonic frequency (given by Eq. (3.5)) from light traveling over different paths do not add coherently at the detector and can cancel each other out. The signals given by Eq. (3.6), however, are independent of optical path, and depend only on the amplitude of the phase modulation and the envelope function. This allows for coherent summation of individual photon contributions at the detector. The signals given by Eqs. (3.5) and (3.6) are strongly dependent on the photorefractive gain. The modulus of $\gamma$ represents the strength of the diffraction grating inside the crystal and the phase of $\gamma$ is associated with the spatial phase shift between the illumination and index of refraction gratings. As mentioned in Section 3.2.2, in the linear detection of small amplitude signals, photorefractive interferometers are typically designed such that the diffracted reference beam and transmitted signal beam are placed in quadrature, denoted by point A in Fig. 3.4. However, in our experiment, it is found that the component of the signal at the ultrasound frequency (Eq. (3.5)) vanishes very quickly with increasing diffusivity compared to the DC offset signal (Eq. (3.6)), and it is the latter component that we propose to use for sensing and imaging applications.

In order to maximize this “DC offset” signal, the PRC-based interferometer configuration shown in Fig. 3.6 is chosen, where the diffracted reference beam and transmitted signal beam are in phase giving pure (real) photorefractive gain. This configuration corresponds to point B in Fig. 3.4, where the optical intensity is maximized so that any phase modulation or distortion in the signal beam will contribute to a decrease of the detected light intensity. While this configuration is relatively insensitive to small
phase modulations, the phase modulation induced by the ultrasound in our experiments is found to be large enough to contribute to a DC offset signal with adequate sensitivity for imaging [20-23].

For the sake of clarity, we briefly summarize this discussion of the origin and nature of the detected DC offset signals. Without ultrasound, the signal and reference beams interfere at the PRC, and this intensity grating is recorded in the PRC as an index grating through the photorefractive effect. The reference beam diffracts from the grating into the signal beam direction with a phase front matched to the signal beam. The signal and diffracted reference beams are in-phase and interfere constructively, providing the maximum output intensity at the photodetector. When an ultrasound pulse is sent through the diffusive medium, part of the scattered signal beam is phase modulated at the location of the traveling ultrasound pulse. Since the duration of the AO interaction remains short compared to the response time of the crystal, the index grating in the PRC remains stationary, and the diffracted reference beam is no longer perfectly in phase with the transmitted signal beam along its complex wave front in space. As a result of the AO interaction, a decrease of the interference intensity (from its maximum) is observed at the optical detector.

At this point, it should be mentioned that, most recently, another PRC-based detection scheme has been developed in Boccara’s group [24]. Their technique differs from ours in the following aspects: (1) they employed two acousto-optic modulators to ensure that the photorefractive detection was only applied to the tagged photons; and (2) they used CW ultrasound, resulting in limited axial resolution.
3.3 Experimental Setup

3.3.1 Description of Experimental Arrangement

The experimental setup is shown in Fig. 3.6. A tissue or tissue-mimicking sample (described below) is submerged in a small glass tank filled with degassed and filtered water. The tank dimensions are 30 cm × 30 cm × 20 cm along the X, Y and Z axes, respectively. A reference coordinate system is given, with the Z axis corresponding to the ultrasonic axis, the Y axis indicating the optical axis, and the X axis being perpendicular to both the acoustic and optical axes.

![Experimental setup diagram](image)

Figure 3.6: Experimental setup for PRC based detection of ultrasound modulated optical signals: FG- function generator, A- power amplifier, M- impedance matching box, TS- translation stage, UT- ultrasound transducer, VBS- variable beamsplitter, RB- reference beam, SB- signal beam, BE- beam expander, BP- optical bandpass filter, APD- avalanche photodiode, PA- preamplifier, LP- lowpass filter.

The output of a frequency doubled Nd:YAG laser source, with 80 mW power and 532 nm wavelength, is sent to a variable beam splitter where it is split into signal beam and reference beams with a power ratio of approximately 25:1. The reference beam is
directed around the test tank and sent directly to the PRC. The signal beam is then sent to the submerged tissue or tissue-mimicking sample via the flat glass wall of the tank. After passing through the sample and exiting the tank, the scattered and ultrasonically modulated light is collected by a lens with an aperture of 5 cm, and a focal length of 10 cm. This collected light is directed into the PRC where it interferes with the reference beam at an angle of ~20°. Our PRC detector employs a BSO crystal with dimensions of 5 mm×5 mm×7 mm along the X, Z and Y axes, respectively, and a holographic cut along the [001], [110] and [1\bar{1}0] directions. A 4-kHz, ~10-kV/cm peak-to-peak AC field is typically applied to the crystal to enhance the grating strength and improve the TWM gain. After the PRC, the signal beam and diffracted reference beam (LO that is wavefront-matched to the signal beam) are sent through another lens (aperture = 5 cm, focal length = 10 cm) and optical band-pass filter to an avalanche photodiode (APD) with a 10-mm diameter active aperture. The signal from the APD is amplified, low-pass filtered at 500 kHz, and sent to a digital storage oscilloscope where the signal is coherently averaged.

The sound source used to modulate the diffuse light is an unbacked, single-element, spherically focused, piezoelectric transducer (Sonic Concepts H101, Bothell, WA). It has a 6.3-cm focal distance and a 7.0-cm aperture. The central frequency of the transducer is 1.1 MHz and the bandwidth is 0.85-1.35 MHz. The axial and radial (in the focal-plane) beam profiles of the transducer are shown in Figs. 3.7 (a) and 3.7 (b),

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8 Depending on experiments, the signal beam could be expanded by 10x before sending to the sample, which could be either tissue-mimicking phantom or real biological tissue (chicken breast), as will be specified later.
respectively. The 3-D focal region, defined by the full-width-at-half-maximum (FWHM) intensity, is a cigar-shaped ellipsoid with a long axis of about 9 mm and a short axis of about 1.5 mm. When driven in a CW fashion, this focal region generally defines the axial and lateral imaging resolution. The peak focal pressure used in the experiments is established given knowledge of the driving voltage and a pressure calibration obtained in

Figure 3.7: Measured transducer beam profiles: (a) axial beam profile—normalized peak pressure amplitude vs. axial distance; (b) radial beam profile—normalized peak pressure amplitude vs. radial distance.
water. The actual pressure in the phantom will be slightly lower due to acoustic attenuation, however, this is a small effect and not deemed important in the context of this work.

The ultrasonic axis is set perpendicular to the laser illumination direction. The transducer is mounted on a 3-D automated translation stage (Velmex), controlled by the computer via a RS-232 port. The transducer is driven by a short pulse train. The pulse train is produced using a standard function generator, amplified by a fixed-gain (55 dB) power amplifier, and sent to an impedance matching box before the transducer. The pulse repetition frequency used typically varies between 100 Hz and 1 KHz and is specified along with the experimental results in the following Chapters.

### 3.3.2 Experimental Samples

Two types of samples have been used in our AOI experiments: tissue-mimicking gel phantoms and *ex vivo* biological tissue (chicken breast). In the first stage of the experiments, tissue-mimicking phantoms are employed because they afford the flexibility to control the optical parameters (such as optical scattering) and are easy to fabricate and manipulate. In the second stage of our experiments, *ex vivo* biological tissue samples (excised chicken breast) are employed.

The tissue-mimicking phantom used in this work consists of an acrylamide gel fabricated based on the recipe given in the appendix. Four hundred nanometer-diameter polystyrene microspheres are added to the gel during fabrication in order to modify the

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9 The calibration is performed using a Precision Acoustics PVDF needle hydrophone in a large tank filled with degassed water. It is found that the transducer possesses a linear response to the driving voltage for conditions used in the experiments.
optical scattering coefficient; the particle-free gel is essentially transparent. The sound speed and the density of the phantom are measured to be about 1500 m/s and 1050 Kg/m$^3$, matching approximately conditions found in human breast tissue [25]. The dimensions of the phantoms are about 4 cm$\times$2.7 cm$\times$4 cm (X,Y,Z). Different sizes of optical absorbers are embedded roughly at the center of the phantom. The optical absorbers are made using the same recipe as its surrounding phantom except that India ink is added to enhance the optical absorption coefficient; the ink has little effect on the acoustic properties of the material. Thus, we obtain a target embedded in the gel possessing high optical absorption contrast and negligible acoustic contrast. A cut-away view of one phantom used in our experiment is shown in Fig. 3.8. In this particular phantom, the target has a depth of 6-7 mm located at the center. It should be mentioned that for this diffusivity of the phantom (10 cm$^{-1}$), the small target embedded at the center of the whole phantom is not visible by the eye.

Figure 3.8: A photograph of a phantom slice (4 cm$\times$4 cm) showing the embedded optical absorber (5 mm$\times$5 mm). The reduced scattering coefficient of the phantom is approximately 10 cm$^{-1}$. The optical absorber is fabricated using the exact same recipe as the surrounding phantom, except that India ink is added to enhance its absorption coefficient.
Chicken breast is used as our biological test medium. The sample is squeezed between two thin transparent plastic plates of thickness 1.3 mm. These two plates are positioned in parallel in XZ plane in order to both hold the biological sample still in space and keep the thickness of the sample somewhat uniform; this arrangement is not unlike that employed for breast examinations using X-ray mammography. Chicken breast is chosen because it approximately matches the optical properties of many human soft tissues [26, 27] and because it is easy to acquire and manipulate. Different optical absorbers are also embedded roughly at the center of the biological sample, by cutting and opening the sample across the XZ plane. The target-embedding procedure is carefully done while submerged in the degassed water bath, thereby minimizing the possibility of trapping bubbles. The optical absorber is fabricated using the same poly-acrylamide recipe as described above with India ink added to enhance the optical absorption coefficient. Detailed physical parameters, such as the dimensions of the biological samples and the absorbers, will be specified as the experimental results are presented in Chapter 5.
References:


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Chapter 4

Experimental Results

4.0 Overview

This chapter presents experimental results demonstrating the detection of ultrasound-modulated optical signals using the PRC-based interferometry system. AO signals obtained in highly diffuse, homogeneous phantoms are first presented and discussed. These results include demonstrations of the DC offset signal, its detection stability, pressure dependence, and pulse length dependence. Following that, the DC offset signal is utilized for 1-D axial line scans, 2-D imaging, and 3-D volumetric imaging. The results show that the use of short pulses of focused ultrasound allows for a 1-D AO image to be obtained along the ultrasonic axis from a single, time averaged AO signal. Two-dimensional AOI can be achieved by scanning the ultrasound transducer in one dimension, and 3-D AOI can be performed by scanning the transducer over multiple planes. It is shown that 3-D information may be obtained in a relatively simple manner, and without tomographic reconstruction. Finally, the axial imaging contrast and axial resolution of the system are investigated. The results show that the axial imaging contrast depends on the spatial pulse length.
4.1 DC Offset Signal

In highly diffuse media, it is expected that a DC offset signal will be observed using the PRC detection system. The physical basis of this signal was discussed in detail in Chapter 3. In this section, experimental results are presented which confirm the existence of the DC offset signal. In addition, the stability of the DC offset signal, and its pressure dependence and pulse length dependence will be experimentally investigated. An understanding of these parameters is important for AOI applications (to be discussed in the next section).

4.1.1 Proof of Principle

![Figure 4.1: Normalized focal pressure responses generated when driving the ultrasound transducer with (a) 1-cycle, (b) 2-cycle, and (c) 4-cycle electrical pulses at a 1 MHz center frequency.](image)

Figure 4.1 shows the normalized pressure waveforms generated by the single-element ultrasound source when driven by different duration electronic pulses (tone bursts) with a
1 MHz center frequency, where (a) (b) and (c) correspond to 1-cycle, 2-cycle and 4-cycle pulses, respectively. Unless otherwise noted, the peak-negative focal pressure used in the following experiments is approximately 0.65 MPa, which falls well within the safe exposure imposed by the FDA for diagnostic ultrasound [1, 2]. From Fig. 4.1, one can see the ring-down effect due to the finite bandwidth of the transducer. Generally, driving pulses in excess of 4 cycles have to be used in order for the focal pressure to reach its steady state as shown in Fig. 4.1(c). As a result, the actual spatial acoustic pulse lengths (FWHM) generated by the 1-cycle and 2-cycle driving pulses are almost identical, and are about 3 mm. In order to achieve the best axial resolution, unless otherwise noted, a 2-cycle pulse is employed for the imaging applications. And the ultrasound pulses are fired at a PRF of 1 KHz.

In the experiment, the transducer is positioned perpendicular to the optical source. Before the experiment, the system is aligned to ensure that the center of the phantom roughly coincides with the center of the focal region of the transducer. The typical ultrasound-modulated optical signals detected in a homogeneous (without any optical absorber), highly diffuse (reduced scattering coefficient: $\mu_s' = 10$ cm$^{-1}$) tissue-mimicking phantom are shown in Fig. 4.2. Figure 4.2(a) shows the response of the system with the reference beam blocked. The signal beam passes directly through the PRC to the APD, and the presence of the crystal has little effect. The ultrasound modulated signal is not

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1 The mechanical index (MI) quantifies the likelihood that inertial cavitation will result from ultrasound exposure assuming that cavitation nuclei are present. The MI is defined as the spatial-peak rarefaction pressure (in MPa) divided by the square root of the center frequency (in MHz) [3]. Current standards recommend that if an ultrasound device is capable of achieving a MI greater than 1.0, then the output display screen must show the appropriate index value for the user to predict the potential for adverse cavitation bioeffects. In our case, the mechanical index is about 0.63.
observed in this case. Figure 4.2(b) shows the signal observed in the presence of the reference beam, when two-wave mixing takes place. This lower trace is referred to as the “DC offset signal”. The amplitude of this signal is related to the magnitude of the ultrasound induced phase modulation. It is evident that the PRC-based interferometer, facilitated by the addition of a high voltage AC bias field, dramatically enhances the DC offset signal level.

Note the lack of any AC signal component in Fig. 4.2(b). In the current configuration (see Fig. 3.6 in Chapter 3), the diffracted reference beam is in phase with the transmitted signal beam such that the gain is real and thus the 1-MHz AC modulation signal is not observed (see Eq. 3.5 in chapter 3). In addition, a 500 kHz low pass filter was employed in the detection system, further reducing any 1-MHz component in the
detected signal. Using polarization optics, the diffracted reference beam was placed in quadrature with the transmitted signal beam, and the low pass filter was then removed. The 1 MHz signal was still observed to be negligible with respect to the DC offset signal, provided the reduced scattering coefficient of the sample was relatively high (typically greater than 1 cm$^{-1}$). In diffusive media, the reduction of the 1 MHz modulated signal relative to the DC offset signal could be attributed to the incoherent summation of signals associated with multiple optical paths possessing random phases. In other words, the 1 MHz signal is not spatially coherent over the wave-front of the diffuse light and the signal modulation is greatly reduced when the scattered light is collected to a single large aperture detector.

The detected time-domain DC offset signal can be converted to a space-domain signal by multiplying the temporal coordinate by the speed of sound in the medium. This yields a measure of the strength of acousto-optic interaction at points along the acoustic axis. This interaction is influenced by three factors: (1) the amplitude of the sound field, (2) the intensity of diffuse light, and (3) the optical characteristics of the medium. The acoustic pulse acts like a probe traveling down the acoustic axis, broadcasting information related to the acousto-optic interaction over that region of space for which the optical field possesses sufficient intensity to yield a detectable DC offset signal. In the case of very short ultrasound pulses traversing optically uniform media, the temporal duration of the DC offset signal defines the region of space along the acoustic axis where both the acoustical and optical fields have sufficient energy to produce a detectable signal. In the case of very long ultrasound pulses, the duration of the DC offset signal is
essentially the duration of the acoustic pulse [4]. The latter case is not particularly interesting from an imaging or tissue characterization perspective. The former allows for delineation of media variability along the ultrasound axis. The detected DC offset signal shown in Fig. 4.2 (b) has a full-width at 10% maximum of ~20 µs, corresponding to a spatial length of 30 mm. This length determines the dimension of the AOI field of view, within which any change in local optical properties along the axis will be manifested in the detected DC offset signal.

### 4.1.2 Stability

The stability/repeatability of the PRC-based interferometry system was tested by measuring the variation in the DC offset signals. In this experiment, the same diffuse phantom with a reduced scattering coefficient of 10 cm\(^{-1}\) was used. A five-cycle ultrasound pulse with a peak pressure of ~0.65 MPa was fired across the center of the phantom, and the detected DC offset signal was coherently averaged for 10,000 sweeps\(^2\), from which the amplitude of the DC offset signal was recorded. At the same position, this same measurement procedure was repeated 15 times. The result is shown in Fig. 4.3, where there is a 1-minute interval between measurements. The maximum and minimum deviations from the mean (average) in these results are 3.5% and 5.13%, respectively. The standard deviation of the measurements is 2.6%. However, it should be mentioned that the measurement could be strongly influenced by ambient room vibration. This is due to the relatively slow response time of the PRC employed in our experiments. As

\(^2\) The measurement of the stability depends on the number of averages. In other words, the signals have to be coherently averaged enough times to minimize the fluctuations of the signals over time and to minimize the error from the otherwise poor SNR.
mentioned in Chapter 3, the response time of the photorefractive BSO crystal used under the experimental conditions is about 150 ms, which means that the PRC can only offset environmental or physiological motions up to a few Hz. This is not sufficient to compensate for the low-frequency environmental noise. Furthermore, for real clinical applications, a faster PRC will be required to compensate for the potential speckle decorrelation associated with the physiological motions and environmental vibrations.

Figure 4.3: Test of the stability/repeatability of the PRC-based system. In this experiment, the signals were coherently averaged for 10,000 sweeps and the amplitudes of the signals were then recorded. The same measurement procedure was repeated 15 times. Finally, each measurement was normalized to the mean value of all the measurements.
4.1.3 Pressure Dependence

The amplitude of the DC offset signal was measured as a function of the focal pressure amplitude\(^3\). In this experiment, 5-cycle pulses with different amplitudes were fired across the center of the homogeneous, diffuse phantom (\(\mu_s'=10\ \text{cm}^{-1}\)) to generate the DC offset signals, and the detected signals were coherently averaged for 10,000 sweeps, from which the amplitude of the DC offset signal was recorded. Fig. 4.4 (a) and (b) show the measured amplitudes of the DC offset signals as a function of pressure and pressure squared, respectively. From Fig. 4.4, it can be seen that the DC offset signals are increasing with the focal pressures within the studied pressure range. For relatively high driving focal pressures (> 0.3 MPa), the relationship between the signal amplitude and the driving pressure becomes somewhat linear (see Fig. 4.4(a)). For relatively low driving pressure (< 0.3 MPa), the curve appears to be quadratic (see Fig. 4.4 (b)). Although the experimental results presented here can not be quantitatively compared with the simple plane-wave model developed in Chapter 3, they qualitatively agree with the characteristics of the zero-order Bessel function. For instance, \(J_0(x) \sim 1 - x^2\) for small \(x\), yields a quadratic dependence of the DC offset signal on the pressure. This assumes that the phase shift is linearly proportional to the focal pressure. For larger phase shifts, on the other hand, the increase in \(J_0(x)\) with \(x\) is more linear over a certain range.

\(^3\) As the transducer is driven harder, nonlinearity becomes more evident. As a result, the absolute value of the peak negative pressure starts to be slightly smaller than that of the peak positive pressure. Here, the focal pressure amplitude denotes the average of the absolute values of the peak positive and peak negative pressures.
4.1.4 Pulse Length Dependence

In AOI, the measured ultrasound modulated optical signals (the DC offset signals in our case) are related to the number of modulated/tagged photons. For a given experimental configuration where both the incident laser beam and the focal region of the ultrasound transducer are fixed, the number of modulated photons is strongly dependent on the region where the acousto-optic interaction is taking place. In our experiment, since ultrasound pulses are used to locally modulate the photons, the strength of the detected DC offset signals should be related to the acoustic pulse lengths. The relationship between the ultrasound modulated optical signals and the acoustic spatial pulse length is shown in Fig. 4.5, where the ultrasound peak focal pressure was fixed at ~0.65 MPa. From Fig. 4.5, it can be seen that the DC offset signals initially increase with the acoustic...
pulse length. This is due to the increase in the acousto-optic interaction volume. This increase eventually “saturates” for longer acoustic pulses. This saturation can be explained as follows. Recall from Chapter 2 that the background (un-modulated) photons possess a Gaussian-like radial distribution around the axis of the incident laser beam. Since the optical and acoustical axes are perpendicular, this implies that as the acoustic pulse propagates down the transducer axis, it will traverse regions of initially increasing and then decreasing background illumination. Consider now spatial acoustic pulses that are so long that they no longer fit inside the background illuminated region. Any further increases in the length of the pulse will have no effect, as the extended acoustic pulse will reside in regions that are not illuminated in the first place; the amplitude of the DC offset signals will appear to saturate. In addition, the DC offset signal shown in Fig. 4.2(b) has a full-width at 10% maximum of ~20 µs, which indicates that the AO interaction region in this experiment is confined to a 30-mm illuminated swath along the acoustic axis. This is
in good agreement with the saturation observed in Fig. 4.5, which occurs around 20 cycles (corresponding to 20 µs in the time domain for our 1-MHz ultrasound transducer).

4.2 Acousto-optic Imaging using the DC Offset Signal

In this section, the DC offset signal detected using the PRC system is used for subsurface imaging in one, two, and three dimensions. In addition, the imaging resolution and axial imaging contrast using the PRC-based AOI system are evaluated.

4.2.1 Imaging along a Scan Line: 1-D AOI

In the following experiment, the 2-cycle ultrasound pulse shown in Fig. 4.6(a) with a peak pressure of ~0.65 MPa was used to generate the AO signal. When a homogeneous scattering phantom (μs′=10 cm⁻¹) was employed, the typical normalized time-domain AO signal detected in our experiment is shown in Fig. 4.6(b), which was coherently averaged for 10,000 sweeps. In comparison, Fig. 4.6(c) shows a typical normalized DC offset signal obtained when the ultrasound beam traverses an optically absorbing target (5x5x6 mm³ along the X, Z and Y axes, respectively) embedded inside a scattering phantom (4x4x2.7 cm³ along the X, Z and Y axes, respectively). These two scenarios are schematically illustrated in Fig. 4.6(d), where the incident laser beam (Y axis) is perpendicular to the page. When the ultrasound beam passes through the absorber, a peak is observed in the middle of the detected DC offset signal. The presence of the peak indicates that the strength of the AO interaction is diminished as the ultrasound pulse traverses the absorbing target. The number of phase modulated photons detected is reduced because of the local light absorption. The signal observed in a homogeneous
phantom does not show this feature. This clearly shows that axial resolution can be achieved by using pulsed ultrasound.

The detected DC offset signal gives a measure of the number of tagged photons generated as the ultrasound pulse travels down the acoustic axis. The number of tagged photons can be reduced by local absorption. This is the essential principle behind the AO imaging concept. Ultrasound modulated/tagged photons generated within the highly absorbing target cannot escape to the detector – thus the peak in the DC-offset signal when the acoustic pulse traverses the target. (Remember that the detector is biased so that the more tagged photons correspond to a more negative signal.)

Figure 4.6: (a): The pressure output at the focus of the transducer; (b), (c): Typical AO signals detected for a homogeneous scattering phantom and a phantom with an optical absorber (5 mm x 5 mm) embedded inside, respectively. These conditions correspond to schematic illustrations (i) and (ii), respectively, in (d).

The detected DC offset signal gives a measure of the number of tagged photons generated as the ultrasound pulse travels down the acoustic axis. The number of tagged photons can be reduced by local absorption. This is the essential principle behind the AO imaging concept. Ultrasound modulated/tagged photons generated within the highly absorbing target cannot escape to the detector – thus the peak in the DC-offset signal when the acoustic pulse traverses the target. (Remember that the detector is biased so that the more tagged photons correspond to a more negative signal.)
This time-domain record of the sample’s AO response was converted to a space-domain scan by multiplying the temporal coordinate by the speed of sound in the medium, as is typically done in B-mode ultrasound imaging. A converted 1-D space-domain acousto-optic image is plotted in gray scale in Fig. 4.7, where the upper and the lower images correspond to the time-domain signals shown in Figs. 4.6(b) and 4.6(c), respectively. These images are 1-D “scan lines” of the acousto-optic interaction at points along the ultrasonic axis. In order to get an AO signal from a given region, one must have both ultrasound and light coexisting in said region. If an optical absorber is present along ultrasound propagation path, it will absorb both the background light and the phase modulated photons, making it less likely for any modulated light to reach the detector and yielding the image contrast observed experimentally.

4.2.2 Imaging in a Plane: 2-D AOI

By scanning the acoustic transducer laterally along the X-axis (see the experimental setup in Chapter 3), we generated a series of adjacent line-scan images which, when displayed
simultaneously, result in a 2-D AO image (X-Z plane). In the experiment, 2-cycle ultrasound pulse with a focal pressure of ~0.65 MPa was used to pump the AO interaction, and the detected DC offset signals were coherently averaged for 10,000 sweeps. The time-domain DC-offset signals were converted to the space domain by multiplying the speed of sound in the sample (1.5 mm/µs), yielding a line-scan image at a given X location. After that, the ultrasound transducer was mechanically moved by 1 mm to the next X location. The above procedure was then repeated until the whole 2-D AO image was obtained. The 2D AO images of a homogeneous phantom and a phantom with an optical absorber embedded inside are shown in Figs. 4.8(a) and (b), respectively. In the case of a homogeneous phantom, the XZ-plane AO image has a “disk” shape, which is associated with the local Gaussian-like distribution of light intensity as discussed in Chapter 2. In the case of an inhomogeneous phantom with an optical absorber embedded, a darkened region was seen in the middle section of the AO image, which corresponds to the location of the optical absorber. The surrounding white area is the effective imaging area, corresponding to the illuminated region where the diffuse light interacts with the scanned ultrasound beam to generate a detectable signal. Only regions confined within this area could be imaged; otherwise the sample or the laser source and detection system have to be scanned in order to sense areas outside this white region.
The tiny, vertically-orientated striations seen in both the AO images are due to mechanical vibrations that are not completely compensated for by the PRC, leading to small variations in system sensitivity over the 2-D scanning time. One way to compensate for these striations is to normalize the 1-D AO images at each scanning X location to unity so that only the image contrast along the ultrasonic axis is maintained. For small
embedded targets, the AO images will not be dramatically distorted by the normalization. The normalized AO image is shown in Fig. 4.9, derived directly from the data shown in Fig. 4.8 (b). From Fig. 4.9, the shape of the imaged object is well delineated. The FWHM of the imaged target along both the X and Z directions (across the center of the target) are ~6.7 mm (see Fig. 4.12). These values are reasonable because they represent the convolution products between the local light intensity profile in the presence of the embedded target (5 mm x 5 mm, X, Z) and the spatial dimensions of the 2-cycle ultrasound pulse along the X and Z directions (~3 mm at FWHM pressure). In highly diffuse media, the local light intensity profiles around the embedded target, along the X, Y and Z directions, are not expected to have sharp edges due to the diffuse (or multiply-scattered) nature of photons. For instance, there is a good chance for photons nearby the absorber to be absorbed. It should be mentioned that ideally, the imaged target (i.e., the optical contrast responsible for the object only) may be extracted by subtracting two AO images obtained in two different samples containing the same host background medium—a homogeneous sample and an inhomogeneous sample with the embedded target. However, in practice, the reference background AO image (obtained in the homogenous sample) is not always available.
4.2.3 Imaging in a Volume: 3-D AOI

In AOI, when highly diffuse photons are employed to form AO images, the three-dimensional information of the sample can be obtained by simply scanning the ultrasound transducer. Two experiments were conducted to demonstrate this. The first experiment involved scanning the ultrasound transducer along three different XZ planes, as depicted in Fig. 4.10(a). These three planes was separated by 6 mm from each other along the incident laser direction (i.e., along the Y axis), with the middle plane crossing the center of the target. The target measures ~5 x 5 x 6 mm along the X, Z, and Y axes, respectively. In the experiment, 2-cycle ultrasound pulse with a focal pressure of ~0.65 MPa was used to pump the AO interaction, and the detected DC offset signals were coherently averaged for 10,000 sweeps. The results, processed following the normalization procedure as applied to Fig. 4.9, are shown in Fig. 4.10 (b), where each of
the three XZ-plane AO images constitutes of 21 scan lines with 1 mm spacing between two consecutive scan lines. It can be readily seen that the target only appears in the AO image when the scanning plane intersects the plane of the absorber.

The second experiment was designed to compare the AO image with the actual target along the laser illumination direction. The same diffuse sample and experimental parameters as those used in the previous experiment were employed. In this case, the transducer was scanned along the Y axis (see Fig. 4.11 (a)). By doing this, the YZ plane AO image can be acquired. The cross-sectional AO images obtained in both the XZ and
YZ planes are shown in Fig. 4.11(b). One-dimensional AO images across the center the target along the X, Y and Z directions are shown in Fig. 4.12, which are 3 line scans...
taken directly from Fig. 4.11 (b). The FWHM of the imaged target along the Y direction is about ~8.2 mm. The slight elongation of the imaged target along the laser illumination direction, compared to the X and Z directions discussed above (after taking into account of the actual size differences along these 3 directions), might be due to two factors: (1) There are fewer photons existing just behind the target along the laser illumination direction [5]; and (2) There is less chance for the photons tagged just before the target to reach the detector in our transillumination configuration.

Figure 4.12: (a), (b), and (c): 1-D AO images across the center of the optical absorber in X-, Z- and Y- directions, respectively. These 3 line plots are taken directly from the images shown in Fig. 4.11 (b), zoomed in around the target.

The above results are important as they indicate that AOI can be used for 3-D volumetric imaging. The fact that AO imaging can be used to resolve subsurface objects in 3 dimensions distinguishes it from traditional ballistic or quasi-ballistic imaging techniques, such as conventional X-ray radiography. In these methods, since direct
photons or ballistic photons are used to generate the images, the 3-D information of the target is projected onto a 2-D plane, and thus the depth information along the source illumination direction is lost, and tomographic reconstruction techniques must be employed to obtain 3-D images. The configuration of ballistic imaging is illustrated in Fig. 4.13, in which the target blocks the direct beam, thus casting a shadow. In order to obtain the depth information, reconstruction is typically needed to derive the 3-D information from multiple measurements conducted along different projection paths\(^4\). In the case of AOI where *highly diffuse* photons are used to form the image, the 3-D information can be *directly* obtained by simply scanning the ultrasound transducer. AOI experiments performed in a clear medium with embedded targets show the pure “shadow effect” illustrated in Fig. 4.13.

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\(^4\) This procedure is called *tomography*, which is the basic principle of computerized tomography (CT).
4.3 Axial Imaging Contrast

In this section, issues regarding the axial imaging contrast are discussed. Results show that the axial imaging contrast is controlled by the spatial acoustic pulse length.

Currently, in most of the AOI systems, continuous-wave (CW) ultrasound is used to generate the ultrasound-modulated optical signals. Although pure CW ultrasound based AOI typically leads to an improved SNR by narrowing the detection bandwidth [6, 7], it results in a very limited axial resolution. While other researchers have shown that axial resolution is possible using CW chirped ultrasound [8], it is desirable (even essential) that we minimize the ultrasound exposure by using pulses. We have already demonstrated that our system possesses sufficient sensitivity to detect ultrasound modulated optical signals from a pulse ultrasound source, and that axial resolution can be achieved using pulsed ultrasound. Now we show that short pulsed ultrasound allows for enhanced axial imaging contrast.

In this next experiment, the ultrasonic axis was aligned across the center of a phantom ($\mu_s \sim 3 \text{ cm}^{-1}$) with an embedded target ($\mu_a \sim 4 \text{ cm}^{-1}$), 5 x 5 x 6 mm along the X, Z, and Y axes, respectively), and different acoustic pulse lengths with a focal pressure of $\sim 1 \text{ MPa}$ were fired at a PRF of 100 Hz to image the absorber. The detected DC offset signals were coherently averaged for 5,000 sweeps. The detected normalized DC offset signals using 1-cycle, 4-cycle and 6-cycle pulses to drive the ultrasound transducer are shown in Fig. 4.14. The signal contrast (i.e., relative change in the DC offset signal resulting from the absorber) clearly decreases with increasing pulse duration. As the spatial pulse length gets long with respect to the absorber size, the pulse is no longer
confined within the absorber at any point in space and the ability to distinguish the absorber from the background signal diminishes. Similar characteristics have also been observed in phantoms with different optical properties and target characteristics. The results above show that the axial imaging contrast is controlled by the spatial ultrasound pulse.

Figure 4.14: The effect of changing the ultrasound pulse length on the DC offset component of the ultrasound modulated optical signal.

It should be mentioned that in the current experiment setup, finer adjustment of the spatial ultrasound pulse length is limited by the frequency and the bandwidth of the single-element ultrasound transducer. A more quantitative relationship between the axial imaging contrast and the spatial ultrasound pulse length will be further explored in the Chapter 5, while using a higher frequency ultrasound transducer array. Nevertheless, the results shown above do indicate that enhanced imaging contrast is possible through the use of higher frequency, broad-band transducers, which further localize the ultrasound
pulse in space. Ultrasound transducers used for biomedical imaging can produce pulses as short as 1.5 wavelengths, and could serve as ideal sound sources for probing the optical properties of diffuse media.
References:


Chapter 5

Fusion of Pulsed AOI and Conventional B-mode Ultrasound Imaging

5.0 Overview

In this Chapter, the combination of AOI and conventional B-mode ultrasound imaging is studied using a commercially available pulsed-ultrasound scanner (Analogic, AN2300) coupled with the PRC-based optical interferometry system described in Chapter 3. The system is designed to operate in both an ultrasound imaging mode and an AOI mode. Using this system, B-mode ultrasound and AO images of different embedded targets are obtained in both highly diffusive phantoms (μs' = 10 cm⁻¹) and in ex vivo biological tissues (chicken breast). Because the same ultrasound probe is used to generate the B-mode images and to excite the AO response, the AO images are intrinsically co-registered with the B-mode ultrasound images. The target differentiation capability of the system is demonstrated through the use of both acoustically-invisible and -visible targets. Results suggest that AOI could be used to supplement conventional B-mode ultrasound imaging by generating additional optical information to color code the ultrasound image in a manner similar to that used for power Doppler imaging.
5.1 Introduction

In previous Chapters we have discussed the principles of AOI and its implementation using short-pulse ultrasound and a PRC–based optical detection system. Experimental studies conducted with a single-element focused ultrasound transducer prove the detection principle and demonstrate the imaging capability of our PRC-based pulsed AOI system. To briefly summarize, the PRC-based detection system has been shown to have sufficient sensitivity to detect pulse-ultrasound-modulated optical signals. As the ultrasound pulse propagates down its axis, an AO “scan line” of a highly diffuse sample is extracted from the time-domain AO signal after being converted to the space domain by multiplying the known speed of sound in the sample. This AO scan line is analogous to the “A-scan” generated by ultrasound imaging machines, and by repeating this procedure for adjacent lines, one can generate a 2-D AO image that spans a swath of the diffuse sample in much the same way that an ultrasound machine generate a B-mode image from a series of adjacent A-scans. The fact that the AOI construction procedure is intrinsically similar to that employed in conventional B-mode ultrasound imaging further serves to facilitate the direct combination of AOI and B-mode ultrasound imaging.

Ultrasound imaging is a well-established clinical imaging technique, yielding information on the bulk mechanical and interfacial properties of the sample. Currently, ultrasound imaging has seen widespread use in clinical practice, for both diagnostic and treatment monitoring purposes [1]. However, when it comes to diagnosing tumors, conventional ultrasound imaging can lack specificity in some cases. For instance, in clinical breast examinations, ultrasound imaging alone has thus far not been deemed
suitable for breast cancer screening\textsuperscript{1}, although it has been routinely used in conjunction with mammography to differentiate simple cysts from solid lesions and to characterize masses that may appear obscured on a conventional mammogram \cite{2}. This mainly arises from the fact that malignant and benign lesions possess similar acoustical properties \cite{3, 4}. In this sense, AOI has the potential to augment conventional ultrasound imaging and improve ultrasound specificity by generating additional functional information regarding spatially-dependent optical properties. The optically related functional information, as mentioned in Chapter 1, could be valuable in detecting and differentiating tumors\textsuperscript{2} \cite{5, 6, 7}. In fact, the use of a pure optical imaging technique (DOT) as an adjunct to ultrasound in differentiating benign from malignant lesions in breast tumor diagnosis has been investigated and has shown promise \cite{8}.

The idea of combining information from both ultrasound imaging and AOI was first proposed by Leveque-Fort \textit{et al.} \cite{9}. In their setup \cite{10}, the ultrasound probe was alternately driven in pulsed mode and in CW mode in order to generate ultrasound images and AO images, respectively. While CW ultrasound supports narrow-bandwidth optical detection systems in AOI and subsequent enhancement in the AO signal \textit{SNR}, it affords limited axial resolution and is not compatible with conventional (pulsed)

\footnote{\textsuperscript{1} Currently, despite its limitations (see Chapter 1), conventional X-ray mammography is the “gold standard” for breast cancer imaging, and ultrasound imaging mainly serves as a secondary, diagnostic test after routine mammography.}

\footnote{\textsuperscript{2} Optical imaging techniques potentially have high sensitivity and specificity for the diagnosis of tumors because tumors could differ from normal tissues in such ways as: (1) The amount of blood needed to serve a tumor’s metabolic needs is often increased over that of normal background tissue; and (2) hemoglobin desaturation in tumors is increased due to the high oxygen demand of cancerous tissue.}
ultrasound imaging\textsuperscript{3}. On the other hand, our PRC-based detection system allows for pulsed-ultrasound based AOI in highly diffuse media, as demonstrated in Chapter 4. Indeed, the results suggest the possibility that conventional imaging machines could be utilized in dual-mode, ultrasound and AOI schemes. In this Chapter, the fusion of AOI and conventional \textit{B}-mode ultrasound imaging will be investigated using a commercially available diagnostic ultrasound imager equipped with a 1-D phased-array transducer. The same transducer will be used to excite the AO response (and generate the AO image) as well.

\section*{5.2 Experimental Setup}

![Figure 5.1: Experimental setup combining the PRC-based interferometry system with a commercially available ultrasound imager: VBS- variable beamsplitter, RB- reference beam, SB- signal beam, BE- beam expander, UP- ultrasound probe, TS- translation stages, APD- avalanche photodiode, PA- preamplifier, LP- lowpass filter.]

\textsuperscript{3} Conventional ultrasound imaging techniques, such as \textit{B}-mode ultrasound imaging, typically employ short ultrasound pulses, and the imaging construction procedure is based on the demodulation of the received echo train and conversion from time to space using an assumed speed of sound.
The experimental arrangement, shown in Fig. 5.1, combines the PRC-based optical detection system with a commercially available, PC-based, diagnostic ultrasound scanner/imager (AN2300, Analogic, Peabody, MA, USA). The PRC-based detection system was described previously in Chapter 3. The main difference between the current experimental setup and the previous one (shown in Chapter 3) is that the ultrasound imager, which employs a 5-MHz linear array (model 8802, BK Medical, Herley,
Denmark) with a bandwidth of ~2 MHz, replaces the single-element ultrasound transducer and the data acquisition/position control computer. The imaging machine projects beam-formed ultrasonic pulses along different axes (the specific spatial orientation of the axis depends on which scan line is generated) to generate both B-mode ultrasound and AO images, following a procedure to be described in the next section. A photograph of the AN2300 is shown in Fig. 5.2. The ultrasound probe is mounted on a translation stage, controlled by a built-in computer inside the ultrasound imager. By mechanically scanning the probe in a direction perpendicular to its imaging plane, 3-D ultrasound and AO images can be obtained. This computer is also used to communicate with the oscilloscope via a GPIB interface, and to acquire B-mode ultrasound images.

The operation of the ultrasound probe relies on a digital beam-forming technique, in which a certain group of elements (typically 64 elements in our case) on the probe are electronically activated with element-to-element phase delays that serve to steer and focus the beam [11]. To calibrate the pressure output of the ultrasound probe, we activated and fired its central 64 elements with a fixed focal length of 50 mm, and mechanically scanned a calibrated PVDF membrane hydrophone with an active element diameter of 0.2 mm (Precision Acoustics Ltd., SN1502-031) to map the ultrasound field in degassed water. Note that the imaging plane of the ultrasound probe was orientated in the XZ plane as shown in Fig. 5.1. Typical acoustic pulses (used for AOI), measured with the hydrophone at the focus of the ultrasound probe, are shown in Fig. 5.3, with plots (a) (b) and (c) corresponding to 3-cycle pulses driven at decreasing amplitudes. The distorted shapes of the pulses are caused by the nonlinear propagation effects [12], which, as
expected, are more evident for higher amplitudes. The acoustic pulses shown in Fig. 5.3 are the shortest pulse lengths we used for AOI\(^4\), corresponding to a spatial pulse length (FWHM) of \(~1\) mm. It should also be mentioned that plot (a) is the highest amplitude used for our AOI experiments and has a Mechanical Index (MI) of \(~0.84\), which is within the safety limits of the FDA [13].

Figure 5.4 shows a full field map of the ultrasound probe along three different transverse planes: XY, YZ, and XZ, with (a) and (b) corresponding to the map for the peak positive pressure and the map for the peak negative pressure, respectively. The field mapping was completed using a 3-cycle ultrasound pulse with the focal output as shown in Fig. 5.3(c). As can be seen, the ultrasound fields are focused along both the X and Y directions, resulting in a focal region possessing a relatively large dimension along the Z

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\(^4\) This is based on the AO SNR consideration. Due to the ring-down effect of the ultrasound probe (associated with its relatively narrow bandwidth), three cycles are the shortest pulse lengths that approximately reach the steady state, yielding the maximum output pressure. In addition, the enhanced SNR is achieved with a larger AO interaction volume.
direction. One-dimensional beam profiles along the X, Y and Z axes (see Fig. 5.5) allow us to further quantify the focal region. The FWHM intensity of the focal region for the peak positive pressure and for the peak negative pressure are ~0.8x1.2x10 mm$^3$ (X, Y, Z) and ~0.8x2.2x18 mm$^3$ (X, Y, Z), respectively.

An important feature of the plots is the side lobes in both the X and Y directions, which could play a role in both ultrasound and AO imaging. For instance, when the ultrasound probe is firing along a scan line through a nearby region of the target, but not through the target, the side lobes of the probe could partly or completely overlap with the target, and thus part of the acoustic energy (originally fired along this scan line) is

![Figure 5.4: Two-dimensional field maps of the ultrasound probe along the XY, YZ and XZ planes: (a) for the peak positive pressure and (b) for the peak negative pressure.](image-url)
diffracted through the target. Therefore, when the data are analyzed for this particular line, the effect of the target will contribute to the signals as if it appears along this scan line, yielding an artificial elongation of the imaged target.

5.3 Experimental Procedure and Parameters

5.3.1 Experimental Procedure

Before the experiment, the system is aligned to ensure that (1) the imaging plane of the ultrasound probe roughly coincides with the XZ plane (or the YZ plane\(^5\)); (2) the beam

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\(^5\) The 3-D imaging of tissue-mimicking phantoms, to be discussed in the following, is the only exception in which the imaging plane of the ultrasound probe is orientated along the YZ plane (instead of the XZ plane).
axis of the ultrasound probe along the Z direction roughly cuts across the middle of the sample; and (3) the laser beam is roughly sent to the center of the front surface of the sample.

After the alignment is completed, experiments are conducted in the following fashion. To ultrasonically scan the XZ plane, the array elements are fired with delays chosen to electronically steer individual beams along different directions in a fan-like pattern originating from the geometric center of the probe. Each beam has the same (fixed) focal length of 50 mm. This electronic steering procedure is called sector scanning [1] and yields a set of 192 ultrasonic scan lines positioned adjacent to each other. Along the direction of ultrasonic propagation, time is converted to space using an assumed sound speed (1.5 mm/μs). To display grayscale images (B-mode images), the ultrasound scanner demodulates the received ultrasound echo train associated with a given scan line and converts the signal envelope function to grayscale. Because the envelope of the time-domain AO signal correlates directly with the photon distribution along the ultrasound path (see Chapters 3 and 4), AO images are constructed in the exact same manner, and can be superimposed on top of the B-mode images. As a consequence, B-mode and AO images are automatically co-registered.

To generate 3-D ultrasound B-mode and AO images, the ultrasound probe is mechanically scanned in the direction perpendicular to its imaging plane. By collecting B-mode images and AO images along successive XZ planes, 3-D information pertaining to both the mechanical properties and opto-mechanical properties of the sample is

For the sake of simplicity, the following experimental procedure will be explained by taking the former case (i.e., the ultrasound probe is orientated inside the XZ plane) as an example.
obtained. It should be noted that: (1) while a single ultrasonic shot can be used to build one ultrasound scan line, multiple ultrasonic pulses are required for AOI to coherently average due to the relatively low AO $SNR$; (2) The fact that both $B$-mode images and AO images are constructed in the same fashion using the ultrasonic excitation signals guarantees that the two imaging modalities are intrinsically co-registered.

### 5.3.2 Experimental Parameters

Before the experimental results are presented, the experimental parameters used will be briefly summarized here. Five MHz center frequency pulses (about 1.5-cycles long) are used to generate the ultrasound images. Alternatively, 5-MHz center frequency sine bursts containing several cycles are used to generate the AO signals. The spatial peak, temporal peak (SPTP) excursion of the sine bursts is typically less than 2 MPa peak negative and 7 MPa peak positive, measured in water. The pulse repetition frequency for AOI is typically on the order of 1 kHz (unless otherwise noted) and each AO signal is coherently time averaged over a specified number of “shots” (less than 40,000) in order to obtain a satisfactory $SNR$. In addition, all the tissue-mimicking phantoms used in this Chapter have the same dimensions ($4 \times 4 \times 2.7 \text{ cm}^3$, $X$, $Z$, $Y$) and the same diffusivity (reduced scattering coefficient $\mu_s'=10 \text{ cm}^{-1}$)

### 5.4 Experimental Results

The experimental results will be presented in two parts. Section 5.4.1 describes the results obtained from the tissue-mimicking phantoms and Section 5.4.2 describes the results acquired in chicken breast $ex \ vivo$. 

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5.4.1: Imaging in Tissue-mimicking Phantoms

5.4.1.1 Fusion of AOI and $B$-mode Ultrasound Imaging

Figure 5.6 shows a step-by-step illustration of the image construction procedure. For the sake of clarity, the experimental configuration is given in Fig. 5.6(a) and the imaging plane of the ultrasound probe is illustrated in Fig. 5.6(b). In the ultrasound imaging plane, short ultrasound pulses (3-cycle pulse at 5 MHz; peak positive pressure of ~7 MPa and peak negative pressure of ~2 MPa, measured in water) were electronically steered to fire along different directions in a fan-like pattern originating from the geometric center of the probe. The ultrasound focal length was fixed at 50 mm.

Consider now 3 lines scanned before—1, through—2, and after—3, the center of the embedded target as an example. We detected the corresponding time-domain AO signals after a coherent average of 10,000 sweeps, which are labeled in Fig. 5.6(c), as (1), (2), and (3), respectively. These time-domain signals were converted to the space domain, resulting in three 1-D line “images” ((i)-(iii) shown in Fig. 5.6(d)) along these three concentric directions. The optically absorbing target was responsible for the peak in the middle of the detected time-domain AO signal (see plot (2) of Fig. 5.6(c)), as well as the bluish (in color print only, and it appears as gray in black and white print) region at 50 mm in the converted 1-D line AO scan (see scan (ii) of Fig. 5.6 (d)). The FWHM of the blue (gray in black and white print) zone in scan (ii) is ~5 mm, which is in good agreement with the actual size (5 mm) of the target measured along the acoustic axial
direction. As expected, the characteristics of these signals are the same as those obtained using a single-element ultrasound transducer described in Chapter 4.

Figure 5.7(a) shows a cut-away photograph of the phantom with dimensions of 40x40x27 mm³ (X, Z, Y) used in the experiment, sliced to expose the 5x5x7 mm³ (X, Z, Y) optical absorber embedded at its center. Figure 5.7(b) shows the B-Mode ultrasound image, (c) the corresponding AO image, and (d) the fusion of AO image with B-mode ultrasound image, in which the AO image was color-coded and superimposed on the top of the B-mode ultrasound image. In the B-Mode image, the bright horizontal line observed at Z = ~30 mm corresponds to ultrasonic reflections from the proximal interface of the phantom caused by a slight impedance mismatch between the phantom and the surrounding water bath. The bright regions located in both distal corners correspond to the plastic phantom holder (used to maintain the phantom still in the water). The optically absorbing target itself is barely visible in the ultrasound image, as expected for such a low-contrast target. The parallel horizontal lines that demarcate the proximal and distal interfaces of the absorber are due to imperfect bonding of the target and phantom materials during the manufacturing process. The AO image has a field of view given by the circular region seen on Fig. 5.7(c), in this case, 20-30 mm in diameter. This distribution of detected modulated light is limited by the light distribution inside the ultrasound imaging plane, but may also be limited by the SNR of the system, as well as the detection aperture and position of the light collection system.

As mentioned in Chapter 4, the imaged sizes of the target represent the convolution products between the local light intensity profiles in the presence of the embedded target and the spatial dimensions of the ultrasound pulse. In this case, since the ultrasound pulse length of ~1 mm is relatively small compared to the actual target dimension (~5 mm) along the ultrasound axis, resulting in a good match in the axial dimension between the imaged target and the actual embedded target.
Figure 5.6: (a) The experimental configuration for the ultrasound probe experiment. (b) Schematic illustration of the ultrasound imaging plane with 3 scan lines selected to traverse the phantom before, through and after the center of the optically absorbing target. (c) The corresponding time-domain AO signals obtained when the ultrasound probe was firing along lines 1-3 shown in (b). (d) The converted 1-D AO images along these 3 concentric scanning lines; note the conversion was done by multiplying the known speed of sound in the medium (1.5 mm/µs).
The “fusion” of the AO image and the $B$-mode ultrasound image is shown in Fig. 5.7(d), in which the AO image was intentionally depicted as semi-transparent. As can be seen, the imaged “target” appears in exactly the same location in both the $B$-mode ultrasound and AO images, due to the fact that pulsed ultrasound originating from the same ultrasound probe was used to both generate the $B$-mode ultrasound and AO image. This is unique in that no software-related image registration is required at all in this case. The FWHM of the imaged target along the X direction is ~6.5 mm, which is slightly
larger than that measured along the axial direction. Similar phenomenon—the imaged target is slightly broadened along the X direction—has also been observed in other experiments (to be shown in the following). This broadening effect might be caused by the side lobe of the ultrasound probe along the X direction (see Section 5.2).

5.4.1.2 Imaging Contrast and Resolution

In this section, issues regarding imaging contrast and resolution will be discussed. As mentioned in Chapter 4, the minimum spatial pulse length that the single-element ultrasound transducer can produce is about 3 mm, thus limiting our axial imaging contrast and resolution, while the ultrasound probe can achieve the spatial pulse length of ~1 mm (or even less).

To explore the role of spatial pulse length, pulses of differing duration were fired along a line through the center of the optical absorber, which is the scenario illustrated in Fig. 5.6(b-2). Typical 1-D AO images thus obtained are shown in Fig. 5.8(a)-(d). These were obtained using 3, 15, 27 and 39 cycles of 5-MHz ultrasound pulses, corresponding to the spatial pulse lengths of ~0.9, 4.5, 8.1 and 11.7 mm, respectively. The AO images shown in Fig. 5.8 confirm that the axial imaging contrast clearly depends on the ultrasonic pulse length. The target can be clearly seen for the first three pulse lengths, but when the 11.7-mm-long ultrasonic pulse (i.e., slightly more than twice the absorber size along the axial dimension) is used to generate the AO signal, the presence of the target is no longer apparent. Additionally, it should be mentioned that the superior SNR of the AO images associated with longer ultrasonic pulses, apparent in Fig. 5.8, are due to the larger AO interaction volumes, as explained in Chapter 4.

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The use of the relatively high-frequency 5-MHz ultrasound probe offers a finer control of the ultrasonic pulse length, and thus allows us to investigate the dependence of the imaging contrast on the spatial acoustic pulse length in a more quantitative manner. To do so, we first define a parameter, which we refer to as the normalized signal contrast (NSC), as the amplitude of the peak in the middle of the detected AO signal (denoted by $V_P$ in Fig. 5.8(b)) divided by the amplitude of the AO signal itself (denoted by $V_A$ in Fig. 5.8(b)), i.e.,

$$\text{NSC} = \frac{V_P}{V_A}. \quad (5.1)$$

The normalized signal contrast is particularly chosen here to reflect the resolvability of the target using different ultrasonic pulse lengths. It is expected that the NSC be
distributed between 0 and 1 for AO line scans generated by different ultrasonic pulse lengths, with the higher value corresponding to the higher resolvability of the target. Figure 5.9 shows that the normalized signal contrast clearly decreases with the spatial ultrasonic pulse length.

![Graph showing the dependence of the normalized signal contrast on the spatial ultrasonic pulse length.](image)

Figure 5.9: The dependence of the normalized signal contrast (defined in the text) on the spatial ultrasonic pulse length.

The NSC can be as large as unity (no AO signal emerging from a highly absorbing target) if the ultrasound pulse is spatially short enough to be confined to the absorber only. However, the signal shown in Fig. 5.8(a) results in a NSC of only about 0.77, and similar values have also been found in highly absorbing targets, which have absorption coefficients of > 10 cm\(^{-1}\). We believe that this might be due to the side lobes of the ultrasound probe in both the X and Y directions (see Section 5.2), which are responsible for some AO interaction outside the absorber, yielding residual AO signal as if it resulted from within the absorber.
Figure 5.10 shows 2-D AO images of a $5\times5\times8 \text{ mm}^3$ (X, Z, Y) optical absorber, obtained using different spatial pulse lengths: 1.2, 6, 9 and 12 mm, respectively. It can be seen that the imaged target blurs and eventually washes out along the ultrasonic axis as longer spatial pulse lengths are employed to generate the AO images, while the lateral resolvability remains roughly the same. This serves to illustrate the advantage of using short pulses for AOI and illustrates the difficulty in forming 2-D AO images using CW ultrasound.
The ability of our system to detect smaller absorbers is demonstrated in Fig. 5.11, where a 2x2x8 mm$^3$ (X, Z, Y) optical absorber embedded at the center of the phantom has been imaged. Figure 5.11(a) shows the $B$-mode ultrasound image of the sample and Fig. 5.11(b) shows the AO image. In the middle of the AO image, the target is clearly visible and is spatially co-registered with the $B$-mode ultrasound image. The FWHM of the imaged target across the center of the target along the ultrasonic axis at X=0 and along a curve (marked in Fig. 5.11(b)) at the same focal depth of 50 mm (i.e., R=90 mm in the polar coordinate, where R=0 corresponds to the geometric center of the ultrasound probe; note that the ultrasound probe itself has a radius of curvature of 40 mm.) are about ~3 and 4 mm, respectively. These values are reasonable after taking into account the

Figure 5.11: $B$-mode (a) and AO (b) images of a 2x2x8 mm$^3$ (X, Z, Y) optical absorber, with 1-D line images across the center of the target: (c) along the ultrasonic axis at X=0 and (d) along the curve of R=90 mm from the geometric center of the probe located at R=0.
pulse length and the ultrasound beam size. The slight broadening of the imaged target along the lateral dimension could be due to the side lobe effect of the ultrasound beam along the X direction.

Figure 5.12 demonstrates the ability of the technique to resolve two identical absorbers within the same phantom (4x4x2.7 cm$^3$, X, Z, Y) with $\mu_s'=10$ cm$^{-1}$. The phantom, containing two identical 3x3x8 mm$^3$ (X, Z, Y) absorbers spaced 3 mm apart, was rotated to illustrate lateral and axial resolution; see Figs 5.12(a) and (b), respectively. The spatial pulse length used in this experiment is ~1 mm. Due to the side lobe effect of the ultrasound beam, the two targets are somewhat blurred along the lateral dimension. In contrast, when positioned along the ultrasonic axis, the two targets are well separated.

5.4.1.3 Target differentiation: supplementing ultrasound imaging with AOI

Figure 5.12: AO images of two identical 3x3x8 mm$^3$ (X, Z, Y) optical absorbers separated by 3 mm. (a) The two targets were aligned perpendicularly to the ultrasound axis. (b) The phantom was then rotated to align the two targets along the ultrasound axis. The ultrasound center frequency and spatial pulse length are 5 MHz and 1 mm, respectively.
To illustrate the ability of AOI to supplement conventional B-Mode ultrasound imaging, a diffuse phantom ($\mu_s' = 10 \, \text{cm}^{-1}$) was constructed with two embedded targets ($3 \times 3 \times 8 \, \text{mm}^3$ along the X, Z, and Y directions, respectively) separated by 3 mm along the X direction. The two targets were made using the same recipe as the surrounding phantom, except that one target contains India ink and the other does not. A cut-away view of the phantom is given in Fig. 5.13. As expected, the two targets appear identical in the B-Mode ultrasound image (Fig. 5.14(a), left), which only shows the interfaces but no acoustic contrast within the targets. On the other hand, the AO image (Fig. 5.14(a), right) leaves no doubt as to the differentiating nature of AOI, especially after comparing it with the case where two embedded targets are equally absorbing (Fig. 5.12).

Figure 5.14(b) shows typical AO signals generated by beams traversing the center of each target. When the ultrasound beam traversed the optically absorbing target on the right, a normalized signal contrast (NSC) of ~60% was observed. In contrast, when the
ultrasound beam traversed the non-absorbing target on the left, the normalized signal contrast was negligible. The above results suggest the ability of AOI to supplement conventional diagnostic ultrasound in distinguishing between optically-distinct biological features that would otherwise appear similar or identical on a conventional ultrasound image.

The above sample mimics the case where there is only optical contrast (but no acoustic contrast) present inside the targets; note that the bright interfaces which appear in the B-mode ultrasound images are only due to the imperfect bounding during the

Figure 5.14: (a) B-mode (left) and AO (right) images of two 3x3x8 mm$^3$ (X, Z, Y) targets separated by 3 mm along the X axis, as shown in Fig. 5.13. The target at X = -3 mm is identical to the background medium, whereas the target at X = +3 mm is optically absorbing. (b) Typical AO signals for separate scan lines traversing across each target.

The above sample mimics the case where there is only optical contrast (but no acoustic contrast) present inside the targets; note that the bright interfaces which appear in the B-mode ultrasound images are only due to the imperfect bounding during the
manufacturing process. Figure 5.15 further shows the target-differentiation ability of the system using two acoustically-scattering targets. In this case, the phantom has the same characteristics as the previous case except that micron-scale acoustic scatterers (hollow glass spheres, SPHERICEL 110P8, Potters Industry Inc., see the appendix) with a volume fraction of ~10% were added to the two embedded targets. The hollow glass spheres appear as white powders, with the mean diameter of 11 microns and the bulk density of 1100 kg/m$^3$. In our experiment, the hollow glass spheres were used to enhance target contrast to ultrasound while minimally modifying the relative optical contrast of the targets, only one of which was infused with India ink. This is intended to simulate the case where you have two echogenic targets with differing optical properties, as might be the case when trying to distinguish a cyst from a highly vascularized malignant tumor. (The latter possesses a greater concentration of hemoglobin.) As can be seen from the B-mode images (Fig. 5.15(a) and (b)), both the targets appear identically brighter inside, due to the scattering of ultrasound waves. In fact, the boundary connecting the two targets is smeared out, making it difficult to distinguish the shapes of the original targets from the B-mode ultrasound images. In contrast, only one target is identified from the AO image (see Fig. 5.15(c)). This is even more convincing in the normalized AO contrast image shown in Fig. 5.15(d), which was obtained by normalizing each scan line to unity, as explained in Chapter 4. From the above experimental results, it is clear that the fusion of AOI and diagnostic ultrasound can help to differentiate targets, either acoustically visible or invisible. This is encouraging from the clinical point of view in that AOI shows
the potential to differentiate tumors, and thus to serve as a supplement to conventional ultrasound imaging.

Figure 5.15: B-mode image of echogenic target pair (a) and its enlarged view (b); corresponding AO image (c) and its normalized AO contrast image (d).

5.4.1.4 Image acquisition time

The time required to acquire an AO image using the PRC-based AOI system depends primarily on: (1) the SNR of the raw (single-shot) data stream; (2) the size of the AO image (number of scan lines in the image); and (3) the desired AO image quality. Here the “image quality” includes both the readability/clarity and the spatial resolution of an AO image. The image quality is directly related to the SNR of the data in the scan line,
which can be improved by coherently averaging over shots. We therefore encounter a trade-off between the AO SNR and the averaging time, which essentially limits the image acquisition speed. The averaging time is determined by the number of samples and the pulse repetition frequency (PRF). The PRF is limited by the speed of the oscilloscope and the AN2300 imaging depth, for the time between subsequent pulses must be greater than the time it takes for the outgoing pulse to traverse the imaging zone and the echo returns to propagate back to the imaging array. For ultrasound pulses with high peak pressures, the PRF can also be limited by the safety regulation on thermal effects imposed by the FDA [13].

The SNR of a single AO shot (without averaging) depends on many parameters, such as the incident laser intensity, the acoustic pulse duration, the acoustic pulse amplitude, the optical properties of the sample, the geometry of the sample, and different kinds of noise sources [14]. In context of AOI, noise sources could include electronic noise, thermal noise, speckle noise, and shot noise. For a given experimental configuration with fixed optical parameters (laser power, APD gain, etc.), the SNR of the AO signal from a single shot strongly depends on the characteristics of the acoustic pulse—both the amplitude and the pulse length. The choice of ultrasonic pulse length is a compromise between the SNR and the desired axial resolution and imaging contrast. Longer pulses improve SNR due to the larger AO interaction volume, which results in a greater flux of phase modulated photons generated at a given point in time. However, long pulses sacrifice the axial resolution and imaging contrast. The amplitude of the acoustic pulse should be as high as possible. However, in the context of in vivo imaging,
the acoustic amplitude is limited by safety considerations, both thermal effect (quantified by thermal index (TI)) or cavitation effect (quantified by mechanical index (MI)) [13].

![Figure 5.16: AO images of a diffuse phantom (\(\mu'_s=10 \text{ cm}^{-1}\)) with an embedded target (5x5x7 mm\(^3\) along the X, Z and Y directions, respectively) obtained using several numbers of averages per scan line (noted by \(N_{av}\)). Each image consists of 41 scan lines. The actual image acquisition times are given on the top of each frame obtained for a PRF of 1 KHz.](image)

The qualitative relationship between image acquisition time and image quality is illustrated in Fig. 5.16, which shows a series of AO images constructed from scan lines that have been averaged over differing numbers of shots (denoted as \(N_{av}\)) and for fixed acoustic pulse parameters (5-cycle bursts at 5 MHz). The upper left image in Fig. 5.16 shows the AO image obtained with one single AO signal per scan line, i.e., without coherent averaging. It clearly shows that the \(SNR\) in this case is too poor to obtain a readable AO image of the embedded target. In fact, the \(SNR\) (calculated from the ratio
between the maximum signal amplitude\(^7\) and the rms value of the noise) obtained for a single AO signal without averaging turns out to be on the order of 1:2; the signal is literally lost in the noise, a fact that is clearly evident in the upper left image. As a function of \(N_{av}\), the SNR turns out to be approximately proportional to \(\sqrt{N_{av}}\), as expected for coherent averaging of uncorrelated measurements. For \(N_{av} \sim 20,000\), the SNR is on the order of 70:1.

It should be mentioned that in our current setup the time it takes for the data transfer between the computer and the oscilloscope through the GPIB interface is not negligible. Indeed, this time dominates the averaging time for the low averaging number of \(N_{av}\). Through dedicated hardware, it is expected that this time could be dramatically reduced, yielding a significant reduction in the actual imaging acquisition time. For instance, the imaging acquisition time of the last AO image shown in Fig. 5.16 (corresponding to \(N_{av}=25600\)) will be reduced by about three quarters if the data transfer and processing time can be neglected.

5.4.1.5 Fusion of 3-D AOI and B-mode Ultrasound Imaging

As mentioned in Chapter 4, the utility of diffuse, rather than ballistic, light in AOI may allow for 3-D imaging of optical inhomogeneities. The absorption of ballistic photons leads to the formation of shadows behind strong absorbers. The idea is that the tortuous paths attained by diffuse photons provide many avenues for photons to get around targets,

\(^7\) In this case, the maximum amplitude of the AO signals is estimated from that obtained with coherent averaging.
and the extent and contrast depth of the shadow should be correspondingly reduced. This allows for a direct fusion of 3-D AOI and B-mode ultrasound imaging.

We tested this concept initially by rotating the imaging transducer by 90 degrees and forming an AO image in the YZ plane. If a highly absorbing target results in the formation of an optical shadow, it will be manifested as a lack of symmetry in the YZ-plane AO image of a symmetrical target. In the experiment, a phantom with a single embedded target (~5x5x8 mm\(^3\) along the X, Z, and Y directions, respectively) was used.

Figure 5.17: AO imaging in the YZ plane: (a) experimental configuration, (b) B-mode ultrasound image, (c) AO image, and (d) normalized AO image. The target is an embedded optical absorber with dimensions of 5x5x8 mm\(^3\) (X, Z, Y).

We tested this concept initially by rotating the imaging transducer by 90 degrees and forming an AO image in the YZ plane. If a highly absorbing target results in the formation of an optical shadow, it will be manifested as a lack of symmetry in the YZ-plane AO image of a symmetrical target. In the experiment, a phantom with a single embedded target (~5x5x8 mm\(^3\) along the X, Z and Y directions, respectively) was used.
Figure 5.17 (b) and (c)(d) show the B-mode and AO images acquired along the YZ-plane denoted as X=0 (corresponding to the center of the target along the X direction). The AO image and its normalized version appear symmetrical, with no obvious indication of the kind of asymmetry in the Y direction to be expected if the target cast an optical shadow.

Three-dimensional fusion of AOI and diagnostic ultrasound can be achieved by mechanically scanning the ultrasound probe (1-D transducer array) along the X direction. At each scanning location along the X direction, the corresponding B-mode and AO images along the YZ plane can be obtained following the same procedure used above. By doing this, 3-D information regarding both the mechanical and opto-mechanical properties of the sample can be obtained.

Figure 5.18 shows sequential B-mode ultrasound images at different locations along the X axis, with X=0 roughly crossing the center of the target. As expected, the two bright lines in the middle of the B-mode images (indicating the top and bottom interfaces of the target) become less apparent as the ultrasound imaging plane is moved away from the center of the target. Figure 5.19 and Fig. 5.20 show the corresponding AO images and its normalized versions at the above X locations as denoted on the top of each individual image. From Figs. 5.19 and 5.20, it is clearly seen that the AO contrast of the target also decreases with the distance from the center of the target, in agreement with the B-mode ultrasound images.

It should be noted that the absolute AO signal amplitudes obtained closer to the laser illumination direction are typically higher (see Fig. 5.19, the left sides of the AO

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8 Three-dimensional AO images could also be electronically achieved through 2-D arrays.
images appear darker/redder than the right sides, especially near the center of the laser illumination). This is because more photons are modulated at the locations where the laser beam first enters the sample (see Chapter 2 about the photon distribution in diffuse media). This asymmetry in the image is not seen in Fig. 5.20, for the normalization process accounts for spatial variability in the diffuse background illumination field.

Figure 5.18: A series of $B$-mode ultrasound images of the phantom with a single embedded target (~5x5x8 mm$^3$ along the X, Z and Y directions, respectively) along different YZ planes (denoted by different X values), separated by 1 mm.
Figure 5.19: A series of AO images of the sample (see the details in the text) in different YZ planes (denoted by different X values), separated by 1 mm.
Figure 5.20: A series of normalized AO images of the sample (see the details in the text) in different YZ planes (denoted by different X values), separated by 1 mm.
5.4.2: Imaging in Excised Biological Tissue

In this section we present results obtained in excised biological tissue (chicken breast). By using \textit{ex vivo} samples, we take into account (approximately) acoustic and optical absorption and scattering microstructure present in many biological tissues. In the first stage of the experiments, the same setup as shown in Fig. 5.1 was used. It is found that in this case the imaging depth is very limited, and the SNR is poor for a biological tissue with a thickness of more than 1.2 cm. This is in large part due to the optical absorption and acoustic absorption of the biological tissue, both of which are small in the diffusive phantoms. Meanwhile, it should be noted that the laser power density used in our current setup ($\sim$20 mW/cm$^2$) is about ten times less than the FDA safety limit of $\sim$200 mW/cm$^2$ for green laser [15].

In order to investigate AOI at relatively large depths in biological tissue, the experimental setup (shown in Fig. 5.1) is updated by employing a more powerful green laser ($\sim$230 mW, 532 nm, frequency doubled Nd:YAG laser source, Model 142, Lightwave Electronics, Mountain View, CA, USA). In the new experimental setup, which has the same arrangement as that shown in Fig. 5.1, the laser beam is sent to the variable beam splitter where it is split into signal and reference beams with a power ratio of approximately 40:1. The signal beam is sent to the submerged biological sample after passing through a 10x beam expander, yielding a final waist diameter of about 2 cm. The resulting power density at the sample surface is about 62 mW/cm$^2$, which is well within the FDA safety limit. The updated experimental setup allows us to image biological
tissue with a thickness of ~2 cm, with reasonably good SNR. The following experiment demonstrates the new system for 3-D fused imaging of thick biological tissue.

In this experiment, chicken breast was used as our biological sample and was squeezed in between two thin parallel transparent plastic plates with a thickness of 1.3 mm. These two plates serve to hold the biological sample still in space and maintain a uniform sample thickness in a manner similar to that used in breast examination by X-ray mammography. The final thickness of the sample along the laser illumination direction (Y-axis) is ~2 cm. Both the sample and the ultrasound probe were submerged in a small glass tank (30 cm × 30 cm × 20 cm along the X, Y and Z axes, respectively) filled with degassed and filtered water in order to achieve a good acoustic coupling. A 4x4x4 mm³ optical absorber was embedded roughly at the center of the biological sample (see Fig. 5.21), by cutting and opening the sample across the XZ plane. The target-embedding procedure was carefully done in the degassed water, minimizing the possibility of bubble trapping. The optical absorber was fabricated using the same poly-acrylamide gel as used in the previous Chapters with India ink added to enhance the optical absorption coefficient. The absorber possesses an optical absorption coefficient of about 3-4 cm⁻¹ and low acoustic contrast.

We followed an experimental procedure similar to that described in Section 5.4.1.5, and can be briefly summarized as follows: starting at a given Y location in the ultrasound imaging plane (the XZ) plane, 3-cycle-long ultrasound pulses are electronically steered to fire along different concentric directions, to both form B-mode ultrasound images and to generate AO signals. Along the direction of ultrasonic
propagation, time is converted to space using a constant sound speed, which is 1500 m/s for both our host tissue and target. Once the imaging acquisition is done for both $B$-mode and AO images in this XZ plane, the ultrasonic probe is mechanically scanned to the next position along the Y direction. By repeating doing this, three-dimensional $B$-mode ultrasound images and AO images are obtained.

Figure 5.22(a) shows the typical normalized AO signals resulting from individual scan lines fired along the Z axis at three different Y locations. At position (2) the scan traverses the center of the absorbing target (Y=0). At positions (1) and (3), the scan is moved 6 mm along the Y axis in either direction. When the ultrasound beam passes through the target, a peak is observed in the detected AO signal, which corresponds to the presence of an optical absorber along the ultrasound scan line. The signals observed when the beam does not intersect the absorber (traces (1) and (3)) are quite similar, and do not

Figure 5.21: A cut-way view of the chicken breast sample (~4x4x2 cm$^3$ along the X, Z, Y directions, respectively) with an optically absorbing target (4x4x4 mm$^3$). The target was made of the same poly-acrylamide gel as used in the previous Chapters with India ink added.
show this feature. Since the light is primarily coming from left to right in Fig. 5.22 (b), the similarity of traces (1) and (3) suggests that, when illuminated with diffusive optical light, the target is resolvable along the laser illumination direction even in real biological tissues. The improved SNR of plot (1) in Fig. 5.22(a) is due to the greater amount of photons modulated when the ultrasound probe is closer to the incident laser beam.

Figure 5.23(a) shows a B-mode ultrasound image acquired along the XZ plane at Y=0. The optically absorbing target appears as a dark, uniform region in the middle of the sample. The image speckle surrounding the target is caused by acoustic scattering from the tissue microstructure. The AO image of the same target is given in Fig. 5.23(b). The AO signals are coherently averaged over 40,000 sweeps, requiring 40 seconds per scan line. The data in Fig. 5.23(b) have been processed using a procedure illustrated in
Figure 5.23(c). First, the raw data (i) is smoothed using adjacent averaging (over 17 adjacent points), with the resulting signal plotted in (ii). The portions of the data from (ii) that precede and follow the target, are then fitted to a Gaussian function, which yields an estimate of the background light intensity distribution, in the absence of the optical absorber. By subtracting (ii) from (iii), we obtain the signal representing the perturbation induced by the optical absorber. The subtracted signal is normalized to the background (iii), and the final processed signal is shown in (iv). This is repeated for each scan line and the resulting signal levels are converted to a color scale and superimposed on the ultrasound image, yielding the AO image in Fig. 5.23(b). The FWHM of the imaged target along the X and Z directions are found to be about 4.8 mm and 4.9 mm, respectively, corresponding to the convolution products between the local light intensity profiles and the spatial extents of the ultrasound pulse along the X and Z directions (along X: ~0.8 mm, along Z: ~1.0 mm, see Section 5.2).

Three-dimensional acoustic and optical information can be obtained by mechanically scanning the ultrasound probe along the Y axis and forming parallel 2-D images, as mentioned in Section 5.4.1. Since the production of 3-D AO images requires far greater acquisition time, longer duration ultrasound pulses are used to enhance the single-shot $SNR$ and to reduce the averaging time per scan line. Using 9-cycle pulses with a spatial length of 2.7 mm, it is found that the target is still well resolvable, and 10,000 averages are sufficient to generate AO signals with a sufficient $SNR$, leading to a 75% reduction in the signal averaging time.
Six AO images corresponding to parallel slices through the sample are shown in sequences in Fig. 5.24. Each image is oriented in the XZ plane and displaced by 2 mm in the Y direction. The target image contrast clearly diminishes as soon as the scan plane is moved out of the target volume (roughly centered at Y=0), and this change is qualitatively similar regardless of whether the Y location is increased or decreased. The AO images agree well with the B-mode images in terms of the location of the target. In addition, a 1-D image across the center of the target along the Y axis allows us to identify the FWHM of the imaged target, which is found to be about 6.7 mm. This value is still reasonable since the focal dimension of the ultrasound probe along the Y direction is 1.2-

![Figure 5.23: X-Z plane B-mode (a) and AO (b) images of the embedded optical absorber (see details in text). The color-coded AO image corresponds to the normalized AO signals processed using a technique depicted in (c).](image)
2.2 mm (see Section 5.2). Other factors that might affect the imaged dimensions of the target include the size-lobe effect of the ultrasound probe, and the imperfect alignment of the system.

When the ultrasound beams traverses the center of the target along the Z axis (corresponding to the scenario illustrated in Fig. 5.22(b)-2), different cycles of ultrasound pulses are used to generate the AO signals. It is found that inside the...
biological sample, regardless of the microstructure and absorptions of the real tissue, the axial imaging contrast is still controlled by the actual acoustic pulse length (see Fig. 5.25). This is consistent with the previous phantom experiments (see Section 5.4.1.2).

5.5 Conclusion

The in vitro and ex vivo experimental results reported herein demonstrate that B-mode and AO imaging can be simultaneously implemented for 2-D and 3-D imaging of highly diffuse media (including real biological samples) using a commercially-available ultrasound scanner. This yields both acoustical and optical contrast information in the form of two automatically co-registered images. The use of short ultrasound pulses to excite the AO response enables the utilization of standard imaging technology to yield a true dual-mode imaging capability sensitive to both acoustical and optical contrast. Good quality AO and ultrasound images of highly diffusive phantoms or biological samples are

Figure 5.25: Time-domain AO signals obtained using different cycles of acoustic pulses.
obtained relatively quickly, with controllable imaging contrast. The dual-mode imaging system could be potentially used to improve the diagnostic accuracy and the specificity of conventional ultrasound imaging.
References:


Chapter 6

Conclusions

6.1 Summary of Work Done

The work presented in this dissertation can be mainly divided into two parts. The first part focuses on designing and developing a PRC-based interferometry system that can enhance the detection of ultrasound-modulated optical signals in highly diffuse media. The detection system is used for subsurface imaging in turbid media, and a pulsed ultrasound source is used for pumping the AO interaction, yielding improvements in axial resolution over systems which use continuous-wave ultrasound. The second part of the work involves the successful fusion of pulsed AOI and B-mode ultrasound imaging using a commercially available diagnostic scanner/imager (Analogic, AN 2300).

The PRC-based interferometer compensates for the complex wavefront of the scattered/diffuse light (signal beam) by providing a wavefront-matched local oscillator (LO). By mixing the signal beam with the LO, the phase modulation encoded on the signal beam by the focused ultrasound is converted to an intensity modulation, which can then be directly detected by a single optical detector. This system allows for multiple speckles to be collected and sent to a single optical detector, and the signals from each of
the speckles add coherently. A theoretical model for the detection of acoustically induced phase modulation in turbid media using the PRC based interferometry has also been developed.

Experiments conducted in highly diffuse phantoms, using a single-element ultrasound transducer, were performed to study the characteristics of the detection system. The results show that the PRC-based system has enough sensitivity to work with pulsed ultrasound. The use of short pulses of focused ultrasound has been shown to be capable of providing mm-scale axial resolution. A 1-D AO image along the ultrasonic axis can be directly obtained from a single, time averaged AO signal by converting the signal from the time domain to the space domain using the speed of sound in the media. Two-dimensional AOI has been achieved by scanning the ultrasound transducer in one dimension. It has also been shown that three dimensional AOI is possible, and that it does not require conventional tomographic reconstruction. The axial and lateral resolutions of the system are controlled by the spatial pulse length and the width of the ultrasound beam, respectively.

The fact that the developed PRC-based AOI system allows for pulsed ultrasound makes a direct fusion of AOI and diagnostic ultrasound possible. The combination of pulsed AOI and conventional B-mode ultrasound imaging has been achieved using a commercially available pulsed-ultrasound scanner (Analogic, AN2300) coupled with the PRC-based optical interferometry system. Using this system, B-mode ultrasound and AO images of different embedded targets have been obtained with millimeter resolution, in both highly diffusive phantoms ($\mu_s'=10 \text{ cm}^{-1}$) and in real biological tissues (chicken
breast). The AO images are intrinsically co-registered with the $B$-mode ultrasound images. Three-dimensional fusion of AOI and $B$-mode ultrasound imaging has also been demonstrated in thick biological tissues of ~2 cm. The results suggest that AOI could be used to supplement conventional $B$-mode ultrasound imaging by generating additional optical information.

In addition, a theoretical model, based on light propagation in turbid media, is used to explore the dependence of the AO response on the experimental geometry, light collection aperture, and target optical properties.

### 6.2 Directions of Future Work

One potential application of dual-mode AO and diagnostic ultrasound imaging is breast cancer detection and diagnosis. However, several technical barriers must be overcome before this technique can be brought to clinical trials. Technical barriers include the limited imaging depth, relatively long image acquisition time, and the requirement of vibration isolation.

For human breast tissue, the clinical useful thickness is 5-10 cm [1]. Therefore, the imaging depth of the current AOI system must be enhanced. Using our current system, AO images have been obtained in excised biological tissue with a thickness of 2 cm. This result is promising, because a green laser (wavelength: 532 nm), with a power density 3 times lower than the maximum permissible exposure (MPE) limit [2] was employed to form the AO image. 532 nm is not the ideal wavelength for biomedical imaging primarily due to the high absorption of biological tissues for this wavelength, limiting the imaging depth. In contrast, near-infrared (NIR) wavelengths offer a much
larger penetration depth. The MPE for 1064-nm wavelength is about 1 W/cm², which is 5 times larger than that for the green laser. Meanwhile, the optical absorption and scattering of biological tissue for 1064 nm are both less than that for green laser (532 nm). In chicken breast, for instance, there is more than 5-fold reduction in absorption coefficient and a 2-fold reduction in reduced scattering coefficient between these two wavelengths [3]. It is therefore possible to achieve a significant improvement in imaging depth by simply switching to a longer optical wavelength, like 1064 nm.

Greater imaging depth may also be achieved by using a higher-power pulsed laser. The currently existing AOI systems make exclusive use of continuous wave (CW) laser sources. This is primarily due to the fact that CW ultrasound is employed to pump the AO response and the light emission measurement is integrated over a long time period. The use of a CW laser source is not beneficial in this case because the SNR is dictated by the average photon flux received by the detection system over the measurement period. In our AOI system, we make transient measurements using pulsed ultrasound, rather than a continuous integrated measurement using CW ultrasound. There is no need to use a CW laser, because the AO response is only excited during the time of ultrasound exposure and the SNR is directly proportional to the modulated photon flux incident on the detector during the transit time of the ultrasonic pulse through the imaging region. Thus, the use of a pulsed laser, firing only during the transmission of the ultrasound pulse through the desired imaging region, is clearly more appropriate. This way, we can increase the peak photon flux and SNR while still remaining below the MPE, which is based on a time average measure.
The image acquisition time, as mentioned in Chapter 5, is related to the SNR of the system and the subsequent imaging depth. By employing the higher peak-power pulsed laser, enhanced SNR can be achieved and the image acquisition time can be reduced. The result is a system that can image at greater depth and with enhanced speed, both of which are desirable in a clinical imaging system.

Another limitation of our current AOI system is that it is required to be isolated in order to compensate for the room vibration and other environmental noises. This is clearly not suitable for real clinical applications. A PRC with faster response time working with the NIR wavelength is desirable to eliminate the room vibration and physiological motion over the measurement time. For instance, GaAs and InP:Fe are both excellent candidate materials for 1064 nm wavelength, with response time on the order of ms or less [4].
References:


APPENDIX A

Fabrication of the AOI phantom

AOI is a hybrid process that involves both light and sound propagation. Thus we seek a test medium that mimics both the acoustical and optical properties of human tissue. The relevant acoustical properties of human tissue include density, speed of sound and attenuation. The important optical properties include optical scattering and optical absorption. As one of the ultimate applications of AOI is for the detection of breast cancer and since breast tissue has an optical absorption coefficient that is small compared to the scattering coefficient, we set out to develop phantoms that replicate the reduced scattering coefficient (optical descriptor), and the density and speed of sound (acoustical descriptors) of living tissue. We make no attempt to recreate the micro-architecture or vasculature of real tissue at this point in time.

Our AOI phantom is a modification of the transparent acrylamide gel phantom [1, 2], with the addition of 0.4 µm-diameter polystyrene microspheres for optical diffusivity. The concentration of particles required to generate a desired optical diffusivity is determined using a standard from a Mie scattering formulation [3]. The fabrication procedure is as follows:

1. 9.375 g of acrylamide and 0.265 g of bis-acrylamide are dissolved in 50 ml of deionized water;
2. The mixture is stirred and degassed (typically, at least several minutes);
(3) The desired amount of microspheres is added to the mixture and the mixture is slowly stirred to avoid entraining bubbles;

(4) 0.02g of ammonium persulfate (a polymerizing initiator) and 0.2 ml of TEMED (Sigma Chemical) are added to the mixture and the fluid-like mixture is quickly poured into a mold;

(5) The mold is covered and the mixture is allowed to cure at room temperature until it is completely solidified;

(6) The phantom is thoroughly rinsed with water and subsequently stored submerged in water. (It is noted that un-polymerized acrylimide is highly toxic and proper precautions must be taken during phantom preparation.)

The dimensions of the phantoms used in this work are about 4.0 cm × 4.0 cm × 2.7 cm and they are oriented such that the laser passes through the 2.7-cm dimension. The measured acoustic properties of the phantom material are listed in Table A in comparison with literature values for human breast tissue. The obvious mismatch in acoustic attenuation is not deemed significant to the work reported herein.

<table>
<thead>
<tr>
<th>Acoustic Properties</th>
<th>Gel Phantom</th>
<th>Human Breast [4]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mass Density (Kg/m$^3$)</td>
<td>1045</td>
<td>990-1060</td>
</tr>
<tr>
<td>Speed of Sound (m/s)</td>
<td>1515</td>
<td>1450-1570</td>
</tr>
<tr>
<td>Attenuation (Np/m/MHz)</td>
<td>0.2</td>
<td>3.4-7.4</td>
</tr>
</tbody>
</table>

Table A: Measured values of the acoustic properties of the AOI phantom, in comparison with literature values for the acoustic properties of human breast tissue.
References:


APPENDIX B

SPHERICEL® Hollow Glass Spheres

SPHERICEL® hollow glass spheres are originally used to enhance performance and reduce viscosity in paints and coatings and as lightweight additives in plastic parts. These spheres are chemically inert, non-porous, and have very low oil absorption. Among them, Grade 110P8 is used in many high performance polymer systems.

In Chapter 5, we use it as acoustic scatterers, taking advantage of its “hollow” property. In addition, the spheres look white, and thus will not dramatically change the absorption properties of the targets. The typical properties of the hollow glass spheres (Grade 110P8) are listed in the following table.

<table>
<thead>
<tr>
<th>Sphericel® Typical Properties</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Shape</strong> Spherical</td>
</tr>
<tr>
<td><strong>Color</strong> White</td>
</tr>
<tr>
<td><strong>Composition</strong> Proprietary Glass</td>
</tr>
<tr>
<td><strong>Density</strong> 1.1 g/cc</td>
</tr>
<tr>
<td><strong>Particle Size</strong> Mean Diameter 11 microns</td>
</tr>
<tr>
<td><strong>Hardness</strong> 6 (Moh’s Scale)</td>
</tr>
<tr>
<td><strong>Chemical Resistance</strong> Low alkali leach/insoluble in water</td>
</tr>
<tr>
<td><strong>Crush Strength</strong> &gt;10,000 psi</td>
</tr>
</tbody>
</table>

Table B: Properties of the sphericel hollow glass spheres.
APPENDIX C

Error Analysis

Error intrinsically exists in the experimental measurements. This is caused by the finite precision and accuracy of the apparatus, the stability/repeatability of the measurement system, etc. [1]. In the AOI experiments, we are measuring the AO signals, which are displayed as voltage (as a function of time) on the oscilloscope. The AO signals are important in terms of both the absolute amplitudes and the relative temporal evolution as the acoustic pulse traverses the medium. The absolute amplitudes of the AO signals reflect the local AO interaction strengths, and the relative shapes of the AO signals yield the spatially-dependent changes of tissue properties (as ultimately manifested in the spatially dependent imaging contrast). Additional important measurements made in this dissertation include the dimensions of the imaged targets, the focal pressure amplitudes, and the acoustical properties of the propagation medium. The following analysis will focus on the main errors in these measurements.

(a) Measurement of the AO signals

The measurement of the AO signal amplitude is mostly affected by the stability or repeatability of the PRC-based interferometry system. As mentioned in Chapter 3, the response time of the photorefractive BSO crystal under the experimental condition is about 150 ms, which means that the PRC can only offset environmental motions up to a few Hz. This makes the current AOI system somewhat sensitive to environmental vibration, which in turn affects the stability of our measurement system. The stability of
our AOI system (built on an air-floated optical table) was tested by repeatedly measuring the variation in the detected AO signals over time using a sample for which all acoustical and optical parameters are assumed to be stationary. Note that the measurement of the stability depends on the number of coherent averages. In other words, the signals have to be coherently averaged enough times to minimize the error from the otherwise poor SNR. In our case, the AO signals (detected from a homogeneous diffuse phantom, see Section 4.1 for details) were coherently averaged over 10,000 repeated sweeps to acquire a satisfactory SNR, and the resulting ensemble averaged, time-dependent voltage was then recorded. This same measurement was repeated many times, while the nominal experimental conditions were kept the same. One typical result is shown in Fig. C\(^1\), where we plot the maximum excursion of the time-averaged AO signal as a function of elapsed time, where the intervening period between the measurements is \(~1\) minute. The maximum and minimum deviations from the mean (average) in these results are 3.5\% and 5.13\%, respectively. The standard deviation of the measurements is 2.6\%. However, it should be mentioned that larger variation (up to 50\%) could occur if the optical table, where the experiment is set up, is subjected to rapid and strong vibrations. These sources of vibrations could include strong natural environmental vibrations due to construction, traffic, and unintentional touching of the surface of the optical table. It should be mentioned that the lab where the optical table is located is relatively noisy—about 10 m away from the highway as well as an air-compressor, and 100 m away from a construction site. The combination of these noise sources makes floating the optical table

\(^1\) The same data were also shown in Chapter 4, but here they are re-plotted to make this appendix of error analysis self-complete.
more important; indeed, the SNR of the AO signals is dramatically reduced if the optical table is not floated.

The fact that these sources of strong vibrations can lead to a large variation in the experimental measurements is evident from the 2-D AO images (see Chapter 4) acquired over a longer period of time, where the striations in the image are due to variability in the AO SNR from one scan line to the next. Typically, less than 4 scan lines out of 30 will see such a strong variation, yielding a probability of occurrence of 13%. From the above evidence, it is clearly seen that the PRC response time, which in part determines the stability/repeatability of our AOI system, is a critical parameter in designing such systems. This is especially true for clinical imaging, where environmental vibrations and physiological motions intrinsically exist. Photorefractive crystals with faster response time are needed for such applications, as mentioned in Chapter 6.

![Figure C: Test of the stability/repeatability of the PRC-based system. In this experiment, we coherently averaged the signals for 10,000 sweeps and recorded the signal amplitudes. The same measurement was continuously retaken 15 times over time. The intervening period between two consecutive measurements is about 1 minute. Finally, the signals were normalized to the mean value of the measurements.](image-url)
The above stability/repeatability of the PRC-based system, however, will not affect the measurements of the shapes of the AO signals. This is because such measurements are relative measurements in which the bias errors due to the stability of the system scale the entire AO signals, without distorting their relative shapes. By the same token, the stability/repeatability of the system is not expected to affect such measurements as the imaged target size along the ultrasonic axis, which only depends on the shape of the time-dependent AO signal, instead of its absolute amplitude. However, the dimensions of the imaged targets along the other two dimensions do depend on the stability of the AO system, although the normalization procedure used in this work can somehow helps to reduce the errors. Additional errors in measuring the sizes of the imaged targets are considered below.

(b) Measurement of the dimensions of the imaged targets

In our experiments, the AO images along the ultrasonic axis are converted from the time-domain AO signals based on a constant sound speed of 1500 m/s. This induces an error of 1% in the measurement of the dimensions of the imaged targets, for the tissue-mimicking phantom experiments (the actual speed of sound in the tissue-mimicking phantom are measured to be 1515 m/s). It should be noted, however, that the speed of sound will not affect the co-registration between B-mode ultrasound images and the AO images since the image construction procedure is exactly the same—the relative position between the AO images and B-mode ultrasound images are always the same.

The other two dimensions of the imaged target are derived from the scanning (either mechanically or electronically) of the ultrasound transducer/probe. The scanning
step size in the case of the single-element ultrasound transducer is typically 1 mm, which is limited by the focal beam waist of the transducer (FWHM: 1.5 mm). In the case of the ultrasound probe, the electronic scanning step size at the focal depth is 0.6 mm. It is important to mention that the side lobes of the ultrasound probe can significantly affect the measurements of the imaged targets along these two dimensions. For instance, from the calibration of the ultrasound probe (see Section 5.2 in Chapter 5), the side lobes in the ultrasound imaging plane are located ~1.5 mm apart from the main lobe, and have the pressure amplitudes of more than 50% of the peak pressure (for the peak positive pressure measurement). Therefore, the side-lobe effect of the ultrasound transducer/probe in designing the AOI systems is another important factor, which requires to be carefully considered.

(c) Measurement of the focal pressure amplitudes

The focal pressures given in the previous Chapters are based on the calibration measurement made in a large tank filled with degassed water. In our AOI system, the diffuse tissue-mimicking phantom was used, and its acoustic properties (see Appendix A—density: $\rho_p = 1045$ kg/m$^3$; speed of sound: $c_p = 1515$ m/s) were measured using an apparatus built in our lab [2]. The acoustic impedance mismatch between the tissue-mimicking phantom and degassed water at room temperature (water density $\rho_w = 997$ kg/m$^3$; speed of sound $c_w = 1497$ m/s) is 6.07%. In addition, the attenuation coefficient of the phantom was measured to be ~0.2 Np/m/MHz (i.e., ~1.7 dB/m/MHz), which is on the same order as the water (~1 dB/m/MHz). These numbers are not considered significant since our acousto-optic imaging depth is less than 20 cm.
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Vita

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