Extracting Material Parameters of Porcine Arterial Tissue at Terahertz with Applications to Vulnerable Plaque Diagnosis

A Thesis Presented

by

Chad Joseph Donahue

to

The Department of Electrical Engineering

in partial fulfillment of the requirements
for the degree of

Master of Science

in

Electrical Engineering

Northeastern University
Boston, Massachusetts

June 2012
Abstract

Acute myocardial infarction (AMI) is a leading cause of death in the United States and industrialized countries [1]. Research conducted over the past 20 years has demonstrated that numerous types of minimal to modest stenotic atherosclerotic plaques, termed vulnerable plaques, are precursors to severe complications, including coronary thrombosis, myocardial ischemia, and sudden cardiac death. Post-mortem analyses have identified the thin-cap fibroatheroma (TCFA), a type of vulnerable plaque, as the culprit lesion in roughly 80% of sudden cardiac deaths [2–4]. Further study is necessary in order to fully understand the morphology, and thus properly diagnose and treat these lesions as means of prevention of coronary artery disease (CAD).

The work presented here attempts to take the first step toward gauging the viability of terahertz imaging as a diagnostic procedure. Characterizing the material parameters of healthy arterial tissue is necessary in order to create electromagnetic models to assess the ability of terahertz to penetrate and characterize the specific structure of healthy artery, and thus be able to distinguish it from a vulnerable plaque.

Though general tissues have already been characterized at these frequencies (epithelium, adipose, muscle, etc.), no study has attempted to characterize arterial tissue. Porcine tissue was chosen for study, as its biological makeup is relatable to that of a humans, and samples were easily available. Utilizing a transmission geometry THz spectrometer, measurements of the tissue’s electric properties were extracted.
5.3 Conclusions and Future Work .......................... 63

References ..................................................... 64
## List of Figures

<table>
<thead>
<tr>
<th>Figure</th>
<th>Description</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Initiation of a Plaque</td>
<td>11</td>
</tr>
<tr>
<td>2</td>
<td>Progression of Plaque</td>
<td>11</td>
</tr>
<tr>
<td>3</td>
<td>Disruption of Plaque</td>
<td>12</td>
</tr>
<tr>
<td>4</td>
<td>Difficulty in Discriminating between Types of Plaque [5]</td>
<td>13</td>
</tr>
<tr>
<td>5</td>
<td>Plaque Makeup [6]</td>
<td>14</td>
</tr>
<tr>
<td>7</td>
<td>Transverse MR images of Arterial Plaque [7]</td>
<td>16</td>
</tr>
<tr>
<td>8</td>
<td>IVUS Images of Difference in Lumen Cross-sectional Area [8]</td>
<td>17</td>
</tr>
<tr>
<td>9</td>
<td>In Vivo OCT Image of Vulnerable Plaque [9]</td>
<td>18</td>
</tr>
<tr>
<td>10</td>
<td>Schematic Diagram of a THz-TDS Spectrometer [10]</td>
<td>20</td>
</tr>
<tr>
<td>11</td>
<td>Example Electric Field Amplitude Measurement for THz Sample and Reference Signals [10]</td>
<td>21</td>
</tr>
<tr>
<td>12</td>
<td>Ray Propagation through a Homogenous Sample</td>
<td>24</td>
</tr>
<tr>
<td>13</td>
<td>Preliminary Signal Processing Flow</td>
<td>26</td>
</tr>
<tr>
<td>14</td>
<td>Sample and Reference THz Pulses through Inner Artery</td>
<td>36</td>
</tr>
<tr>
<td>15</td>
<td>Wave Phase through Inner Artery</td>
<td>37</td>
</tr>
<tr>
<td>16</td>
<td>Theoretical Transfer Function of Inner Artery</td>
<td>38</td>
</tr>
<tr>
<td>17</td>
<td>Refractive Index of Inner Artery</td>
<td>39</td>
</tr>
<tr>
<td>18</td>
<td>Absorption of Inner Artery</td>
<td>40</td>
</tr>
<tr>
<td>19</td>
<td>Complex Permittivity of Inner Artery</td>
<td>41</td>
</tr>
<tr>
<td>20</td>
<td>Conductivity of Inner Artery</td>
<td>41</td>
</tr>
<tr>
<td>21</td>
<td>Sample and Reference THz Pulses through Middle Artery</td>
<td>42</td>
</tr>
<tr>
<td>22</td>
<td>Wave Phase through Middle Artery</td>
<td>43</td>
</tr>
<tr>
<td>23</td>
<td>Theoretical Transfer Function of Middle Artery</td>
<td>44</td>
</tr>
<tr>
<td>24</td>
<td>Refractive Index of Middle Artery</td>
<td>45</td>
</tr>
<tr>
<td>25</td>
<td>Absorption of Middle Artery</td>
<td>46</td>
</tr>
<tr>
<td>26</td>
<td>Complex Permittivity of Middle Artery</td>
<td>47</td>
</tr>
<tr>
<td>27</td>
<td>Conductivity of Middle Artery</td>
<td>48</td>
</tr>
<tr>
<td>28</td>
<td>Sample and Reference THz Pulses through Outer Artery</td>
<td>49</td>
</tr>
<tr>
<td>29</td>
<td>Wave Phase through Outer Artery</td>
<td>50</td>
</tr>
<tr>
<td>30</td>
<td>Theoretical Transfer Function of Outer Artery</td>
<td>51</td>
</tr>
<tr>
<td>31</td>
<td>Refractive Index of Outer Artery</td>
<td>52</td>
</tr>
<tr>
<td>32</td>
<td>Absorption of Outer Artery</td>
<td>53</td>
</tr>
<tr>
<td>33</td>
<td>Complex Permittivity of Outer Artery</td>
<td>54</td>
</tr>
<tr>
<td>34</td>
<td>Conductivity of Outer Artery</td>
<td>54</td>
</tr>
<tr>
<td>35</td>
<td>Refractive Index of All Artery Sections</td>
<td>55</td>
</tr>
<tr>
<td>36</td>
<td>Conductivity of All Artery Sections</td>
<td>56</td>
</tr>
<tr>
<td>37</td>
<td>FDFD Model of Healthy Artery vs Artery with Plaque</td>
<td>57</td>
</tr>
<tr>
<td>38</td>
<td>Quasi-Space Values for Determining Thickness of Inner Artery</td>
<td>59</td>
</tr>
</tbody>
</table>
List of Tables

1  IVUS and OCT Image Findings for Corresponding Image Pairs [9] . . . 19
2  Computed Thickness of Arterial Wall Sections in Polyethylene Bag . . . 21
3  Complex Dielectric Constants Used in Computational Model . . . . 33
1 Introduction

Acute myocardial infarction (AMI) is a leading cause of death in the United States and industrialized countries [1]. Research conducted over the past 20 years has demonstrated that numerous types of minimal to modest stenotic atherosclerotic plaques, termed vulnerable plaques, are precursors to severe complications, including coronary thrombosis, myocardial ischemia, and sudden cardiac death. Postmortem analyses have identified the thin-cap fibroatheroma (TCFA), a type of vulnerable plaque, as the culprit lesion in roughly 80% of sudden cardiac deaths [2–4]. Over 90% of TCFAs occur within the most proximal 5.0 cm segment of each of the main coronary arteries [left anterior descending (LAD); left circumflex (LCx); and right coronary artery (RCA)] [2, 4]. The following features typically characterize the TCFA histologically: (1) thin fibrous cap (<65 μm), (2) large lipid pool, and (3) activated macrophages near or within the fibrous cap [2, 4, 6, 11]. It is hypothesized that these particular features predispose TCFAs to biomechanical-stress-induced rupture [12,13]. When ruptured, procoagulant proteins are released, such as tissue factor. Following these events, a substrate for thrombus formation is created, leading to an acute coronary event [14]. While TCFAs have been associated with the majority of AMIs, recent autopsy studies have demonstrated that coronary plaques with erosions or superficial calcified nodules may also precipitate thrombosis and sudden occlusion of a coronary artery [2, 4, 14, 15].

Although autopsy studies are valuable in determining features of culprit plaques, the ability to quantify the risk of an individual plaque for causing an acute coronary thrombosis is lost. TCFAs are a frequent autopsy finding in asymptomatic patients and are found just as frequently in culprit and nonculprit arteries of subjects having suffered acute coronary syndromes. TCFAs have also been found in 10% of non-cardiac deaths [16]. These factors, coupled with recent findings of multiple ruptured plaques and increased systemic inflammation in acute patients [17], have challenged the notion of a single vulnerable plaque acting as a precursor to AMI. Further study is necessary in order to fully understand the morphology, and thus properly diagnose and treat these lesions as means of prevention of coronary artery disease (CAD).

A useful approach to studying vulnerable plaques is either noninvasive or intracoronary imaging of individual lesions over periods of time. Unfortunately, conventional imaging approaches, such as intravascular ultrasound (IVUS) [8], coherence tomography (CT) [18], and magnetic resonance imaging (MRI) [7], are unable to reliably identify characteristics of the vulnerable plaque. While experimental intracoronary imaging techniques such as angioscopy [8], fluorescence spectroscopy [19], near-infrared spectroscopy [20], optical coherence tomography (OCT) [9], and thermography [21] are being investigated for the detection of vulnerable plaque, no method to date has been able to reliably identify all of the
characteristic features.

The specific presentation seen in vulnerable plaque lends itself well to the resolution achieved at terahertz frequencies. Presumably, given the depth of each layer in the plaque, terahertz would be able to achieve suitable resolution to discern the material properties of each layer. Thus it would be possible not only to diagnose a plaque as being present, but also diagnose its level of vulnerability. The high absorption of water at terahertz frequencies may also be a useful indicator, as hydration quality between healthy tissue and plaque is considerably different.

The work presented here attempts to take the first step toward gauging the viability of terahertz imaging as a diagnostic procedure. Characterizing the material parameters of healthy arterial tissue is necessary in order to create electromagnetic models to assess the ability of terahertz to penetrate and characterize the specific structure of healthy artery, and thus be able to distinguish it from a vulnerable plaque.

Though general tissues have already been characterized at these frequencies (epithelium, adipose, muscle, etc.), no study has attempted to characterize arterial tissue. Porcine tissue was chosen, as its biological makeup is relatable to that of a human's, and samples were easily available. The Boston University Physics Department was gracious enough to allow use of their transmission terahertz time-domain spectroscopy instrumentation. Though parameter extraction of absorbing media, like tissue, is difficult in transmission compared to reflection geometries, it is still possible with extensive signal manipulation.
2 Background

2.1 Origin and Progression of Atherosclerosis

2.1.1 The Dysfunctional Endothelium

The two major hypotheses on the origin of atherosclerosis are the thrombogenic and the lipidic [15]. Today the two theories can be integrated into one multifactorial theory involving a common step — endothelial dysfunction — triggering subsequent events leading to atherosclerotic lesions.

The endothelium is a monocellular layer that lines the luminal surface of the entire vascular network. It is a dynamic autocrine and paracrine organ that regulates contractile, secretory, and mitogenic activities in the vessel wall as well as hemostatic processes in the vascular lumen. Endothelial dysfunction, defined as reduced synthesis or release of nitric oxide (NO), is considered to be an early pathological signal of atherosclerosis [11]. NO exhibits vasorelaxation and antiatherogenic properties, including decreased platelet aggregation, monocyte adherence, and smooth muscle cell proliferation. Dysfunctional endothelium is pivotal in the pathogenesis of atherothrombosis beginning with expression of surface adhesion molecules that bind to various leukocytes. Additionally, dysfunctional endothelium modulates the permeability of plasma lipoproteins, release of prothrombotic and antithrombotic factors, growth factors, and vasoactive substances.
Dysfunctional endothelial cells promote the migration and internalization of monocytes, lymphocytes, and the proliferation of smooth muscle cells (Figure 1). The entry of inflammatory cells into the arterial wall is governed by the interaction between adhesion molecules on the surface and their ligands on leukocytes. The direction of inflammatory cells into the subendothelial space coupled with increased lipid accumulation and increased connective tissue synthesis leads to atheroma formation (Figure 2). These factors all play a role in allowing plaques to progress to the stage of rupture (Figure 3), where the previously described contents, along
with necrotic tissue, spill out into the artery, cause an occlusive arterial event that may lead to severe complications, such as AMI.

2.1.2 Pathological Characterization of the Vulnerable Plaque

Despite a common pathologic pathway to atherosclerosis, the lesions themselves are not homogeneous (Figure 4). Individual plaques vary greatly in composition, and the risk of a person with coronary atherosclerosis developing an acute ischemic event depends on a number of factors. The morphological criterion that supports definition of the TCFA, or vulnerable plaque, results from the simple idea that lesions preceding rupture bear a strong resemblance to the ruptured lesions themselves.

A first characteristic of plaque rupture is an overlying thin-ruptured cap infiltrated by macrophages and lymphocytes. The thickness of the fibrous cap near the rupture site measures $23+/−19\mu m$, with 95% of caps measuring $<65\mu m$ [6]. Given these similarities, TCFA differ from ruptured plaques by exhibiting a smaller necrotic core, fewer macrophages within the fibrous cap, and less calcification [22].

Secondly, vulnerable plaques exhibit a large lipid core. Studies have demonstrated that lipid cores were much larger in arterial segments with plaque rupture, than in those with intact surfaces [14,23]. The nature of the lipid core itself may be an additional factor, as lipid in the form of a cholesteryl ester softens the plaque, whereas crystalline cholesterol may have the opposite effect [23].

Finally, an inflammatory-cell infiltrate is a marker for plaque vulnerability. Atherosclerotic plaques with thin fibrous caps showed a surface zone dominated by
macrophages intermingled with T lymphocytes. Conversely, plaques with a larger fibrous cap consisted mainly of extracellular matrix (mostly collagen). However, at the site of erosion, the superficial parts of the cap were dominated by macrophages and T lymphocytes [4,14,15]. T lymphocytes within the plaque can be converted to macrophage foam cells, which then secrete tissue proteases that support the breakdown of collagen and elastin to peptides and amino acids (Figure 3). Similarly, morphologic studies using human autopsy material demonstrate a loss of smooth muscle cell in ruptured plaques due to apoptosis. Though the origin of the apoptotic stimulus is not currently known, the cell death occurs largely due to the activation of caspases, a large family of cysteine proteases [2]. This loss of structural molecules provided by the extracellular matrix can thin and weaken the fibrous cap.

2.1.3 Mechanical Stress as Related to Plaque Rupture

Understanding the distribution of mechanical stress in an atherosclerotic plaque is an important factor in understanding plaque rupture. The mechanical stress within the plaque is determined by the complex properties and variable mixture of plaque components. Recent studies that correlated pathological data with mathematical
models suggest that the stiffness of components of the plaque is an important determinant of the stress distribution, and thus the propensity toward fissuring [12,13,16]. The results of these studies suggest that shear stress plays a large role in plaque rupture, as circumferential planes slide against one another. Moreover, collagenous structures tend to be more resistant to tensile stress than to shear stress, though the effect of shear stress may be decreased by the typical presence of proteoglycans in atherosclerotic lesions [12]. More research is necessary in order to fully understand the mechanical dynamics involved with plaque rupture.

2.1.4 Classification Scheme for TFCAs

One should note the differences between the main resultants of TFCAs: rupture/erosion and the calcified nodule (Figure 4). Though rupture and erosion can be easily confused, it is critical to note that ruptures can include incidental events. A second type of lesion, though a less frequent cause of thrombotic occlusion without rupture, is referred to as a calcified nodule. This term refers to a lesion with a disrupted fibrous cap and thrombi associated with eruptive, dense, calcific nodules [3]. Though the origin of this lesion is not known, it is thought to
be associated with healed plaques. It has also been hypothesized that the physical forces exerted by these nodules could be the cause of fibrous cap breakdown [3].

2.2 Approaches for Diagnosis and Treatment

2.2.1 Localized Approach

Though systemic treatments for those at high-risk for MIs and sudden cardiac death are necessary (for example, aspirin and cholesterol-lowering with statins), adverse events still occur in spite of aggressive management. Recent studies have emphasized that many unstable patients have a second or even a third vulnerable plaque [17]. This raises an important question as to how invasive and noninvasive techniques to locate vulnerable atherosclerotic plaques can be best utilized. A possible solution may be the individual treatment of each lesion located. Though this would likely be more expensive in the short-term, this could be offset by substantial reductions in morbidity and mortality [5].

Thus, in addition to systemic therapy, investigators have been looking at the potential role of local or regional therapy for vulnerable plaques. Ambrose outlines five prerequisites in order for a local approach to be viable: 1) ability to identify the TCFA, 2) ability to identify erosion-caused plaques, 3) a known and limited number of plaque occurrences, 4) a natural history of the vulnerable plaque with optimal systemic therapies, and 5) an interventional event applied locally to an asymptomatic vulnerable plaque is proven to reduce future events relative to systemic therapy [5]. Though such a process to prove efficacy is daunting, and only the first has been accomplished thus far, numerous imaging modalities are being studied in order to solve this multi-faceted problem.

2.2.2 Diagnostic Imaging Modalities

- Computed Tomography Angiography

Computed Tomography Angiography (CTA) has been applied to detecting vulnerable plaques in combination with Positron Emission Tomography (PET). In recent studies, Aziz et al. demonstrated the ability to detect vulnerable plaques using CTA by monitoring fluorine-18 fluorodeoxyglucose (FDG-18) uptake in plaques [18]. This uptake rate has shown to be proportional to the degree of inflammation and macrophage density [24]. Using this method, CTA was able to detect the presence of platelet thrombi in 13 of 14 aortic segments identified by gross examination and histology. Additionally, this method diagnosed the absence of thrombi in 25 of 28 segments.

PET has a relatively low resolution (~6.5mm), while CTA has demonstrated an ability to detect a thrombus as small as 3mm [18]. Thus, it is suggested
that PET and CTA be used concurrently. In this type of system, CTA would be used for localization, while PET is used for characterization of the plaque. Though this partially overcomes the resolution limitation, it is still not sufficient to satisfy the requirements listed previously. Though the CTA/PET system has been shown to distinguish between plaques considered small (<10mm in length) and large (>10mm in length), it is unable to determine with accuracy the vulnerability of lesions affected by erosion [18].

- Magnetic Resonance Imaging

Magnetic Resonance (MR) imaging presents a noninvasive form of imaging without ionizing radiation, instead opting for the use of a strong magnetic field. The main function of MR imaging is to provide a strong contrast between the different soft tissues of the body. Though MR has been shown to be useful in imaging certain plaque criteria, it is unable to identify all of them. Moreover, the acquisition of images for certain features requires different number or types of MR sequences than necessary to image others [7]. Thus, MR imaging may be useful at identifying the macroscopic difference between a stable and vulnerable artery (Figure 5), but would be unable to monitor the microscopic criteria indicative of less obvious atherosclerotic lesions.

![Figure 7: Transverse MR images of Arterial Plaque [7].](image)

- Thermography

Madjid, et al. performed studies using thermography, a technique measuring surface temperatures of biological tissue, to aid in detecting vulnerable plaques. It is hypothesized that the severe inflammatory response elicited by the plaque would be readily detected by this technique [21]. Unfortunately, due to the heterogeneity of the thermal qualities of these lesions, an ultimate conclusion as to the efficacy of this particular method has yet to be reached.

- Intravascular Ultrasound

Intravascular Ultrasound (IVUS) has been used extensively to image atherosclerotic plaques, and is considered the current gold standard for intracoronary imaging [9]. IVUS allows for the evaluation of plaque morphology, vascular
remodeling, and vessel wall distensibility. These values are based upon the cross sectional area (CSA) of the lumen. Takano, et al. demonstrated the ability for IVUS to detect and analyze thrombi based on these parameters.

Figure 8: IVUS Images of Difference in Lumen Cross-sectional Area [8]

An IVUS system typically employs a catheter with an ultrasound probe attached to the distal end of the catheter. The ultrasound waves allow the ability to see outward from inside of the artery, and thus image the endothelium. This imaging of physical plaques demonstrates an immediate advantage to angiography, which can only detect chemical factors. IVUS has the ability to achieve images through blood with approximately 100µm resolution and a depth of penetration of approximately 1.0cm [9]. Thus it is able to both locate atherosclerotic regions and gain information as to its composition underneath the surface of the arterial wall. The disadvantages to IVUS are its expense and its inability to resolve several surface features of plaques due to resolution limitations.

- Near-Infrared Spectroscopy

Near-infrared (NIR) spectroscopy — a technique routinely used in the physical sciences to determine the chemical composition of substances — is currently being studied as a technique to detect specific features of the vulnerable plaque. NIR takes advantage of the fact that different substances absorb and scatter NIR light (wavelengths from 900 to 2,500 nm) to different degrees at various wavelengths. This scattering can be both an aid and a hindrance when it comes to tissue spectroscopy. Scattering can provide important information as the content of the tissue, however tissue scattering typically means the loss of most NIR light emitted. Work to further the use of NIR in tissue spectroscopy is ongoing, though recent studies have suggested a
chemical analysis of biological tissue millimeters to centimeters deep with an acquisition time of <1s [20].

- Optical Coherence Tomography

Intracoronary optical coherence tomography (OCT) is an invasive microscopic imaging technology that has been developed for the identification of vulnerable plaques. OCT can acquire cross-sectional images of tissue reflectance, utilizing near-infrared light, and is readily adaptable to coronary catheters via optical fiber.

Ex vivo studies have demonstrated the ability of OCT to discriminate between types of atherosclerotic plaque [9]. OCT is also capable of identifying additional plaque components that may be associated with acute coronary events, such as calcific nodules, thrombus, macrophages, and cholesterol crystals.

![Figure 9: In Vivo OCT Image of Vulnerable Plaque [9]](image)

OCT observations in clinical studies were consistent with IVUS [9]. Although IVUS is unable to resolve microstructural features associated with vulnerable plaque, it can identify normal vessels, large thrombi, calcific deposits, and pronounced arterial disruptions. A study was conducted comparing 17 OCT-IVUS image pairs obtained from 10 patients (Table 1). OCT was able to identify all plaques detected by IVUS. OCT was additionally able to detect cases of intimal hyperplasia, thrombus, intimal disruption, and lipid pool not identified by IVUS [9].

One should not assume that OCT can replace IVUS as a diagnostic method. OCT can obtain images with much higher resolution than IVUS, but cannot penetrate as deeply (~2 mm) [9]. As a result, OCT is particularly well suited for analyzing microscopic surface qualities of atherosclerotic plaques, but, as a limitation of the driving NIR light, cannot reach the back wall of thick lesions.
### Table 1: IVUS and OCT Image Findings for Corresponding Image Pairs [9]

<table>
<thead>
<tr>
<th>Feature</th>
<th>Identified by OCT and IVUS</th>
<th>Identified by OCT Alone</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intimal hyperplasia</td>
<td>3 (3 patients)</td>
<td>8 (7 patients)</td>
</tr>
<tr>
<td>Internal elastic lamina</td>
<td>not evaluated</td>
<td>11 (8 patients)</td>
</tr>
<tr>
<td>External elastic lamina</td>
<td>not evaluated</td>
<td>10 (7 patients)</td>
</tr>
<tr>
<td>Plaque</td>
<td>17 (10 patients)</td>
<td>0</td>
</tr>
<tr>
<td>Fibrous plaque</td>
<td>13 (10 patients)</td>
<td>0</td>
</tr>
<tr>
<td>Calcific plaque</td>
<td>4 (4 patients)</td>
<td>0</td>
</tr>
<tr>
<td>Echolucent region</td>
<td>2 (2 patients)</td>
<td>2 (2 patients)</td>
</tr>
</tbody>
</table>

3 Methods

3.1 THz Time-Domain Spectroscopy

3.1.1 Hardware Description

THz-Time-Domain Spectroscopy (TDS) allows for extraction of the complex parameters of materials by the coherent generation and detection of ultrafast pulses [10]. In our case, looking at a dielectric, it provides the index of refraction and absorption coefficient of the materials under study.

Sub-picosecond terahertz radiation is generated and detected via photoconductive techniques triggered by femtosecond laser pulses. The duration of the terahertz waveform is close to a single cycle oscillation of the electromagnetic field, and will thus have a high bandwidth, spanning a spectral range from tens of gigahertz to several terahertz. Using an optical gating pulse much shorter than the terahertz pulse, the electric field profile of the THz pulse can be directly recorded as a function of time at the detector, by varying the delay between the excitation and detection laser pulses. The time resolution is on the order of a picosecond.

The experimental set-up used at the Boston University Physics Department utilized THz-TDS in a transmission geometry. This geometry transmits the terahertz waveform through the sample, producing a reshaped waveform due to the dispersion and absorption of the sample. THz-TDS in transmission is typically suited for measurements on non-absorbing samples, but a reflection geometry system was not available for use. Biological tissue samples, due to their water content, are very absorbing at terahertz frequencies, and thus the SNR was relatively low. This problem required precise measurements of sample thickness in order to properly fit a theoretical transfer function to that of the measured sample.

As seen in Figure 10, the THz TDS consists of (1) a femtosecond laser source, (2) a THz transmitter, (3) a chopper, (4) collimating and focusing optics, (5) the sample, (6) a THz detector, (7) a variable delay line, (8) a current pre-amplifier,
Figure 10: Schematic Diagram of a THz-TDS Spectrometer [10]

(9) a lock-in amplifier, and (10) a computer. A radiation of a THz pulse is triggered at the transmitter by a laser pulse. The THz pulse is then collimated and focused onto the sample, and then refocused onto the THz detector. A portion of the laser beam is plotted off at the beam splitter to gate the THz detector in order to measure the voltage waveform. The resulting photocurrent at the THz detector is then detected by the pre-amplifier and the lock-in amplifier, which is referenced to the chopper. The THz detector and transmitter are gated synchronously. By varying the delay line, one can reconstruct the entire time-dependent electric field of the transmitted THz pulses.

3.1.2 Time-Domain Analysis

In order to extract the complex material parameters of a sample, THZ-TDS requires two measurements. In the first measurement, a set of averaged scans of the temporal profiles \( E_{\text{sig}}(t) \) of the THz pulses transmitted through the sample are recorded. In the second measurement, a set of averaged scans of the temporal profiles \( E_{\text{ref}}(t) \) of the THz pulses transmitted through a reference with known parameters are recorded.

In the case of an optically thick sample, echoes of the THz pulse, due to many reflections in the sample, are temporally well separated. Thus, when the transit time of the THz pulse is much larger than its duration, the THz signal is zero between any two echoes. In order to analyze a single THz pulse, the data is temporally windowed in order to discard the echoes.

The sample and reference signals are typically shifted in time, as seen in Figure 11. In the case of extremely thin samples, it is required to artificially shift the reference as to allow a phase shift suitable for curve fitting. The time shift between
the total scan time. However, since the measurement is performed in the time-domain, it is much more convenient to window out reflections in the raw data than to remove the reflections in the frequency-domain.

Even when there are no reflections the THz pulse is often windowed to smooth the data to prevent spectral leakage. The finite-length data is multiplied by a window whose amplitude varies smoothly and gradually goes to zero at the edges. This reduces the discontinuity at each period of the sampled data. In the case of THz pulses with a sampling period of $t_s = 400 \mu s$, the sampling rate is $f_s = 25THz$, and the Nyquist frequency is $f_s/2 = 12.5THz$. The duration of a THz pulse is typically only a few ps, and a scan is typically 10 ps or longer, giving plenty of room to bring the edges to zero. In most cases it is sufficient to gently window the data with a weakened Hanning window, or to exponentially bring the edges to zero on the first and last 20−30 data points.

![Graph](image)

Figure 2.7: Measured THz waveforms of a 0.5 mm LaAlO$_3$ substrate as the sample scan and air as reference displaying the time delay between the two scans. The sample scan is displaced vertically with respect to the reference scan for clarity.

Figure 11: Example Electric Field Amplitude Measurement for THz Sample and Reference Signals [10]

sample and reference pulses determines the real refractive index ($\varepsilon_r = \frac{L}{T}$), and the decrease in amplitude determines the imaginary index.

Finally, zero padding is used to increase the frequency resolution of the Fourier Transform of the THz pulse by artificially increasing the number of data points.

3.2 Tissue Sample Preparation

Porcine tissue samples were procured at Adam’s Farm in Athol, MA. All samples were collected within regulation for use of animal tissue samples for scientific research. Specifically, a pig aorta was removed from a freshly killed pig and put on ice for transport to the laboratory. Transport time to the laboratory was approximately two hours. Samples were then further dissected at the laboratory. The entirety of the artery wall allowed no THz transmission, so it was required to separate the arterial wall into three sections, referred to as inner, middle, and outer.

Samples were placed into polyethylene bags that were then squeezed within the sample chamber. Initial measurements were made as to the sections’ thicknesses (2), but the samples were too thin for the equipment used for measurements. Thus, it became necessary to assess sample thickness after measurements were made.

<table>
<thead>
<tr>
<th>Sample</th>
<th>Estimated Thickness</th>
</tr>
</thead>
<tbody>
<tr>
<td>Inner Artery</td>
<td>355(\mu m)</td>
</tr>
<tr>
<td>Middle Artery</td>
<td>353.1(\mu m)</td>
</tr>
<tr>
<td>Outer Artery</td>
<td>323(\mu m)</td>
</tr>
</tbody>
</table>

Table 2: Computed Thickness of Arterial Wall Sections in Polyethylene Bag
3.3 Modeling of the Material Transfer Function

An algorithm was developed to derive an experimental transfer function using electric field information propagated through both the material and a reference. Material parameters are then computed in order to create a theoretical transfer function of the material that matches the experimental results. This process was adapted largely from [25–27].

3.3.1 Material Transfer Function as an Inverse Problem

The material parameters are computed based on the effect of the sample in question on the electric field of the THz wave. Since the parameters are not measured directly, but found through the effect on the electric field, this is classified as an inverse problem.

The temporal profile of the THz pulse propagated through a material follows from the convolution in the time domain of the THz wave with the pulse response of the material. This operation becomes trivial in the frequency domain, where we compare two signals: the signal propagated through the material of interest and a reference signal: denoted \( E_{\text{sample}}(\omega) \) and \( E_{\text{ref}}(\omega) \) respectively, where \( \omega \) represents the angular frequency.

In our case, the experimentally recorded sample signal, \( E_{\text{exp samp}}(\omega) \) was propagated through the sample, which was contained and compressed in a polyethylene bag. The experimentally recorded reference signal, \( E_{\text{exp ref}}(\omega) \) was propagated through an empty bag. We can recover the experimental transfer function, \( H_{\text{exp}}(\omega) \), by taking the quotient of our frequency-domain sample and reference signals, which is analogous to their deconvolution in the time domain:

\[
H_{\text{exp}}(\omega) = \frac{E_{\text{exp samp}}(\omega)}{E_{\text{exp ref}}(\omega)}.
\]

(1)

Let \( H_{\text{theory}}(\omega) \) be a transfer function of the sample material theoretically derived through use of the material parameters. Additionally, we will denote the complex refractive index of some material 1: \( n_1(\omega) = n_1(\omega) + k_1(\omega) \), where \( n_1(\omega) \) is the real refractive index and \( k(\omega) \) is the extinction coefficient describing the absorption. Also of interest is the absorption coefficient, \( \alpha_1(\omega) \), which is related to the extinction coefficient by \( k(\omega) = \frac{\alpha_1(\omega)c_0}{2\omega} \), where \( c_0 \) is the speed of light in air.

The crux of this inverse problem is to compute material parameters of the sample material, so that for every \( \omega \) in the frequency range of interest, the value of \( H_{\text{theory}}(\omega) \) is as close as possible to that of \( H_{\text{exp}}(\omega) \).
3.3.2 Assumptions and Caveats

In order to maintain validity of the theoretical model, a few assumptions are necessary. Due to the nature of the materials being investigated, caveats are noted which may have added additional error to the results from this model:

- Homogeneity of the sample is assumed in the theoretical model. Obviously, tissue contains many different types of material and thus is rather inhomogeneous. Due to the small thickness of the sample, it is assumed that minimal error is introduced by this inhomogeneity.

- Roughness and curvature of the sample, as well as scattering effects at the surfaces inside the material, are ignored. It is assumed that all surfaces are perfectly flat and parallel, which is imposed to some degree by the compression of the sample in the chamber.

- Typically, a dry atmosphere environment is assumed. Due to the nature of our experiment, water content was included and is, in fact, very relevant to the overall aims of these experiments. Tissue was freshly excised in order to closely mimic in vivo measurements.

- Orthogonal incidence of the THz waves are assumed at the irradiated sample. As described in [25], an inclination error up to $5^\circ$, leads to deviations in the refractive index and extinction coefficient smaller than 0.002. Thus, this error is considered negligible.

Additionally, standard notations used throughout this work include:

- $c_0$ is the speed of light in air, which is approximated as that in a vacuum with a value $c_{\text{vacuum}} = 2.99796 \times 10^8$ m/s.

- $\tilde{n}_0$ is the refractive index of air which is approximated at $\tilde{n}_0 = 1 - j0$.

- $x$ is used to describe the geometrical length between the emitter and receiver antenna.

- $l$ is used to denote the thickness of the investigated sample.

- $E_0$ is the frequency-dependent electric field leaving the emitter antenna.
3.4 THz Wave Propagation through Material

This section will consider the problem of how the electric field is theoretically affected when propagating through a material of interest. $E_0$, the magnitude of an initial electric field entering the material. In this description, the index of 0 will correspond to air, while an index of 1 will correspond to the material. As the field propagates through the material, it is described by the following relation:

$$E(z) = E_0 P_1(z),$$  \hspace{1cm} (2)

$$P_1(z) = e^{-j\omega(n-jk)z},$$  \hspace{1cm} (3)

where $E(z)$ is the electric field at material propagation length $z$ and $P_1(z)$ is the frequency-dependent propagation coefficient for material 1.

Figure 12: Ray Propagation through a Homogenous Sample

The ray propagation through the material is shown in Figure 12, which portrays many transmissions and reflections at the two air-material boundaries beginning with the initial field $E_0$. 

24
We can define Fresnel reflection and transmission coefficients, which describe the transmission and reflection of the THz wave at the interface between air and material:

\[ R_{01} = \frac{\hat{n}_1 - \hat{n}_0}{\hat{n}_0 + \hat{n}_1} \]  \hspace{1cm} (4)

\[ T_{01} = \frac{2\hat{n}_0}{\hat{n}_0 + \hat{n}_1}. \]  \hspace{1cm} (5)

The various rays pictured in Figure 12 represent the infinitely many reflections between boundaries. Of importance to this investigation are those which are additive at the detector and thus have a superscript of (+). Signals reflected out of the material are lost, and are designated with a superscript of (-).

In the first stage, as \( E_0 \) enters the material, there is a reflection \( E_{01}^{1-} \) which is lost. There is also a transmission into the material, \( E_{01}^{1+} \). As this ray hits the opposite end of the material, there is again a reflection \( E_{11}^{1-} \) which heads back into the material, and a transmission \( E_{10}^{1+} \) which will reach the detector. This process repeats indefinitely, though the exponential decay imposed by the propagation coefficient, \( P_1(z) \) limits the significant effects only to a small number of iterations. This point will be elaborated upon in subsequent sections.

In terms of Figure 12 and the Fresnel coefficients, The initial portion of \( E_0 \) transmitted at the air-material interface becomes \( E_{01}^{1+}(0) = E_0 T_{01} \) and propagates through the sample. As it propagates, attenuation will occur due to the propagation coefficient, and thus \( E_{01}^{1+}(z) = E_0 T_{01} P_1(z) \). At the right material-air interface, \( E_{01}^{1+}(l) = E_0 T_{01} P_1(l) \). The portion of \( E_{01}^{1+} \) transmitted through the right interface will be described by \( E_{01}^{1+}(l) = E_0 T_{01} P_1(l) T_{10} \) and will propagate through air to the detector. Each ray that reaches the detector is additive to form the \( E_{\text{amp}} \) used for subsequent analysis.

Considering the infinitely many internal reflections which may occur, we will simplify some of our notations to derive a relationship defining our final \( E_{\text{amp}} \), the electric field integrated at the detector. The effect of the propagation through the material can be described as \( P_1(l) \), the notation of which we will simplify to \( P_1 \). Additionally, the effects of propagation through the air around the sample must be taken into account. This attenuation is described by \( P_0(x - l) \), or more simply \( P_0 \), where \( (x - l) \) gives the distance the ray has travelled through air.

Summing all electric field successfully propagated through the sample, we arrive at an equation describing \( E_{\text{amp}} \):
The integer $N$ in (6) represents the number of reflections taken into account when computing the final $E_{samp}$. In theory, this number is infinitely large. Practically, we are limited by both the exponential decay seen during propagation, and the finite collection time of the electric field. Due to high attenuation seen in the specific samples we use, we limit our calculation of $E_{samp}$ to only the initial transmission of the electric field, considering all reflections negligible. This will be shown in a subsequent section.

The reference signal’s detected electric field, $E_{ref}$, is much simpler to calculate. Since the rays will pass only through air, the following equation describes the relationship with propagated electric field:

$$E_{ref} = E_0 P_0(x).$$

Recalling that $P_0$ is equivalent to $P_0(x-l)$, we can use (3), (6), and (7) to yield the theoretical transfer function:

$$H_{theory} = \frac{E_{samp}}{E_{ref}} = P_0(-l) T_{01} P_1 T_{10}[1 + \sum_{i=1}^{N} (R_{10}^2 P_1^2)^i].$$

3.5 Extracting Tissue Parameters

The algorithm to compute material parameters was adapted originally from [25–27] and modified by the Boston University Physics Department. Additional modifications were made to allow parameter extraction from samples with thickness less than 100 µm utilizing methods from [28] and [29]. This section outlines the process from initial electric field data to material parameters and computation of the material’s theoretical transfer function.

3.5.1 Initial Signal Processing

Before performing parameter extraction, a number of preliminary signal processing steps are taken:

![Figure 13: Preliminary Signal Processing Flow](image-url)
1. An initial guess for $n$ is made at the outset of the analysis, and is chosen based on the typical refractive indices present in the literature [30], since arterial tissue shares many qualities with epithelium and adipose. This guess for $n$ helps the error minimization algorithm find the appropriate fit for the transfer function by looking near the appropriate local minimum. Similarly, an initial guess value for the extinction coefficient, $k$, is calculated by guessing a value for the absorption coefficient, $\alpha$, found in the literature:

$$k_{\text{guess}} = \frac{\alpha c}{4\pi v}.$$  

(9)

2. Due to the small thickness of the sample, a suitable time delay was not observed between the reference and sample at data collection. The extraction algorithm requires a time delay in order to properly compute phase, so an artificial time delay is created prior to parameter extraction as a function of the difference between the initial guess for the refractive index of that sample and the refractive index of air, $\Delta n$, as well as the path length of the sample, $l$:

$$t_{\text{delay}} = \frac{l\Delta n}{c}.$$  

(10)

This time delay is then applied to the reference.

3. It is assumed that there is a linear offset in the experimentally measured field data. This offset is estimated by taking the mean both from several data points prior to incidence of the pulse and data points at the end of the measurement. This offset is then subtracted from the experimental data.

4. The reliable frequency range over which to characterize the material was determined empirically. Typically, as in [25], a noise floor is computed and the frequency range considered is that where the signal rises above the noise floor. Due to the large absorption seen in tissue, the signal often falls below the noise floor in our measurements. The frequency range used in our process was 200 GHz to 1 THz, as this is the range where parameter values were well-behaved and correctly assessed by the algorithm when comparing material parameters to those found in the literature [30] for various tissue types (skin, muscle, adipose).
5. Finally, a simple Hann window is applied to the data in order to smooth any possible tails to zero.

3.5.2 Fitting Theoretical Transfer Function

Having performed the preliminary signal processing, the experimental transfer function, $H_{\text{exp}}(\omega)$, is now used along with initial guesses for $n$ and $k$ in order to compute the fitted, theoretical transfer function, $H_{\text{theory}}(\omega)$.

A standard MATLAB function, fminsearch [31], was used to minimize the error in computing a fitted transfer function. In general, fminsearch finds the minimum of a scalar function of several variables, starting at an initial estimate, and is considered an unconstrained nonlinear optimization.

fminsearch uses the Nelder-Mead simplex algorithm as described in [32]. This algorithm uses a simplex of $n+1$ points for $n$-dimensional vectors $x$. The algorithm first makes a simplex around the initial guess $x_0$ by adding 5% of each component $x_0(i)$ to $x_0$, and using these $n$ vectors as elements of the simplex in addition to $x_0$. Then, the algorithm modifies the simplex repeatedly according to the following procedure:

1. Let $x(i)$ denote the list of points in the current simplex, $i = 1,...,n+1$.

2. Order the points in the simplex from lowest function value $f(x(1))$ to highest $f(x(n+1))$. At each step in the iteration, the algorithm discards the current worst point $x(n+1)$, and accepts another point into the simplex.

3. Generate the reflected point,

$$r = 2mx(n+1)$$

where

$$m = \sum_{i=1}^{n} \frac{x(i)}{n}, i = 1...n$$

and calculate $f(r)$.

4. If $f(x(1)) \leq f(r) < f(x(n))$, accept $r$ and terminate this iteration.

5. If $f(r) < f(x(1))$, calculate the expansion point $s$, where

$$s = m + 2(mx(n+1))$$
and calculate $f(s)$.

(a) If $f(s) < f(r)$, accept $s$ and terminate the iteration
(b) Otherwise, accept $r$ and terminate the iteration.

6. If $f(r) \geq f(x(n))$, perform a contraction between $m$ and the better of $x(n+1)$ and $r$:  

(a) If $f(r) < f(x(n+1))$ (i.e., $r$ is better than $x(n+1)$) calculate

$$c = m + (rm)/2$$  \hfill (14)

and calculate $f(c)$. If $f(c) < f(r)$, accept $c$ and terminate the iteration. Otherwise, continue with Step 7.

(b) If $f(r) \geq f(x(n+1))$, calculate

$$cc = m + (x(n+1)m)/2$$  \hfill (15)

and calculate $f(cc)$. If $f(cc) < f(x(n+1))$, accept $cc$ and terminate the iteration. Otherwise, continue with Step 7.

7. Calculate the $n$ points

$$v(i) = x(1) + (x(i)x(1))/2$$  \hfill (16)

and calculate $f(v(i)), i = 2, ..., n + 1$. The simplex at the next iteration is $x(1), v(2), ..., v(n + 1)$.

This process is used in our case to compute refractive index, $n$, and extinction coefficient, $k$, by minimizing the error in the computed theoretical transfer function. The transfer function is computed via the transmission and reflection coefficients and their dependence upon $n$ and $k$, which are the real and imaginary parts of the complex refractive index, respectively:
\[ R_{01} = \frac{n_1 - n_0}{n_1 + n_0} \]  
\[ R_{10} = -R_{01} \]  
\[ T_{01} = \frac{2n_0}{n_1 + n_0} \]  
\[ T_{10} = \frac{2n_1}{n_0 + n_1} \]  
\[ P_0 = e^{i\omega_{\text{metal}}/c} \]  
\[ P_1 = e^{i\omega_{\text{metal}}/c} \]  

where \( n_1 \) is the complex refractive index of the sample, such that \( n_1 = n - jk \), \( n_0 \) is the refractive index of air, and \( S \) is the summation term defined as

\[ S = \frac{1 - (R_{10}P_1)^{2(\Delta t+1)}}{1 - (R_{10}P_1)^2}. \]  

The error function being minimized is the difference between the magnitude and phase of the experimental and theoretical transfer functions:

\[ M(\omega) = |H_{\text{theory}}(\omega)| - |H_{\text{exp}}(\omega)| \]  
\[ A(\omega) = \angle H_{\text{theory}}(\omega) - \angle H_{\text{exp}}(\omega) \]  
\[ \text{Error} = \sum_w (|M(\omega)| + |A(\omega)|). \]  

This function is minimized with a tolerance of \( 1 \times 10^{-8} \) and the algorithm is run for an infinite number of iterations until an appropriate minimum is located.

Once the algorithm has minimized the error in the theoretical transfer function over the entire specified frequency range, the complex refractive index is used to compute the final theoretical transfer function.

### 3.5.3 Computing Material Parameters

Since the computed theoretical transfer function is created by the real and imaginary parts of the complex refractive index, these parameters are immediately available. Computation of the permittivity and conductivity over the specified frequency range is then performed as:

\[ \tilde{\epsilon} = (n + ik)^2 = \epsilon' + i\epsilon'' \]
where $\epsilon''$ is the imaginary part of the complex permittivity, and

$$
\epsilon'' = \frac{\sigma}{\omega}.
$$

(28)

Thus, the conductivity of the sample in SI units is determined by

$$
\sigma = \epsilon'' \varepsilon_0 \omega.
$$

(29)

### 3.6 Determining Sample Thickness

When working with samples with thicknesses around 100 $\mu$m, it becomes difficult to remain precise in physical thickness measurements. The differential data acquisition technique used in the experiments to perform THz Time Domain Spectroscopy is unfortunately susceptible to errors produced in this measurement. Thus, in order to properly compute the material parameters via the theoretical transfer function, it is important that the thickness of the sample be accurate.

The key problem in measuring material parameters in a THz transmission geometry is the presence of Fabry-Perot (FP) oscillations. If a standard data extraction was performed without an appropriate measurement of the path length, the computed material parameters would be superimposed with a spectral modulation. To avoid this problem, an algorithm to compute tissue path length after data extraction was adapted, largely from [29].

We begin with a computed theoretical transfer function of the form:

$$
H(\omega) = A_0 e^{-i\frac{\pi}{\varepsilon_0}[\tilde{n}-1]l} + A_1 e^{-i\frac{\pi}{\varepsilon_0}[3\tilde{n}-1]l} + ...
$$

(30)

The arguments for the exponents in the transfer function are linearly dependent. This implies that using an incorrect value for the sample thickness would induce oscillations in the calculated refractive index. The FP oscillations will only disappear when an appropriate value for the thickness is used.

The correct thickness is determined by an iterative method, where the sample thickness is varied and the subsequent FP oscillations are minimized. Since the FP oscillations introduced are assumed to be periodic, we apply a Fourier transform to the extracted data, entering into a quasi-space (QS). Now in the QS, the periodicity of the FP oscillations will correlate with a discrete peak.

The QS values are obtained by:

$$
QS_k = \sum_{n=0}^{N-1} [y(\omega_n)e^{-i\frac{\pi}{\varepsilon_0 kn}}, k = 0, ..., N - 1,
$$

(31)

where the value $y(\omega_n)$ corresponds to a material parameter: refractive index, extinction coefficient, or absorption, and $N$ is the amount of sampling points. The
refractive index, $\tilde{n}$, was chosen to be used in these experiments, as the parameter is less affected by amplitude fluctuations than the others [33].

As the sample path length is altered, the QS values are computed across all specified frequencies, and a minimum QS value is chosen. Path lengths used are those around the values found via physical measurement.

The path length values found via this method are then used to compute the final, corrected theoretical transfer function of the sample, and thus properly extract its material parameters.

3.7 Solution Verification via Time-Domain Waveform Reconstruction

In order to verify the transfer function fitted from the error minimization algorithm previously discussed, the time-domain waveform is rebuilt using the derived theoretical function and the reference THz pulse [34]. Typically in THz-TDS the material parameters are taken indirectly from their effect on the electric field, thus it is a solution to an electromagnetic inverse problem. When the THz wave is rebuilt in the time domain and compared to the measured sample THz waveform, we are instead solving a forward problem.

Analytical formulas have been derived for a single-layer homogeneous sample in a transmission mode. When the THz pulse of temporal profile $e_0(t)$ propagates through a certain sample, the transmitted pulse $e(t)$ can be defined as the convolution of $e_0(t)$ with some response function $h(t)$ of the sample:

$$e(t) = e_0(t) * h(t)$$  \hspace{1cm} (32)

and its frequency domain form is defined as:

$$E(\omega) = E_0(\omega) \cdot H(\omega).$$  \hspace{1cm} (33)

Using these two equations, we can represent $e(t)$ by an inverse Fourier transform:

$$e(t) = \frac{1}{2\pi} \int_{-\infty}^{\infty} E_0(\omega) H(\omega) e^{i\omega t} d\omega.$$  \hspace{1cm} (34)

The $e(t)$ can be measured as $e_{\text{measure}}(t)$ and numerically rebuilt as $e_{\text{rebuild}}(t)$. These two quantities can then be compared to ensure that a suitable solution for the theoretical transfer function has been reached.

Since the transfer function has been defined as $H(\omega) = \frac{E_{\text{sample}}(\omega)}{E_{\text{reference}}(\omega)}$, it follows that a simple multiplication in the frequency domain will allow us to reconstruct the frequency domain transmitted pulse:

$$E_{\text{sample}}(\omega) = H(\omega) \cdot E_{\text{reference}}(\omega).$$  \hspace{1cm} (35)
Taking the inverse Fourier transform of $E_{\text{sample}}(\omega)$ will then allow us to compare it with the originally measured signal.

### 3.8 Computational Electromagnetic Model

In order to demonstrate the efficacy of THz as a diagnostic method for vulnerable plaque detection, a finite-difference frequency domain model was created. The goal of this model was to demonstrate the ability to discern vulnerable plaque based on reflections from the various boundaries exhibited in the plaque and arterial wall, and showing that there is a considerable difference when probing a healthy artery as opposed to an artery with plaque.

The solution space was discretized such that the distance between each point was $\lambda_{150}$. A perfectly matched layer was placed at each end of the computation space. These layers were defined to be 10 points wide, and introduced attenuation, while remaining matched, by ensuring that $\epsilon' = \mu'$ and $\frac{\mu_0}{\mu_0} = \frac{\sigma}{\epsilon_0}$.

Arterial sections and plaque elements were modeled as lossy dielectrics with $k^2 = \mu_c \epsilon_c$, where $\mu_c = \mu_0$ and $\epsilon_c = \epsilon_0 (\epsilon' - j \frac{\sigma}{\omega \epsilon_0})$. The complex dielectric constants for all elements were a function of frequency. The values used for each frequency can be found in Table 3:

<table>
<thead>
<tr>
<th>Frequency</th>
<th>$\epsilon_{\text{inner}}$</th>
<th>$\epsilon_{\text{middle}}$</th>
<th>$\epsilon_{\text{outer}}$</th>
<th>$\epsilon_{\text{fat}}$</th>
</tr>
</thead>
<tbody>
<tr>
<td>400 GHz</td>
<td>7.37 - j3.37</td>
<td>6.28 - j3.58</td>
<td>5.76 - j3.50</td>
<td>3.610 - j0.034</td>
</tr>
<tr>
<td>450 GHz</td>
<td>7.19 - j3.38</td>
<td>6.13 - j3.37</td>
<td>5.63 - j3.30</td>
<td>3.610 - j0.030</td>
</tr>
<tr>
<td>500 GHz</td>
<td>7.07 - j3.22</td>
<td>6.01 - j3.20</td>
<td>5.51 - j3.17</td>
<td>3.610 - j0.027</td>
</tr>
<tr>
<td>550 GHz</td>
<td>6.98 - j3.09</td>
<td>5.92 - j3.06</td>
<td>5.38 - j3.05</td>
<td>3.610 - j0.025</td>
</tr>
<tr>
<td>600 GHz</td>
<td>6.91 - j2.99</td>
<td>5.86 - j2.93</td>
<td>5.26 - j2.92</td>
<td>3.610 - j0.023</td>
</tr>
<tr>
<td>650 GHz</td>
<td>6.85 - j2.91</td>
<td>5.81 - j2.83</td>
<td>5.19 - j2.81</td>
<td>3.610 - j0.021</td>
</tr>
<tr>
<td>700 GHz</td>
<td>6.77 - j2.86</td>
<td>5.74 - j2.78</td>
<td>5.11 - j2.74</td>
<td>3.610 - j0.019</td>
</tr>
<tr>
<td>750 GHz</td>
<td>6.66 - j2.82</td>
<td>5.66 - j2.70</td>
<td>5.05 - j2.67</td>
<td>3.610 - j0.018</td>
</tr>
<tr>
<td>800 GHz</td>
<td>6.55 - j2.75</td>
<td>5.58 - j2.58</td>
<td>4.99 - j2.59</td>
<td>3.610 - j0.017</td>
</tr>
<tr>
<td>850 GHz</td>
<td>6.49 - j2.65</td>
<td>5.53 - j2.49</td>
<td>4.93 - j2.51</td>
<td>3.610 - j0.016</td>
</tr>
<tr>
<td>900 GHz</td>
<td>6.47 - j2.59</td>
<td>5.50 - j2.42</td>
<td>4.91 - j2.41</td>
<td>3.610 - j0.015</td>
</tr>
</tbody>
</table>

Table 3: Complex Dielectric Constants Used in Computational Model

The model for a healthy artery consisted of the arterial layers described previously (inner, middle and outer). A plaque was modeled by inserting a lipid pool beneath a thin layer of the inner artery section, acting as a fibrous cap. The middle and outer artery sections lie beneath the lipid pool. The lipid pool’s parameters were modeled as the values for adipose tissue reported in the literature [30].
matched layer was placed at the innermost layer of both the healthy and pathological models. This layer represents the lumen, where a hypothetical catheter antenna would be located.

The $E$ field was computed by solving the form of $Ax = b$. In order to easily add the frequency responses and thus compute the reflections seen at the antenna by separating the incident fields, a 'soft source' implementation was used. This was accomplished by adding a source excitation at the excitation point in the matched layer to the fields that would exist in a homogeneous space for each frequency step. Thus, the $A$ matrix becomes that of a source-free system with a typical tridiagonal structure. An impulse is added to the $b$ matrix at the excitation point, which is analogous to multiplying by $-2 + (k\Delta)^2$.

The frequency responses for both the healthy and pathological cases were added together to determine the reflection seen at the matched antenna space. The difference in magnitude between the complex $E$ field in the healthy and pathological cases was then easily computed with a simple subtraction.
4 Results

The results presented here are for samples of the wall of freshly excised porcine aorta. There was little to no THz transmission through the entirety of the arterial wall, so three thin sections were made to analyze separately.

In each case, a figure of the THz transmitted pulse overlaid with the reference pulse is displayed. In every case, it is shown that the transmitted THz pulse is much smaller in amplitude when compared to the reference, due to the absorptive nature of the media through which the pulse is being transmitted. The resulting low SNR made the measurement of the sample thickness extremely important in properly extracting materials. The thickness of each sample was computed after measurements had been taken. The steps toward computing the thickness of each sample are presented in the Discussion section.

Also plotted are the phase difference, theoretical transfer function, real refractive index, absorption, complex permittivity, and conductivity. A comparison of real refractive index and conductivity is plotted on the same figure for all arterial sections.

Finally, results from the FDFD computational model are plotted for healthy artery and artery with plaque. A plot showing the difference seen at the receiver for these two cases is also included.
4.1 Inner Section of Artery

Figure 14: Sample and Reference THz Pulses through Inner Artery
Figure 15: Wave Phase through Inner Artery
Figure 16: Theoretical Transfer Function of Inner Artery
Figure 17: Refractive Index of Inner Artery
Figure 18: Absorption of Inner Artery
Figure 19: Complex Permittivity of Inner Artery

Figure 20: Conductivity of Inner Artery
4.2 Middle Section of Artery

Figure 21: Sample and Reference THz Pulses through Middle Artery
Figure 22: Wave Phase through Middle Artery
Figure 23: Theoretical Transfer Function of Middle Artery
Figure 24: Refractive Index of Middle Artery
Figure 25: Absorption of Middle Artery
Figure 26: Complex Permittivity of Middle Artery
Figure 27: Conductivity of Middle Artery
4.3 Outer Section of Artery

Figure 28: Sample and Reference THz Pulses through Outer Artery
Figure 29: Wave Phase through Outer Artery
Figure 30: Theoretical Transfer Function of Outer Artery
Figure 31: Refractive Index of Outer Artery
Figure 32: Absorption of Outer Artery
Figure 33: Complex Permittivity of Outer Artery

Figure 34: Conductivity of Outer Artery
4.4 Comparison of All Sections

Figure 35: Refractive Index of All Artery Sections
Figure 36: Conductivity of All Artery Sections
4.5 Computational Model

Figure 37: FDFD Model of Healthy Artery vs Artery with Plaque
5 Discussion and Conclusions

5.1 Determining Sample Thickness

The results for the real refractive index produced by the algorithms match well with general curve behavior and mean values seen in the literature for hydrated epithelial tissue [30].

In making these measurements, there were a number of limitations that needed to be considered and overcome. Most important, due to our operation in a transmission geometry, was correct measurement of the sample thickness. Physical measurement made in the laboratory were not precise enough at the small thickness lengths exhibited by the tissue. When extracting parameters from the sample using incorrect thickness measurements, Fabry-Perot oscillations will be introduced which affect the computed material parameters.

To overcome this limitation in making physical measurements, a computational method was used to correctly evaluate sample thickness. Since the Fabry-Perot oscillations exhibit periodicity, it follows that the Fourier transform of data with oscillations should expose the frequencies of the oscillations. Thus, if many path lengths are chosen, and the resulting data is analyzed in this fashion, there should be a minimum value considering all functions that points to the signal without these oscillations. The path length producing this minimum value would be the true path length of the tissue sample.

The figures below show the minimum values produced using this method as a function of path length. Taking the Fourier transform of the frequency-domain data puts the data into a quasi-space domain, whose values are of interest only in that a minimum is produced. The physically estimated path lengths were used to investigate minima that were apparent within the neighborhood of the estimated lengths.
Figure 38: Quasi-Space Values for Determining Thickness of Inner Artery

Figure 39: Quasi-Space Values for Determining Thickness of Middle Artery
Figure 40: Quasi-Space Values for Determining Thickness of Outer Artery
As is seen in the figures, each sample section contains a quasi-space minimum value in the neighborhood of the estimated physical value. Once these thickness values were computed, the parameter function was empirically tested for smooth curve behavior at path lengths around that computed by the algorithm. The path length values found to produce well-behaved curves in this neighborhood are those reported in the experimental results.

5.2 Solution Verifications by Time-Domain Reconstruction

To ensure that the material parameters being computed were accurate, the original time-domain transmitted signal was reconstructed. The theoretical transfer function computed for each tissue section was multiplied with the measured reference signal to rebuild the original sample signal in the frequency domain. Following with an inverse Fourier transform, the time-domain transmitted sample signal is recreated.

The figures below compare the recreated sample signal with that originally measured by the THz detector. Errors in the reconstructed signal are likely due to the low SNR exhibited by the transmitted THz pulse, as well as the failure of the THz pulse to penetrate at frequencies greater than 1THz. The general shape of the reconstructed time-domain pulse matches that of the transmitted THz pulse. This implies that the theoretically computed sample transfer function is a good estimate of the tissue’s behavior.

![Figure 41: Reconstructed Pulse through Inner Artery](image-url)
Figure 42: Reconstructed Pulse through Middle Artery

Figure 43: Reconstructed Pulse through Outer Artery
5.3 Conclusions and Future Work

The experiments point to a distinguishable difference in the material properties of the different arterial sections. Additionally, the arterial wall’s properties differ from those of adipose tissue reported in the literature [30]. Figure 37 demonstrates the ability to detect a change in the reflections from the arterial wall depending on whether a vulnerable plaque is present, as the reflection from an arterial wall containing a plaque is roughly five times larger than that of a healthy arterial wall.

An immediate next step would entail the utilization of a reflection geometry THz system to measure the reflections resulting from a healthy arterial wall and those from an arterial wall containing plaque. These results could be compared to the computational model and prove the system’s efficacy.

Given these results, a catheter-based wide-band terahertz instrument could be constructed to probe the arterial wall and detect any vulnerable plaque. One could find a matching fluid in which the area between the antenna and arterial wall could be immersed. The THz transceiver could be placed at a number of nominal positions to measure reflection from the signal transmitted into the arterial wall. These reflections could then be compared to measurements at other positions and anomalous signals could be explored further to diagnose the presence of plaque.
References


[34] Xiangjun Li, Zhi Hong, Jinlong He, and Yuquan Chen. Precisely optical material parameter determination by time domain waveform rebuilding with thz time-domain spectroscopy. *Optics Communications*, 283(23):4701–4706, 2010.