

A comparison between Diffuse Reflection Spectroscopy and Electrical Impedance Spectroscopy to distinguish between different vertebrae tissue during spinal fusion surgery

by

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Preface

As I stand on the brink of completing my master's thesis, I am filled with gratitude and a sense of accomplishment. This journey has been one of immense learning, challenge, and, ultimately, success. There were times when I couldn't see the way forward, and I'm grateful to those who guided me through.

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As I reflect on the past two years, I am filled with immense pride in reaching this milestone. It has been a journey marked by growth, resilience, and determination, and I am thankful for every experience, both difficult and rewarding, that has led me to this moment.

To everyone who has played a role, no matter how small, in helping me complete this study, I extend my heartfelt thanks. This thesis is a testament to the power of perseverance, the importance of support, and the boundless potential within each of us.

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Delft, May 2024*

Abstract

Accurate placement of screws in spinal surgery is vital to mitigate risks like instability, nerve damage, or spinal cord injury, which can lead to various complications such as pain, sensory loss, muscle weakness, or paralysis below the injury site [33]. However, success rates in screw placement vary widely, ranging from 27.6% to 100% [56].

Advanced techniques, like pedicle screw placement (PSP) with enhanced guidance systems, aim to provide surgeons with better spatial awareness to prevent cortical breaches. Various guidance methods, such as fluoroscopy, computer-assisted techniques, neurophysiological monitoring, and Electrical Impedance Spectroscopy (EIS) enabled by the PediGuard, have been developed and utilized in spinal fusion surgeries [18]. Despite their efficacy in reducing complications, these systems have limitations such as increased radiation exposure, prolonged surgery time, or lack of real-time feedback.

This study compares two sensing techniques, Electrical Impedance Spectroscopy (EIS) and Diffuse Reflection Spectroscopy (DRS), for spinal fusion surgery. Both methods are employed to detect cortical breaches during PSP by distinguishing between cancellous and cortical bone. Before experimentation, certain gaps in understanding must be addressed, including exploring the working principle of EIS for vertebrae tissue and developing classifiers for both single and multiple frequencies. Additionally, efforts are made to create a vertebrae phantom with realistic electric and optical properties.

EIS demonstrates an increase in impedance for cortical bone compared to cancellous bone due to the latter's weblike structure with highly vascularized yellow bone marrow. Single-frequency analysis outperforms multiple-frequency analysis in distinguishing between vertebrae tissues. However, the development of a better model or the use of multiple single-frequency classifiers may enhance predictive accuracy. Despite attempts to create an accurate vertebrae phantom, limitations in adjusting dielectric properties result in the utilization of the best-fit recipe.

Comparison between EIS and DRS reveals both are effective in detecting cortical breaches and tissues, with DRS exhibiting a longer look-ahead distance. EIS operates more like a step function, making it susceptible to distortions, suggesting DRS outperforms EIS in spinal fusion surgeries.

Contents

Preface	i
Abstract	ii
List of Figures	vi
List of Tables	vii
Nomenclature	viii
1 Introduction	1
1.1 Spine Anatomy	1
1.2 Spinal fusion surgery	3
1.3 Pedicle screw placement	3
1.3.1 Procedure	4
1.3.2 Complications	4
1.3.3 Enhanced pedicle screw placement	5
1.4 Problem statement	6
1.5 Thesis outline	6
2 Theory	7
2.1 Electrical Impedance Spectroscopy	7
2.1.1 Basic working Principles	7
2.1.2 Electrical Impedance Spectroscopy in Biological Tissue	8
2.2 Diffuse Reflection Spectroscopy	8
2.2.1 Absorption	9
2.2.2 Scattering	9
I Preliminary Testing - Filling in the gaps of knowledge	10
3 Electrical Impedance Spectroscopy Parametric Model	11
3.1 Method	11
3.1.1 Measurement Setup	11
3.1.2 Measurement Protocol	12
3.1.3 Data Analysis	14
3.2 Results	15
3.2.1 Single frequency analysis	17
3.2.2 Multiple-Frequency Analysis	18
3.3 Conclusions	20
4 Development and Analysis of Phantom	21
4.1 Method	21
4.1.1 Measurement setup	21
4.1.2 Phantom mixture	22
4.1.3 Measurement Protocol	24
4.1.4 Data Analysis	24
4.2 Results	24
4.3 Conclusion	26

II	Final Testing	27
5	Method	28
5.1	Measurement Method	28
5.1.1	Measurement Protocol	29
5.2	Data Analysis	30
6	Measurements and Results	32
6.1	Electrical Impedance Spectroscopy	32
6.2	Diffuse Reflection Spectroscopy	33
6.3	Evaluation Criteria	33
6.3.1	Look-ahead distance	34
6.3.2	Capability of tissue detection and breach detection	34
7	Discussion	35
7.1	Highlighted results and limitations	35
7.1.1	Preliminary testing	35
7.1.2	Final Test	37
7.2	Further work	38
8	Conclusion	39
8.1	Part I - Preliminary Testing	39
8.2	Part II - Final Testing	40
	References	41
A	Conductivity experiments	45
B	Benchmark Data & Model	47
C	Single-frequency Predictive Value	49
D	Multiple-frequency Modelling	55
E	References impedance spectra for cancellous and cortical bone	58
F	Electrical Impedance Spectroscopy Results	59
G	Diffuse Reflection Spectroscopy Results	62

List of Figures

1.1	Anatomy of the spinal column [16]	2
1.2	Anatomy of a vertebrae [39]	2
1.3	Overview of spinal fusion surgery [1]	3
1.4	Overview of the procedure of Pedicle screw placement [48]	4
1.5	Cortical Breach occurrences [27]	5
2.1	The frequency-dependent impedance properties of biological tissues and their equivalent circuit modelling: electrical current conduction through the biological cells in an animal tissue [4]	8
2.2	Light interaction with tissue [71]	9
3.1	Setup for the parametric model measurement of vertebrae, i.e. cortical and cancellous bone	12
3.2	Electrode configuration of the PediGuard Probe	12
3.3	Measurement protocol for the Electrical Impedance Spectroscopy Parametric Model	13
3.4	Magnitude and Phase plots for the averaged impedance of vertebra, i.e. cancellous and cortical bone, with whiskers indicating the quantiles at 25% and 75%	15
3.5	Real and Imaginary impedance plots for the averaged impedance of vertebra, i.e. cancellous and cortical bone, with whiskers indicating the quantiles at 25% and 75%	16
3.6	Normalized impedance plots for the averaged impedance of vertebrae, i.e. cancellous and cortical bone, with whiskers indicating the quantiles at 25% and 75%	17
3.7	Boxplot for the magnitude, real and imaginary impedance, (a) Magnitude at 10Hz, (b) Magnitude at 1000Hz, (c) Real impedance at 1000Hz and (d) Imaginary impedance at 1000Hz	18
3.8	Fitted curve for (a) cancellous bone and (b) cortical bone to a two-pole Cole model with CPE	19
3.9	Boxplot for the two-pole Cole parameter (a) R_1 parameter (b) α_1 parameter	19
4.1	Impedance measurement setup for phantom tissue	21
4.2	Modified PediGuard Probe combining DRS and EIS	22
4.3	Phantom production overview	23
4.4	Phantom production setup and phantom example	23
4.5	Phantom Cortical bone	25
4.6	Phantom Cancellous bone	25
5.1	Measurement setup for comparing EIS with DRS	28
5.2	Modified PediGuard Probe combining DRS and EIS	29
5.3	Phantom used for mimicking spinal surgery	29
5.4	Measurement Protocol	30
6.1	Magnitude of the impedance at different depths in the phantom	32
6.2	Intensity results at different depths in the phantom	33
A.1	Conductance for various conductivity solutions	46
B.1	Comparison measured data and IT's database [24]	47
D.1	Fitted curve for (a) cancellous bone and (b) cortical bone to a Cole model	55
D.2	Fitted curve for (a) cancellous bone and (b) cortical bone to a one-pole Cole model with CPE	56

LIST OF FIGURES

D.3	Fitted curve for (a) cancellous bone and (b) cortical bone to a two-pole Cole model with CPE	57
F.1	EIS measurements at point 1	59
F.2	EIS measurements at point 2	60
F.3	EIS measurements at point 3	60
F.4	EIS measurements at point 4	61
F.5	EIS measurements at point 5	61
G.1	DRS measurements at point 1	62
G.2	DRS measurements at point 2	63
G.3	DRS measurements at point 3	63
G.4	DRS measurements at point 4	64
G.5	DRS measurements at point 5	64

List of Tables

3.1	P-value for the magnitude, real and imaginary impedance at 10Hz and 1000Hz	17
3.2	P-value parameters two pole Cole model with CPE	19
4.1	NaCl concentration added to the vertebrae phantom, i.e. cancellous and cortical bone .	22
4.2	Ingredient list for the optical phantom of vertebrae tissue, i.e. cancellous and cortical bone, based on 100ml of phantom	23
4.3	Fitting phantom with cancellous and cortical bone and their corresponding MSE	26
6.1	Fitting results	34
6.2	Ratio capability of breach and tissue detection	34
A.1	Geometry factor PediGuard Probe	46
C.1		49
C.2		52
D.1	MSE for Cole, Cole with CPe and two-Cole with CPE model	57

Nomenclature

CPE Constant Phase Element. 14, 18

DRS Diffuse Reflection Spectroscopy. ii, v, 6, 8, 21–24, 28–30, 34, 37, 38, 40

EIS Electrical Impedance Spectroscopy. ii, v, 5–8, 10, 21–24, 28–32, 34, 35, 37, 38, 40

EMG Electromyography. 5

MSE Mean Squared Error. 15, 24, 25, 38

NIR near-infrared. 9, 33

PSP pedicle screw placement. ii, 3–6

Introduction

Recently there has been a notable rise in spinal fusion surgeries globally, influenced by the expanding older age demographic and the widening spectrum of signs for the procedure, as well as advancements in surgical techniques [51, 34]. Yet, spinal fusion remains a challenging procedure. During this surgical procedure, screws are inserted through bone to interconnect adjacent vertebrae, thereby establishing mechanical stability [23]. However, the misplacement of these screws can have severe consequences due to the spine's proximity to vital structures such as neural and vascular structures [9, 46]. Exploring and evaluating innovations that aim to decrease the likelihood of complications in spinal fusion surgeries is crucial. This chapter will provide more details on the clinical picture and intervention, to define an objective and research question to assess the effectiveness of promising sensing techniques used during spinal fusion surgeries.

1.1. Spine Anatomy

The human spine comprises bones, nerves, muscles, tendons, and ligaments. Its primary function is to support the body while protecting the spinal cord and enabling movement. The spinal column consists of 33 individual bones, called vertebrae, which are divided into five regions, as seen in Figure 1.1: cervical, thoracic, lumbar, sacral, and coccyx [16]. Each region has unique features and performs specific functions.

The cervical spine (7 vertebrae), also known as the neck, supports the weight of the head and has the greatest range of motion. The first and second vertebrae enable nodding and side-to-side motion.

The thoracic spine (12 vertebrae) protects the heart and lungs and holds the rib cage. Its range of motion is limited.

The lumbar spine (5 vertebrae) bears the weight of the body and has larger vertebrae to absorb the stresses of lifting and carrying heavy objects.

The sacrum connects the spine to the hip bones, and five sacral vertebrae are fused.

The coccyx region is an attachment point for ligaments and muscles of the pelvic floor. Four fused vertebrae make up the tailbone or coccyx region [42, 16].

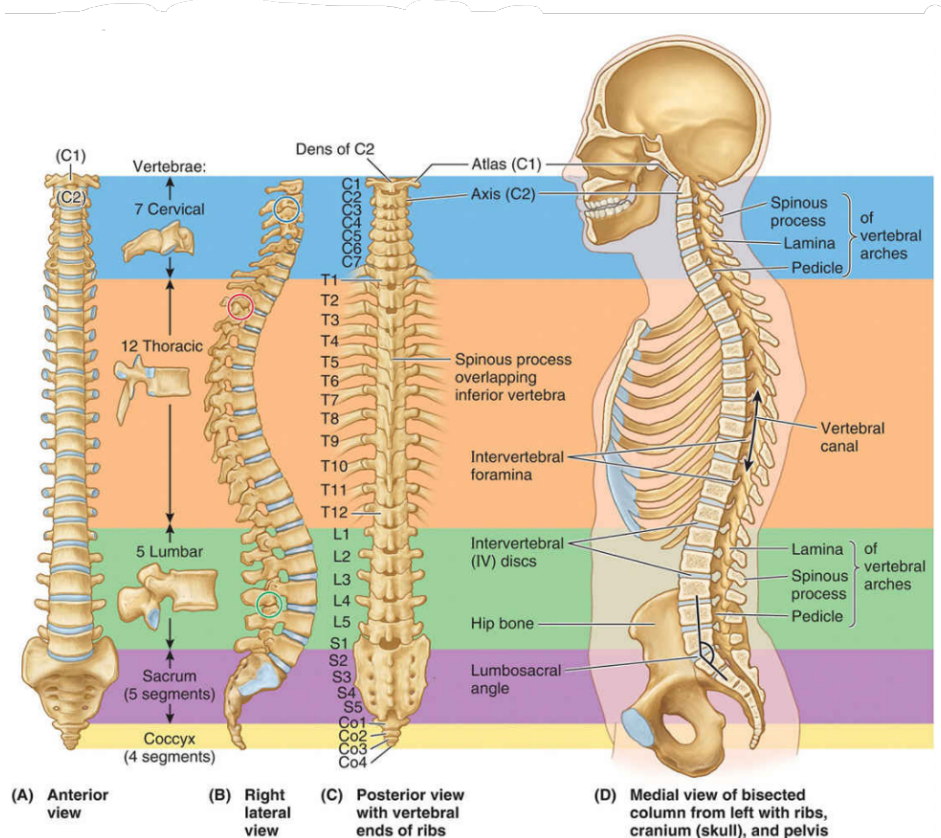


Figure 1.1: Anatomy of the spinal column [16]

Although each vertebra varies in shape and function, they can all be divided into two sections: the vertebral body and the vertebral arch, see Figure 1.2. The vertebral body is a box-shaped block of bone with flat surfaces on the top and bottom, which makes it optimal for resisting vertical loads [66]. The block comprises an outer shell of cortical bone, while a web of trabecular bone occupies its internal space. This design provides a lightweight structure. The spaces between the trabecular bone enable blood vessels to flow through the bone, and in some bones—for example the vertebral body—these spaces contain bone marrow [35, 47].

The vertebral arch is a bony ring that fuses with the posterior aspect of the vertebral body. It consists of two laminae with three processes (one spinous process and two transverse processes) and two pedicles. The spinous processes serve as points where muscles attach to stabilize the spine and enable trunk movement. Meanwhile, the two pedicles protect the spinal cord and nerves and create a link between the front and back portions of the spine [66].

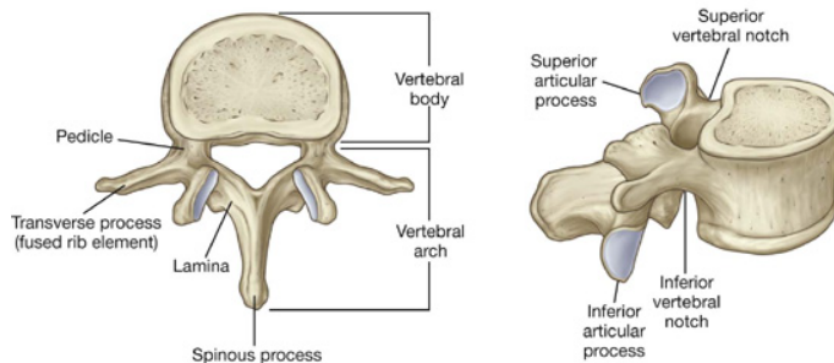


Figure 1.2: Anatomy of a vertebrae [39]

The vertebrae are stacked on top of one another to form the S-curved spine. They are connected by inter-vertebral discs that are made of soft, pad-like material. These discs provide the spine with flexibility and elasticity and also help to absorb any forces that may act on it. The spinal cord, fat, and blood vessels are all located within the hollow spinal canal, which is the space that lies between the body and the arch of the vertebrae [39].

1.2. Spinal fusion surgery

The placement of spinal screws is a complex process and requires a surgeon's technical proficiency to ensure patient safety. It necessitates a detailed understanding of the spine's anatomy, which is complex and mostly hidden, having only limited visible landmarks. Additionally, the proximity of critical neural and vascular structures, along with variations in morphology among patients, presents further difficulties [60, 59]. Improperly positioned screws can lead to insufficient fixation and pose a considerable risk to these vital structures. Surgeons, thus, rely on their experience, guidance techniques and sensing techniques to ensure accurate placement of the screws [9].

Spinal fusion surgery, also referred to as spinal arthrodesis, is a medical procedure in which two or more vertebrae grow rigidly together by added bone graft, such that no movement between them is possible anymore, see Figure 1.3. The medical procedure is often applied to release pain and treat spinal diseases by eliminating any relative motion between the affected vertebrae and improving the spine's stability. A diverse range of spinal diseases and disorders can lead to pain, deformities, and dysfunction [49]:

- **Spondylosis**, a degenerative osteoarthritis of the joints between the centres of the spinal vertebrae and intervertebral foramen.
- **Spondylolisthesis**, a condition in which one vertebrae slips forward relative to the vertebrae above or below it
- Instability and pain caused due to **excessive motion between vertebrae**
- **Bulging or herniated disk**, which can cause compression of the spinal nerves.
- **Spinal deformities** such as Scoliosis or Kyphosis.
- **Trauma** to the vertebrae [61].

Spinal fusion surgery is performed in two main steps. The first step is to perform decompression by either dissecting or removing the affected intervertebral disc and inserting bone graft material. The second step involves the insertion of spinal instrumentation, such as pedicle screws and rods, to fixate the vertebrae relative to each other. This reduces the load on the spine and enables spinal fusion [49].

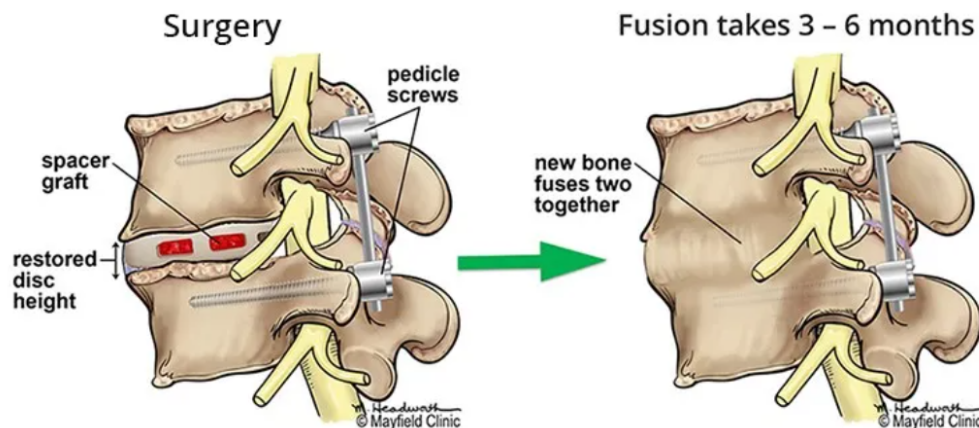


Figure 1.3: Overview of spinal fusion surgery [1]

1.3. Pedicle screw placement

The predominant technique used for spinal surgery is pedicle screw placement (PSP). This technique has a higher fixation strength compared to other techniques, primarily attributed to the higher cortical

bone content in the pedicle. The strength of cortical bone is higher than trabecular bone [52]. Studies indicate that around 60% of the fixation strength in thoracic and lumbar PSP placement originates from the pedicle bone segment, with 15-20% attributed to the vertebral body and 20-25% to the anterior cortex [29].

1.3.1. Procedure

The free-hand technique was one of the earliest techniques used for placing pedicle screws [28]. In this method, the surgeon only relies on anatomical landmarks, experience and tactile feedback to correctly position and place the screws. The most common way of placing pedicle screws is through the posterior approach. This involves performing either an open or a minimally invasive surgery to access the transverse process and midline structures, see Figure 1.4 [63].

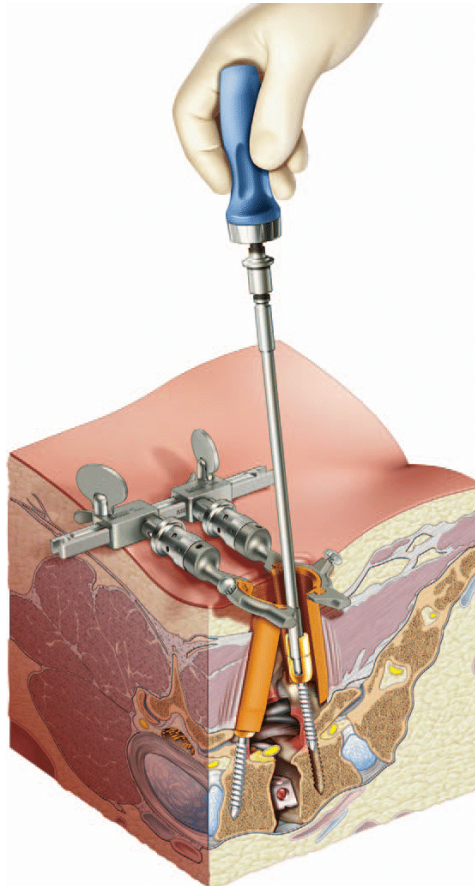


Figure 1.4: Overview of the procedure of Pedicle screw placement [48]

To start the spinal fusion surgery procedure, an entry point is determined, typically located at the junction of the transverse process and the facet joint. After this, a drill or awl is used to create a hole at the entry side. When the drill reaches the cancellous bone, a blunt probe is used to carve the correct trajectory inside the cancellous bone of the pedicle and the vertebral body. At this stage, the neural or vascular structures are at high risk. Therefore, a feeler or ball-tipped probe is used to assess the tract's integrity. Optionally, a screw tape may be inserted to prepare the hole further along the trajectory of the probe. Finally, the screw is inserted into the hole to complete the procedure [63].

1.3.2. Complications

Spinal fusion procedures are associated with increased complication rates compared to other surgeries, characterized by extensive dissection, prolonged operative times, heightened mortality risk, and elevated blood loss [11]. According to Vaccaro and Garfin, complication rates as high as 63% have been reported, with approximately 5% attributed to pedicle screw misplacement. Misplacement, often

defined as a cortical breach, poses risks to neurological and vascular structures. With cortical breaches being either lateral or medial, see Figure 1.5. An additional difficulty is pedicle screw breakage, which occurs in 3-30% of cases, further complicating surgical outcomes.[30].

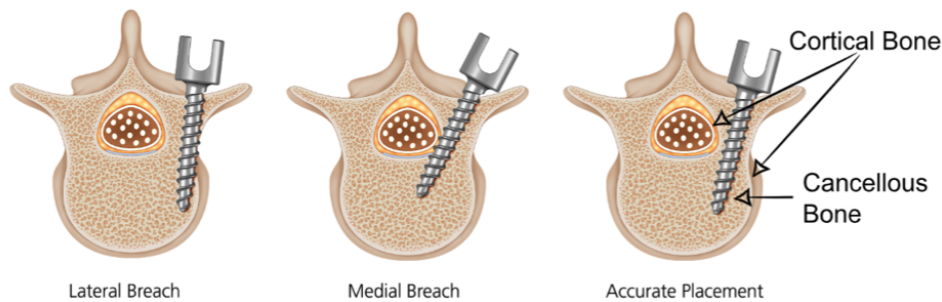


Figure 1.5: Cortical Breach occurrences [27]

1.3.3. Enhanced pedicle screw placement

In response to the high risks associated with spinal fusion surgery, several innovative techniques have been developed to enhance the accuracy of PSP. These techniques primarily aim at improving the trajectory of pedicle screws to minimize the risk of cortical breach [62]. These guiding techniques can be either global, providing a general overview, or local, offering information at a specific point. Global guiding techniques provide spatial orientation, while local guiding techniques use sensing techniques at the point of the tip to estimate a safe trajectory.

Global Guidance Techniques

2D Fluoroscopy-Guided Technique relies on sequential X-ray imaging to monitor the trajectory of screws in real-time. By using an image intensifier system, surgeons can acquire anterior-posterior and lateral views of the vertebral levels during surgery [15]. This method offers the advantage of real-time visualization, improving accuracy rates. Additionally, fluoroscopy enables the surgeon to perform the surgery minimally invasive, which has several extra benefits such as reduced tissue damage, blood loss, surgical site infections, and faster recovery times. However, surgeons and patients experience increased radiation dosage compared to other procedures, which could be harmful [65].

Computer-Assisted Surgical Technique combines navigation software with imaging techniques, such as fluoroscopy or CT images, to plan screw trajectories and navigate through anatomy in real-time. This technique improves intraoperative path planning and provides a more intuitive experience for surgeons. The 3D CAS technique has demonstrated improved PSP accuracy and reduced radiation exposure. However, potential drawbacks include workflow interruptions and thus extended operation times [41].

Local Sensing Techniques

Neurophysiological Monitoring Technique improves the traditional free-hand technique by repeatedly evaluating the function of the nervous system during critical procedural steps. This technique employs various monitoring techniques, such as stimulated or triggered Electromyography (EMG) monitoring, to protect the spinal cord and spinal nerves [50]. However, it has also been known to have a relatively low sensitivity for pedicle screw malposition detection. EMG monitoring can often only indicate the presence of a nerve injury after it has occurred thus not helping mitigate the risk of injury [31].

Electrical Impedance Spectroscopy (EIS) measures the dielectric properties, conductivity and permittivity, of various tissue types including blood, cortical, and cancellous bone. By detecting differences in electrical conductivity, this technique can anticipate cortical breaches. A notable device is the PediGuard probe developed by SpineGuard, which provides audio and visual feedback to warn surgeons [70]. Clinical use of the PediGuard has demonstrated increased accuracy in pedicle screw placement, particularly in the thoracic region, along with reduced insertion time and radiation exposure [12]. However, independent researchers have found that the PediGuard is sensitive to pressure variations, affecting the interpretability of the feedback. For example, when a surgeon does not maintain steady probe pressure, blood can reach the tip, which could lead to false positive results [13, 25].

Diffuse Reflection Spectroscopy (DRS) measures the optical properties, scattering and absorption, for various tissue types. By detecting differences in the returned light signal this technique can anticipate cortical breaches. DRS is a new emerging technique. A research group from the TU Delft has performed several studies which show that the reflectance signal obtained in cancellous bone was significantly different to the signal obtained from cortical bone [58]. Due to the short acquisition time of DRS, it could have a high potential for real-time tissue distinction.

1.4. Problem statement

Accurate screw placement is crucial in spinal surgery to avoid complications such as poor stability, nerve damage, or spinal cord injury, which can result in pain, loss of sensation, muscle weakness, or even complete paralysis below the level of injury [33]. The success rates of screw placement are highly variable, ranging from 27.6% to 100% [56].

Enhanced PSP techniques have been developed to provide the surgeon with spatial awareness. If estimation can be done on the location of the tip of the probe, cortical breaches can be detected and prevented. There are multiple guidance techniques developed and used during spinal fusion. These can either be global or local guiding techniques. Certain techniques include fluoroscopy, computer-assisted techniques, Neurophysiological monitoring, and EIS enabled by the PediGuard [18]. Even though these systems decrease the risk of complications, they all impose limitations influencing the success rate of the procedure, such as radiation, increased surgery time or no real-time feedback [22, 18].

This study focuses on local sensing techniques. Global guiding techniques, although useful, are expensive, require expert interpretation and are time-consuming. Local sensing techniques can provide real-time feedback by giving spatial awareness of the tip during surgery while not prolonging surgery time. Real-time feedback at the tip of the pedicle screw is essential to detect misplacement during insertion and enable surgeons to make immediate trajectory adjustments [40]. A new emerging sensing technique, DRS, has been proven to be able to discriminate different spinal tissue in a non-harmful way [58]. However, this technique is not compared and evaluated against the current local sensing technique, EIS enabled by the PediGuard sensing device.

This thesis aims to compare emerging techniques with the latest state-of-the-art techniques, to offer real-time tissue feedback during spinal surgery. Specifically, the focus is on detecting breaches between cancellous and cortical tissue. As explained above, the screws are inserted into the bone, which has an outer cortical bone layer and an internal space cancellous bone. By testing both sensing techniques in a controlled environment, tissue-mimicking phantom, an answer can be given to the following question:

What is the comparative performance between diffuse reflective spectroscopy and electrical impedance in detecting a breach between cancellous and cortical bone in spinal fusion surgery?

1.5. Thesis outline

This thesis is organized into two parts with eight chapters. First **Chapter 2** will discuss the necessary theory that is required to understand this thesis. The theory is divided into two sections: introducing electrical impedance spectroscopy and introducing diffuse reflection spectroscopy. Then we will dive into the preliminary research. During the preliminary research, missing knowledge gaps needed for this research will be tested. It was seen in the theory that there is limited knowledge of the working principle of the Pediguard and impedance measurement for spinal fusion surgery. **Chapter 3** will try to fill these knowledge gaps and explore the working principles of the Pediguard. Furthermore, limited research was found on optical and dielectric phantoms. **Chapter 4** will try to find a potential phantom which mimics the optical and dielectric properties of vertebrae. The second part of the thesis contains the final experiment. The comparison of DRS with EIS. **Chapter 5** elaborates on the methodologies used to use EIS and DRS in spinal fusion and how to compare these. **Chapter 6** provides an in-depth discussion of the measurements and results found. This chapter is divided into two sections: the findings regarding the impedance model for vertebrae and the comparison between EIS and DRS. **Chapter 7** contains the discussion of the research findings and recommendations for future research. Finally, **Chapter 8** includes the most important conclusions of this thesis.

2

Theory

2.1. Electrical Impedance Spectroscopy

Electrical Impedance Spectroscopy (EIS) is used to investigate the interaction between an alternating electric field and a given system. This method characterises the electrical properties of a system by observing its time-dependent response to an applied current across a spectrum of frequencies. Currently, EIS finds applications in diverse sectors, including material characterization, battery assessment, biosensor development, and the identification of biological tissues [32].

Bio-impedance is a methodology used in biological research to determine electrical characteristics of biological tissues and their ability to resist the flow of electrical current [26, 6]. This property can be measured by monitoring the tissue's response to electrical stimulation [6]. The bio-impedance of a given biological structure depends on factors such as tissue composition, structural arrangement, and physiological or pathological properties at the molecular level within the tissue [8, 69].

2.1.1. Basic working Principles

EIS measurements are performed through an open-loop electric configuration. The closing of this electric circuit occurs when contact is established with the sample under examination, typically enabled by a group of electrodes configured in specific arrangements. These electrodes can be categorized as either working, reference, or counter electrodes. Measurements are taken by directing a known voltage or current through the working electrode, crossing the biological tissue, and eventually reaching the counter electrode. The tested system can vary significantly in scale, ranging from comprehensive assessments such as whole-body composition analysis to pinpoint evaluations of specific tissue regions, such as mucosal surfaces [21].

Before we dive deeper into EIS and its application to biological tissue, a basic understanding of impedance is required. Impedance is represented as $\mathbf{Z}$ and, like resistance, it resists the flow of electric current. In simple terms, impedance is connected to Ohm's law, which relates voltage, current, and resistance, as shown in Equation 2.1.

$$U = I\mathbf{Z} \quad (2.1)$$

With U being the electrical potential difference, voltage [V], and I being the electrical current, ampere [A].

Therefore, to calculate electrical impedance, we measure how it behaves when we use alternating current or voltage. Due to the alternating current Impedance can be described as a complex resistance and thus is a complex number. We can describe it using Equation 2.2, as mentioned in [64].

$$Z = \frac{u(\omega)}{i(\omega)} = |Z|e^{j\phi} = R + jX \quad (2.2)$$

In the Cartesian form of Equation 2.2, R represents the resistance and X represents the reactance [64]. The resistance (R) is the real component of the complex, $R = |Z|\cos\phi$ impedance and the reactance (X) is the imaginary portion, $X = |Z|\sin\phi$.

2.1.2. Electrical Impedance Spectroscopy in Biological Tissue

EIS involves creating an electrical circuit that mirrors the impedance of the sample being analyzed. As seen in Figure 2.1, the parallel RC circuit is an equivalent circuit for a living cell membrane since it has high conductivity at a high-frequency current and low conductivity at a constant current. The semi-permeable membrane found around living cells enables specific ions to pass while blocking others, behaving like a capacitor [4, 57]. A capacitor, consisting of two conductive plates separated by an insulating layer, represents this charge-storing ability. Within the cell membrane, the lipid bilayer separates conductive salt solutions of intracellular and extracellular fluids. The resistor symbolizes the membrane's resistance, while the capacitor describes its geometrical capacitance[43].

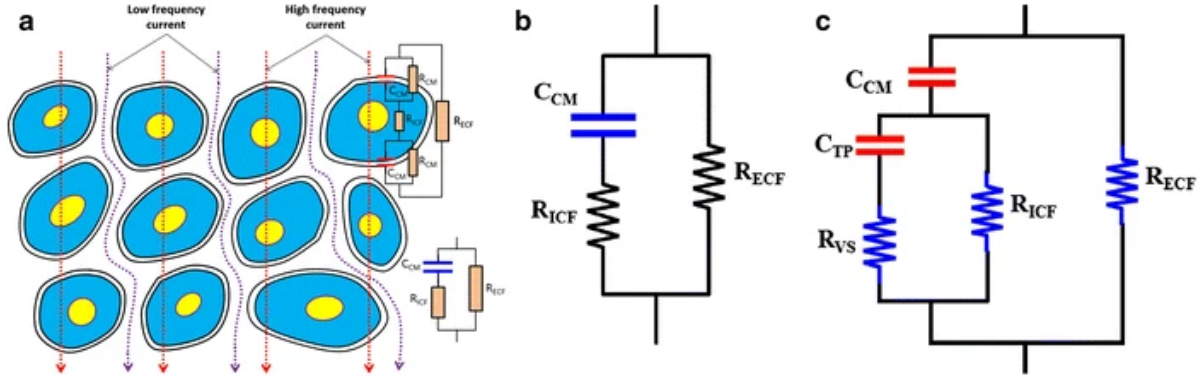


Figure 2.1: The frequency-dependent impedance properties of biological tissues and their equivalent circuit modelling: electrical current conduction through the biological cells in an animal tissue [4]

Biological tissues exhibit diverse electrical properties, chemical compositions, and tissue structures, resulting in distinct frequency characteristics. In 1957, Schwan identified three main dispersions of electro-bioimpedance spectra: the α -, β -, and γ -dispersion [54]. The low-frequency range, α -dispersion, reflects the influence of extracellular space, whereas the intracellular space affects higher frequencies, β -dispersion. Due to their high capacitance, low frequencies are hindered by cell membranes and traverse extracellular space. Conversely, high frequencies easily penetrate cell membranes, enabling passage through both cell and intracellular spaces. As a result, different cell properties manifest in different frequency regions [43, 4].

2.2. Diffuse Reflection Spectroscopy

Diffuse Reflection Spectroscopy (DRS) is a technique used to examine the interaction between incident light and tissue by using a broad range of light wavelengths. Light is transmitted into the tissue through an emitting fiber directly in contact with it, while another fiber collects the light that has traversed the tissue. Diffuse reflection relies on two primary interactions between photons and tissue: absorption and scattering. Unlike specular reflection, where light reflects off a surface at equal and opposite angles, diffuse reflection involves the scattering of light in various directions due to the material's composition, colour, and surface irregularities. A depiction of these photon-tissue interactions resulting in diffuse reflectance detected at the tissue surface is illustrated in Figure 2.2. The collected light results in a spectrum that correlates reflectance with wavelength [58].

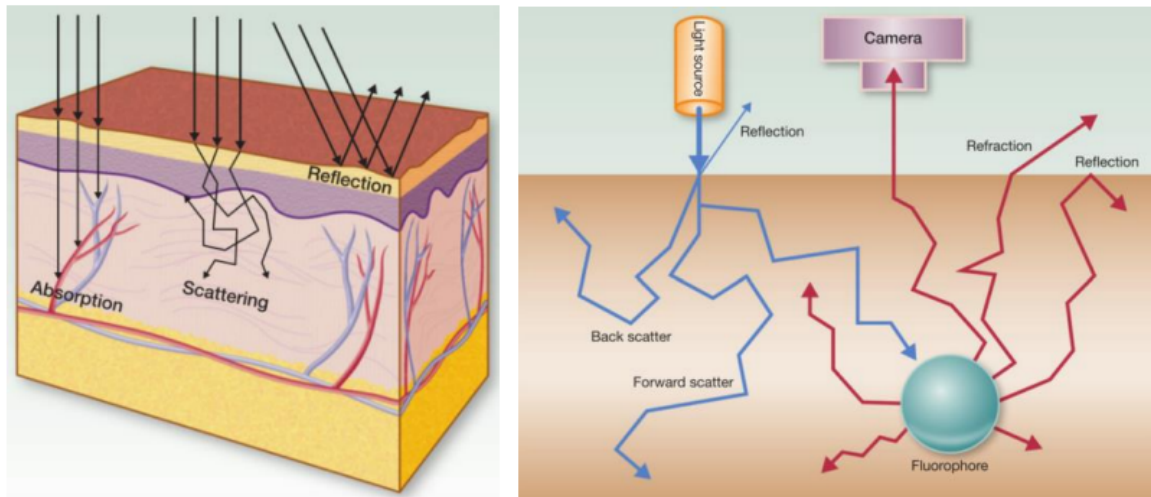


Figure 2.2: Light interaction with tissue [71]

2.2.1. Absorption

Absorption, a fundamental property, is described by the absorption coefficient (μ_a), which varies with wavelength. μ_a signifies the absorption in inverse length units (cm^{-1}). Key absorbers in tissue include oxy- and deoxygenated hemoglobin (HbO_2 and Hb), water, and fat. Hemoglobin mainly absorbs visible light (400 to 800 nm), whereas fat displays strong absorption in the near-infrared (NIR) range. Other tissue chromophores that absorb light include bile, bilirubin, β -carotene, and methemoglobin. Water and fat primarily absorb in the NIR spectrum (800-1600 nm), alongside collagen and elastin [71].

2.2.2. Scattering

Scattering occurs when photons are not absorbed but instead redirected due to structural variations or fluctuations in refractive index. The scattering coefficient (μ_s) represents the likelihood of photon scattering per unit length and depends on particle size and refractive index. Although the exact cause of scattering in tissue remains unclear, it is widely believed to stem from the microscopic variations and inhomogeneities of the refractive index, which correspond to various scattering centres present. Tissue scattering is primarily Mie scattering, influenced by larger structures such as mitochondria and collagen fibers. In DRS applications, the reduced scattering coefficient (μ_{0s}) is often utilized, derived from diffuse scattering signals [45, 58].

Part I

Preliminary Testing - Filling in the gaps of knowledge

Chapter 1 and chapter 2 of this study highlight the gaps in our current knowledge. Unfortunately, limited experimentation and literature are found on the use of Electrical Impedance Spectroscopy in spinal fusion surgery and creating a phantom with both electric and optical properties. Information on the working principle of the PediGuard device is not well-documented and could only be found in patents and studies mimicking the PediGuard device. Furthermore, while literature describes tissue-mimicking phantoms to simulate the optical properties of vertebrae bone, knowledge of dielectric phantoms is limited. Additionally, there is not much literature describing phantoms that can mimic both the optical and dielectric characteristics. The first part of this study aims to gain knowledge on these knowledge gaps to enable the final experiment. First, impedance measurements will be performed on bone using a PediGuard device, to gain an understanding of the working principle of the device. Second, the study will attempt to create phantoms that can mimic both the electric and optical properties of vertebrae, i.e. cancellous and cortical bone.

Electrical Impedance Spectroscopy Parametric Model

This chapter aims to get a better understanding of the working principles of the PediGuard and the impedance of vertebrae tissue. By measuring the dielectric properties of vertebrae, i.e. cancellous and cortical bone, with an altered PediGuard probe an assumption will be made on the operating frequencies and discriminatory parameters. These assumptions will be compared with the literature found. Second, collecting this data will allow us to investigate the full dielectric spectrum which could show more trends and discriminatory parameters. This chapter will discuss the measurement methods, data analysis, results and conclusions to answer the following two questions missing in current theory:

1. What is the basic working principle of the PediGuard with regards to the difference in conductivity of spinal tissue, i.e. cancellous and cortical bone and at what frequency is this measured?
2. Can the impedance of spinal tissue, i.e. cancellous and cortical bone, be modelled and what are the classification features?

3.1. Method

The objective is to conduct electrical impedance measurements on vertebrae bone, i.e. cancellous and cortical, to establish a dataset on the dielectric properties. With this dataset, single-frequency and multi-frequency analyses will be done to identify classification features. These features will be compared with the literature found to gain a better understanding of the working principle of the PediGuard device and evaluate if more extensive analysis would increase the performance of the classification features.

3.1.1. Measurement Setup

The measurement setup can be seen in Figure 3.1. The electrical measurements are performed using a Hewlett Packard 4192A LF HP impedance analyzer connected to a laptop. The impedance analyzer can measure either absolute impedance and phase angle or capacitance and conductance. We use NI LabVIEW to read the data provided by the analyzer. With Labview, the frequency range and the number of steps can be specified. For this study, we conduct measurements on the absolute impedance and phase angle, in the α and β dispersion, covering a frequency range of 10 Hz to 1 MHz with 101 steps.

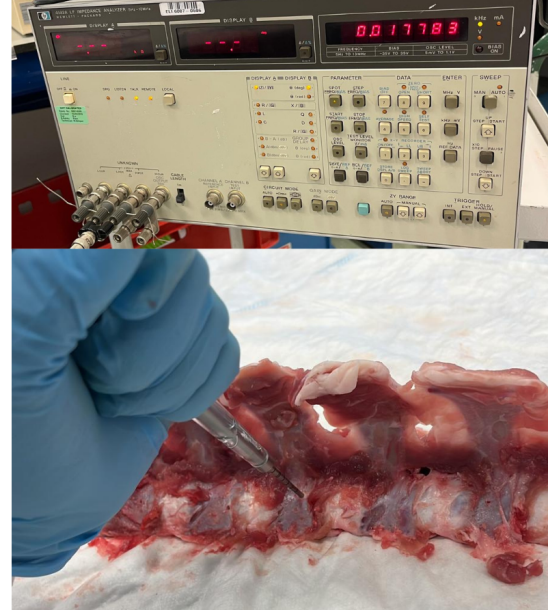
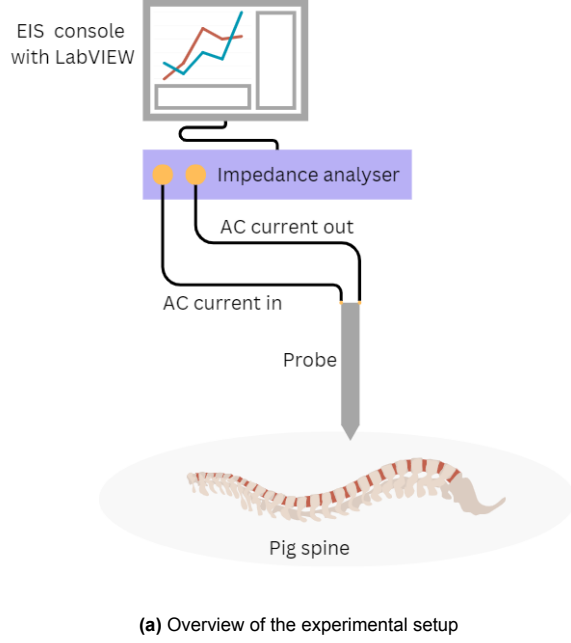


Figure 3.1: Setup for the parametric model measurement of vertebrae, i.e. cortical and cancellous bone

Measurements are taken using a PediGuard probe altered to enable a connection to the impedance analyzer. The alterations entail removing the battery and adding a connection for the impedance analyzer. The PediGuard probe uses a coaxial bipolar probe, with respective contact areas of $A_{e,1} = 10\text{mm}^2$ and $A_{e,2} = 4\text{mm}^2$. The distance between the electrodes is $D_e = 1\text{mm}$, as cited by US7580743B2 [14], see Figure 3.2. One electrode is linked to a low potential output, while the other is connected to a high potential output. By using the same electrode layout our measurements are comparable to the PediGuard as contact impedance and impedance polarization are both related to the electrode design.

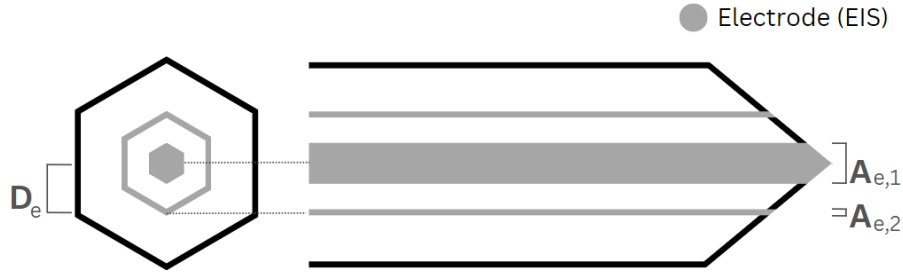


Figure 3.2: Electrode configuration of the PediGuard Probe

3.1.2. Measurement Protocol

A porcine spine was chosen for the experiments as it has similar dielectric properties to the human spine [67]. The porcine spine was obtained from a local butcher, de Groene Weg in Rotterdam, to ensure freshness. The sample was kept cool but not frozen until it arrived at the laboratory. This will limit the dehydration of the tissue. The porcine spine was then left to rest for about 30 minutes at room temperature before the experiments.

The impedance analyzer was initiated in advance, enabling a minimum warm-up period of 30 minutes to minimize noise during the process. The probe was cleaned using 96% alcohol and distilled water. To verify the system's operability, a test measurement was conducted by holding the probe still and measuring the impedance of the surrounding air. If no anomalies were detected, measurements were then taken.

The surgeon guided the process by indicating the areas to be measured and distinguishing between

cortical bone, cancellous bone, and soft tissue. Measurements on the impedance magnitude and phase were performed 3 times at 15 different locations for each tissue, with the probe rinsed between measurements to eliminate any residual tissue. The measurement protocol outlined in Figure 3.3 was followed.

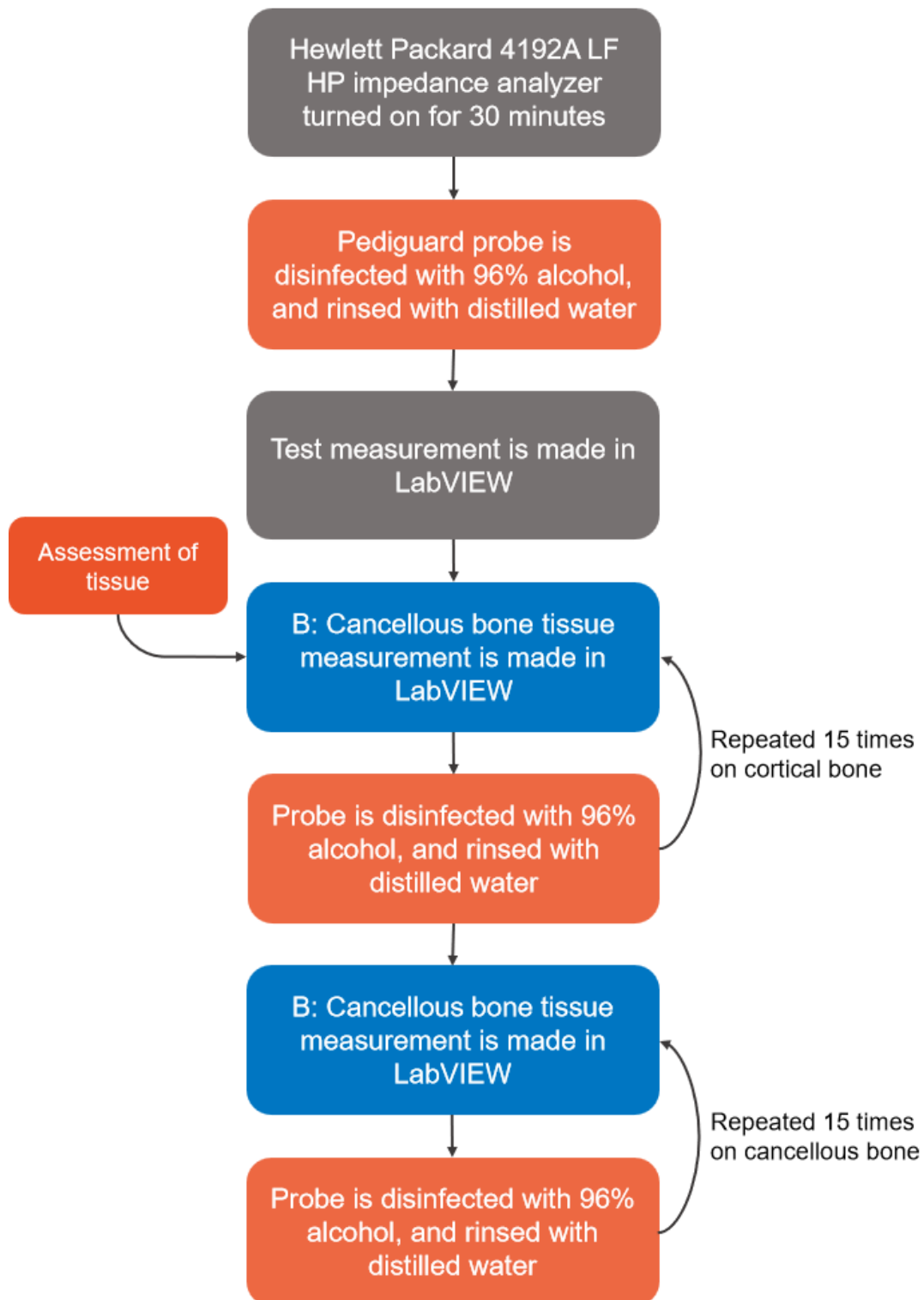


Figure 3.3: Measurement protocol for the Electrical Impedance Spectroscopy Parametric Model

3.1.3. Data Analysis

For the data analysis, it was chosen to separate between single-frequency analysis and multiple-frequency analysis. The method for both techniques is discussed below. Appendix B compares the found data with the IT's database to see if similar results were found.

Single-frequency analysis

The first analysis done is a single-frequency analysis. Classification features of data are found for specific frequencies and not the entire spectrum. These features can either be the magnitude, phase, real, or imaginary part of the impedance at a specific frequency. As explained in chapter 2, the magnitude stands for the change in amplitude in resistance and the phase is the delay in frequency. The real impedance or resistance is described as the opposition of the medium to the flow of electric current and imaginary impedance or reactance is defined as the opposition of the medium to a change of electric current.

For each frequency, a Kolmogorov–Smirnov test is used to evaluate the normality of each property. If the data follows a normal distribution an ANOVA T-test will be used and otherwise a non-parametric Wilcoxon rank-sum test to differentiate between cancellous or cortical bone. The significance level for the analysis was set at $p < 0.05$.

Multiple-frequency analysis

The second analysis is a multiple-frequency analysis. In this type of analysis, the entire spectrum is examined. Analyzing biological impedance spectra poses a challenge due to the multivariate nature of the data. To simplify the interpretation and reduce the dimension of the measurements, the entire spectrum is fitted against a model or equivalent electric circuit, which represents the expected behaviour of the tissue. So to gain insights from impedance data, a model or equivalent electric circuit is used to condense the multivariate data of the impedance spectra into a set of relevant parameters.

1. Parameterization Methods

This section discusses the Cole impedance model used to interpret Electrical Impedance data. The chosen model in this study is the Cole impedance model, which is a theoretical model used to describe tissue impedance. Appendix D discusses other possible models and validates the choice of a Cole impedance model for the measured data and frequency range. The Cole impedance model is extensively used to describe different tissue types and is represented by the equation shown in Equation 3.1.

$$Z = R_{\infty} + \frac{R_0 - R_{\infty}}{1 + (j\omega\theta)^{\alpha}}, \theta = C/G_{var} \quad (3.1)$$

Here, Z represents the complex impedance, R denotes the resistance at an infinite frequency, j is the imaginary unit, ω is the angular frequency, and θ is determined by the ratio of capacitance to variable conductance.

Parameters in the Cole impedance model have been subject to discussion. While some argue that certain parameters lack physical significance, others declare that R_0 signifies the resistance at zero frequency, θ corresponds to the characteristic time constant of the system aligned with a characteristic angular frequency, and α is a dimensionless exponent ranging between zero and one. The α factor accounts for a distribution of relaxation times, enabling the broadening of the dispersion curve.

The impedance model presented in Equation 3.1 is a single-dispersion model, addressing only one dispersion. Although the alpha dispersion and beta dispersion are measured, the composition of the bone with a bone matrix ensures only ionic dispersion. Moreover, Constant Phase Element (CPE) model is included to account for contributions from electrode polarization, see Equation 3.2

$$Z_{CPE} = K(j\omega)^{-m} \quad (3.2)$$

Here, K represents the ion concentration at the electrode-tissue interface, and m is associated with the surface roughness of the electrode. Combining these elements with two Cole models, a two-pole Cole model with a CPE model could describe tissue with two dispersion and electrode polarization. The equation of a two-pole Cole model is given in Equation 3.3

$$Z = R_{\infty} + \frac{R_1}{1 + (jF/F_c)(1 - \alpha)} + \frac{R_2}{1 + (jF/F_c)(1 - \alpha)} + K(j\omega)^{-m} \quad (3.3)$$

2. Fitting Method

The parametric model is fitted to the measured impedance spectra. The used method for this fitting process is the nonlinear least squares method, commonly used with the Nelder-Mead algorithm. In this study, we use the `fminsearchbnd` function in Matlab.

The accuracy of the model fit is assessed through the Mean Squared Error (MSE) calculated for both the real and imaginary parts of the impedance, along with the robustness of the parameters. The MSE is calculated following Equation 3.1.3

$$MSE = \sum (Z_{im,data}(w) - Z_{im,model}(w))^2 + \sum (Z_{re,data}(w) - Z_{re,model}(w))^2 \quad (3.4)$$

The model fitting process involves using a set of initial parameters, and the fit is iteratively performed with the best-fit parameters until the lowest MSE is achieved for both the real and imaginary parts of the impedance. However, if the MSE improves by a value smaller than 5 at the cost of a parameter, the fitting process is halted. Parameter bounds are set at 0 (minimum) and infinity (maximum) for all parameters except for the exponents. For the exponents, α_1 , α_2 , and m , the upper bounds are specifically set at 1.

Multiple sets of initial parameters are tested to ensure the best model fit is found and not a local minimum. The initial parameters that show the lowest MSE are chosen.

3. Statistical analysis

For each parameter a Kolmogorov–Smirnov test is used to check normality. If the data follows a normal distribution an ANOVA T-test will be used and otherwise a nonparametric Wilcoxon rank-sum test to differentiate between cancellous or cortical bone. The significance level for the analysis was set at $p < 0.05$.

3.2. Results

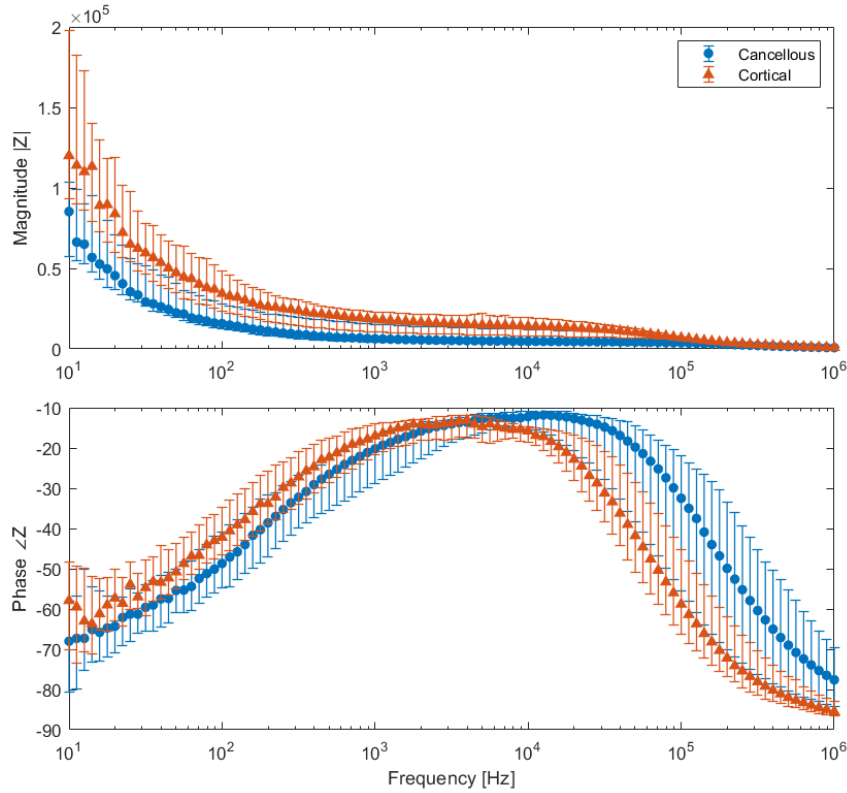


Figure 3.4: Magnitude and Phase plots for the averaged impedance of vertebra, i.e. cancellous and cortical bone, with whiskers indicating the quantiles at 25% and 75%

We measured the magnitude and phase of the impedance for cortical and cancellous bone tissues covering the frequency range of 10 Hz to 1 MHz. The average results with whiskers indicating the quantiles at 25% and 75% are shown in Figure 3.4. The top graph displays the impedance magnitude for cortical and cancellous bone across the frequency range. In contrast, the bottom graph illustrates the phase of impedance for the cortical and cancellous bone over the same frequency span. The magnitude graph shows that the average impedance for cortical bone is higher than for cancellous bone. Cortical bone was expected to have a higher impedance than cancellous bone as cancellous bone has a higher ratio in extracellular fluids as mentioned in chapter 2. The phase graph shows a shift to the right when comparing cortical bone with cancellous bone. This also suggests a higher ratio of extracellular fluids.

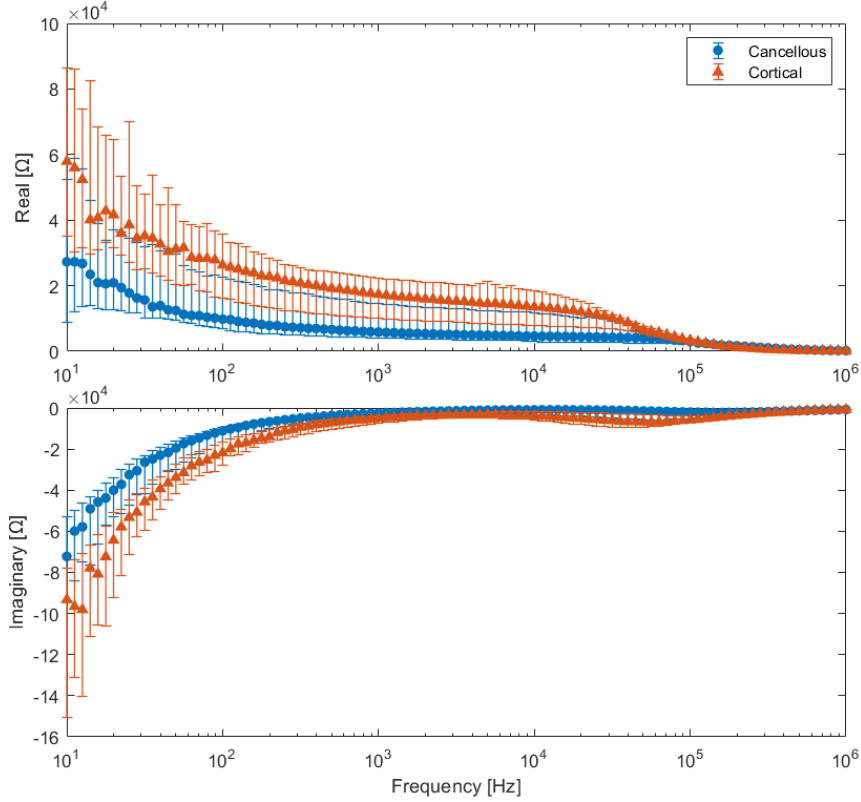


Figure 3.5: Real and Imaginary impedance plots for the averaged impedance of vertebra, i.e. cancellous and cortical bone, with whiskers indicating the quantiles at 25% and 75%

From the magnitude and phase, the real and imaginary parts of the impedance can be calculated. Figure 3.5 shows the average real and imaginary impedance for cancellous and cortical bone with whiskers indicating the quantiles at 25% and 75%. In the low-frequency range, the real and imaginary impedance increases. While in the high-frequency range, the curve flattens. For cortical bone, another decrease is seen for the real impedance in the high-frequency range between a wavelength of 10^4 and 10^5 . The total impedance decreases while the frequency increases, which is expected as the ions travel shorter distances and the tissue lacks time to react to the travelling ions. The total impedance of cortical bone is higher than cancellous bone.

Furthermore, the whiskers (quantiles) in Figure 3.4 and Figure 3.5 suggest a higher variability in impedance in lower frequencies. However, as the signal decreases and starts to approach zero, the variance is expected to decrease and be proportional to the amount of signal. The normalized variance is calculated by dividing the impedance, Z , by the average impedance of the cancellous bone Z_{can} , see Figure 3.6. This gives no insight into the physical nature of the impedance measurement, however, it does show how the variance is proportional to the amount of signal measured. At lower frequencies, the variance fluctuates but stays in approximately the same bandwidth. At higher frequencies, above 10^5 Hz, the variance decreases.

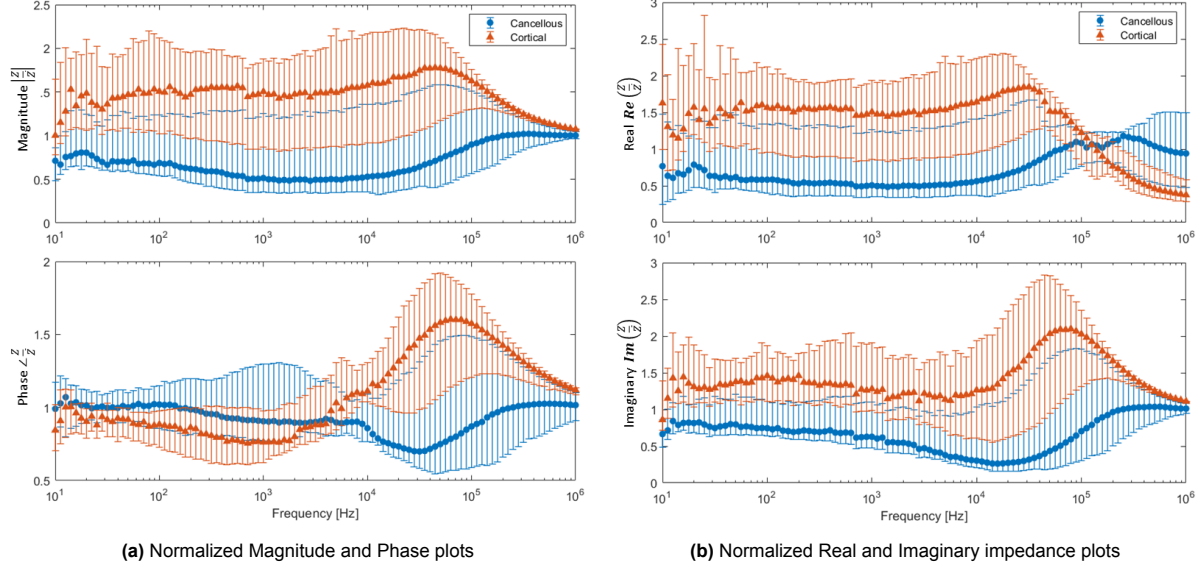


Figure 3.6: Normalized impedance plots for the averaged impedance of vertebrae, i.e. cancellous and cortical bone, with whiskers indicating the quantiles at 25% and 75%

3.2.1. Single frequency analysis

Four features were analysed in the single frequency analysis, the magnitude, phase, real or imaginary impedance. Each of these features could be used as a classifier for tissue detection. The Kolmogorov–Smirnov test indicated that the measurements for all four features per frequency spot do not follow a normal distribution. Therefore, a Wilcoxon sum test was performed to determine the predictive value. The mean and predictive values for all frequencies and features can be found in Appendix C. If the predictive value is below the threshold of 0.05, the feature is expected to be a good classifier. Almost all features at all frequencies had $p - value < 0.05$. At high frequencies, above $10^5 Hz$ the p-value increases. Figure 3.6 supports these findings as the measurements for cortical and cancellous bone differ substantially, with limited overlap in frequencies below $10^5 Hz$. The phase angle is shown to be the worst predictive feature.

Table 3.1: P-value for the magnitude, real and imaginary impedance at 10Hz and 1000Hz

		Cancellous bone		Cortical bone	p
		Mean [Ω]		Mean [Ω]	
Magnitude	10 Hz	85300		120000	2.96E+05
	1000 Hz	6300		18400	1.09E+05
Real	1000 Hz	17340		5842	1.89E-05
Imaginary	1000 Hz	-2487		-5077	3.10E-06

The lowest p-values per feature were identified and analyzed to determine the frequency which has the highest predictive value. The frequency 1000 Hz was highlighted as it had good prediction values for the magnitude, real and, imaginary impedance of bone tissue. Table 3.1 show the p-values of all features at a frequency of $10^3 Hz$ with the corresponding mean value for cancellous and cortical bone. All p-values are lower than the set 0.05 value meaning that they could be a good predictor. Furthermore, the frequency 10 Hz was also highlighted as it is most in line with the working frequency found in literature [36]. Figure 3.7 shows the boxplots for all four features discussed above. Cortical and cancellous bone is individually displayed. For all four parameters, differences are visible in the data found. All features decrease when comparing cortical bone with cancellous bone.

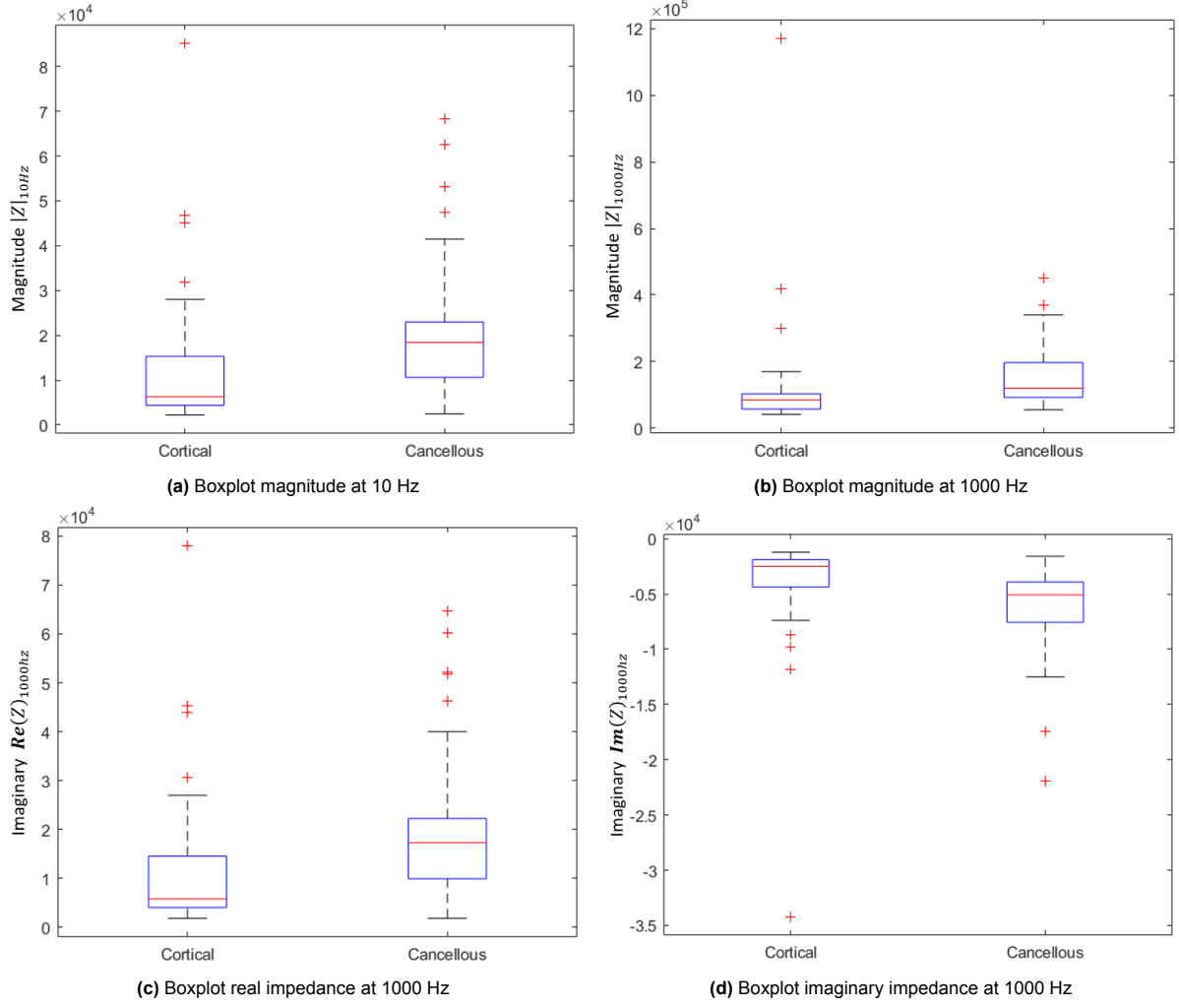


Figure 3.7: Boxplot for the magnitude, real and imaginary impedance. (a) Magnitude at 10Hz, (b) Magnitude at 1000Hz, (c) Real impedance at 1000Hz and (d) Imaginary impedance at 1000Hz

3.2.2. Multiple-Frequency Analysis

For the multiple-frequency analysis, the complete spectrum of the impedance is analysed. A model is used to reduce the dimension of the data. A combination of a CPE model with a two-pole Cole model is fitted to the measured impedance data. The fitting method and formula are given in section 3.1. The initial parameters $[R_1, \Theta_1, \alpha_1, R_2, \Theta_2, \alpha_2, K, m, R_\infty]$ were set to $[4.94 \times 10^3, 1.36 \times 10^{-6}, 0.819, 2.66 \times 10^3, 0.0164, 5.83, 5.98E \times 10^{-7}, 0.765, 1.02 \times 10^2]$. These parameters were also the features used to discriminate between cancellous and cortical tissue.

One of the fits is displayed in Figure 3.8. The real impedance data is compared with the total model fit and the contribution of both the electrode polarization model and the two-pole Cole model. A similar figure appears for most other fits as well. The CPE part describes the increase in the spectrum in the low-frequency range for both the real and imaginary parts of the impedance. The contribution of the term disappears for frequencies above 50kHz . The first Cole term describes the data in the low-frequency range and the second Cole term describes the data in the low-frequency range.

It can be seen that the fit is less accurate at lower frequencies, mostly due to the noise in the original data. At higher frequencies, the impedance flattens out, especially for cancellous bone. For cortical bone, a second dispersion is identified at around 10^5 . The model fits the imaginary impedance better than the real impedance terms. A high MSE was found for all fits suggesting the current approach can not be used to model bone tissue.

The parameters and classification features found by fitting the impedance data to a model were analyzed. The Kolmogorov-Smirnov test showed that the parameters were not normally distributed.

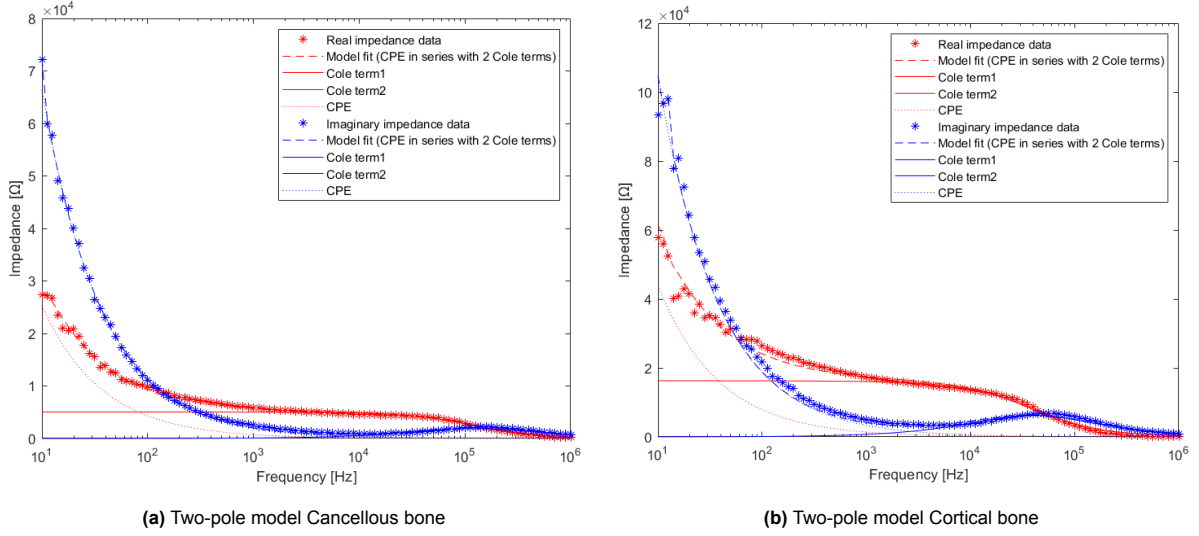


Figure 3.8: Fitted curve for (a) cancellous bone and (b) cortical bone to a two-pole Cole model with CPE

Therefore, a Wilcoxon sum test was performed to determine the prediction value. Table 3.2 shows the p-values found. α_1 has the lowest p-value satisfying the threshold, <0.05 . R_1 has the second lowest p-value. R_1 is the impedance expected at the 10^3Hz till 10^5Hz frequencies, so the flattened part of the impedance. At higher frequencies, the impedance is not dependent on the electrode polarization. Furthermore, K and m are parameters describing the polarization model and do not describe the underlying tissue. The other two-pole Cole parameters, θ_1 , R_2 , θ_2 , α_2 and R_∞ do not conform to the set p-value and are not suitable predictors for cancellous and cortical bone.

Table 3.2: P-value parameters two pole Cole model with CPE

	R_1	θ_1	α_1	R_2	θ_2	α_2	R_∞
p	0.0081	0.4481	4.34E-04	0.9936	0.0601	0.7653	0.4104

The boxplots for the two-pole Cole parameters are shown in Figure 3.9. The R_1 decreases when comparing cortical to cancellous bone and α_1 decreases when comparing cortical to cancellous bone

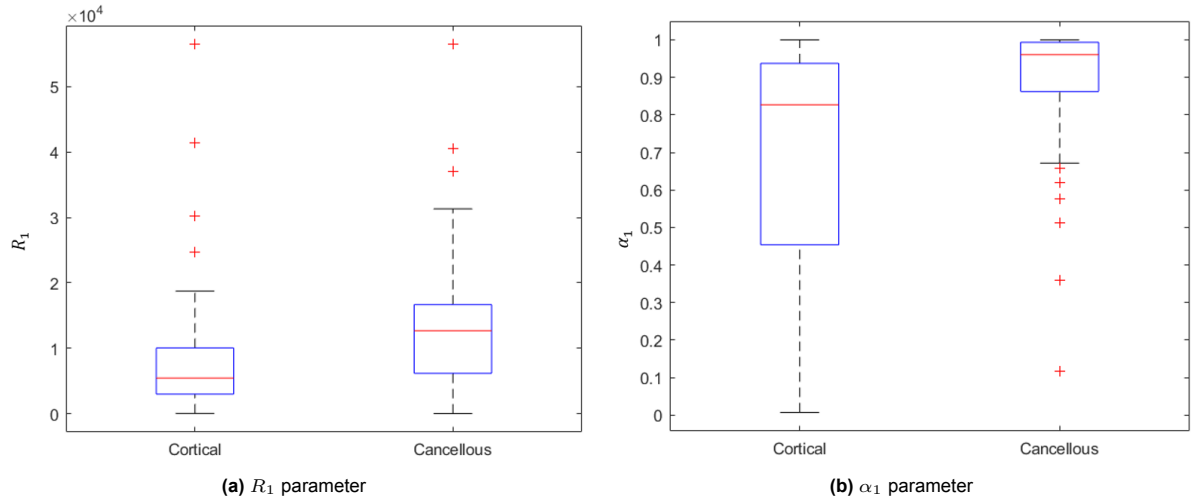


Figure 3.9: Boxplot for the two-pole Cole parameter (a) R_1 parameter (b) α_1 parameter

3.3. Conclusions

What is the basic working principle of the Pediguard with regards to the difference in conductivity of spinal tissue, i.e. cancellous and cortical bone and at what frequency is this measured?

Based on the available literature, it is suggested that the Pediguard operates at a frequency of 5 Hz. However, after comparing the different parameters, including magnitude, phase, real, and imaginary parts of impedance, it was found that the magnitude at 10 Hz was the most effective in differentiating between samples, in line with the research of Li et al. (2018). Nevertheless, other frequencies had better prediction values, indicating that increasing the frequency might lead to better results. However, the low prediction values and high variability observed could be due to electrode polarization. It is important to note that in vivo experiments may yield different results, as bone marrow is highly vascular and contains more blood, which could significantly affect the performance of low-frequency measurements in the extracellular matrix.

Moreover, it was found that the best frequencies to distinguish between cancellous and cortical bones are between 10^3 and 10^5 Hz, as these frequencies have low p-values and no CPE effects. However, high variances were observed across all frequencies, which could be due to the handheld measuring technique used, causing excessive noise. Additionally, bone tissue is highly anisotropic and heterogeneous, and different locations could result in different measurements. Furthermore, it is difficult to measure specific tissue exclusively, as "pure" cortical bone is thin, and it cannot be guaranteed that no other tissues are being measured simultaneously.

Can the impedance of spinal tissue, i.e. cancellous and cortical bone, be modelled and what are the discriminative factors?

An attempt was made to describe bone tissue using a parametric model, a two-pole Cole model with CPE. This model showed that CPE has a significant influence on frequencies below 50 kHz, while the Cole terms influence higher frequencies. The parameters obtained from this fitting could be used for a discriminatory evaluation. However, only the parameter R_∞ showed potential as a discriminatory factor. The high mean squared error resulting from the fit suggests that the modelling approach used in this thesis is insufficient to describe bone tissue accurately. Signal-frequency analysis showed lower p-values for each frequency, indicating that a single-frequency approach would be suitable for this application.

Development and Analysis of Phantom

This chapter aims to develop a tissue-mimicking phantom with approximately the same optical and dielectric properties as vertebrae, i.e. cancellous and cortical bone. By using this phantom a controlled environment can be simulated in which both the electrical impedance spectroscopy and diffuse reflective spectroscopy can be tested. Mostly the focus will lie on the concentration of additives to manipulate the dielectric properties, as for the optical properties a phantom was previously developed [37, 7]. Hence answering the question:

Can we develop a phantom mimicking the dielectric values of spinal tissue, i.e. cancellous and cortical tissue, in the frequency range of 10^3 Hz to 10^5 Hz?

4.1. Method

The objective is to modify a currently used optical phantom to also include dielectric properties. The focus will lie on the effect of dielectric additives and finding a good fit for the dielectric properties.

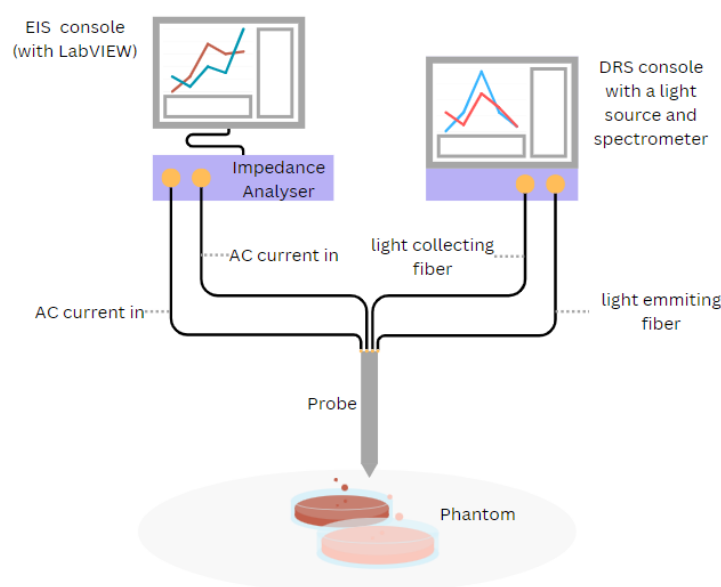


Figure 4.1: Impedance measurement setup for phantom tissue

4.1.1. Measurement setup

As can be seen in Figure 4.1, two separate systems are used to take EIS and DRS measurements. All electrical measurements are performed using a Hewlett Packard 4192A LF HP impedance analyzer

connected to a laptop. The impedance analyzer can measure either absolute impedance and phase angle or capacitance and conductance. We use NI LabVIEW 2018 (LabVIEW) to read the data provided by the analyzer. Within LabVIEW, we can specify the frequency range and the number of steps. For this study, we conduct measurements on the absolute impedance and phase angle with a frequency range of 10 Hz to 1 MHz in 101 steps covering the α and β dispersion.

Optical imaging measurements are performed using a DRS console. The light-emitting fiber is connected to a tungsten halogen broadband light source with an integrated shutter, while the light-collecting fiber is connected to a VIS spectrometer (Andor Technology, DU420ABRDD) and a NIR spectrometer (Andor Technology, DU492A-1.7) featuring an InGaAs detector. The spectrometer captures light across 255 distinct wavelengths, ranging from 839.65 nm to 1624.27 nm. To carry out these measurements, we use a custom software named FlexPn developed in-house at Philips using LabView. The measurements generate intensity spectra with a wavelength range from 400 nm to 1400 nm containing both visual and near-infrared.

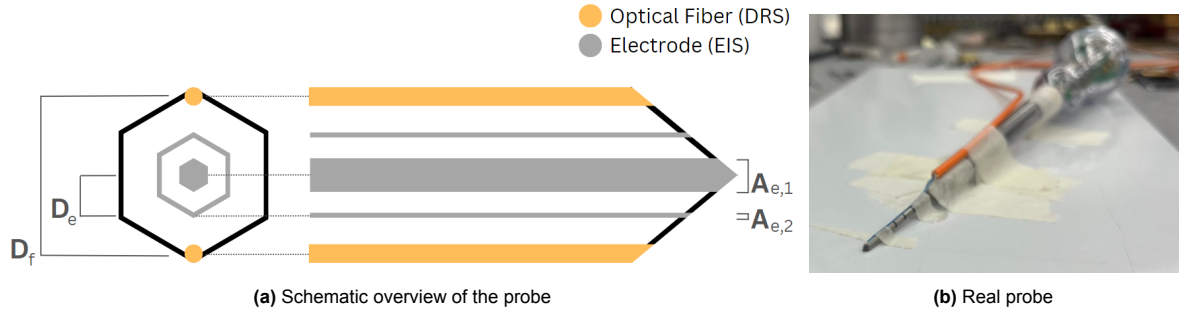


Figure 4.2: Modified PediGuard Probe combining DRS and EIS

Measurements are taken using a modified PediGuard probe, which is illustrated in Figure 4.2. The probe is a modified PediGuard device. The alteration included adding two optical fibers (step-index multimode fiber optic patch cables, core diameter 200 μm , NA = 0.22, low OH, Thorlabs Inc., Newton, NJ, USA) on the sides of the probe positioned at a distance of $D_f = 1.7\text{mm}$. The PediGuard probe uses a coaxial bipolar probe, with respective contact areas of $A_{e,1} = 10\text{mm}^2$ and $A_{e,2} = 4\text{mm}^2$. The distance between the electrodes is $D_e = 1\text{mm}$, as cited by US7580743B2 [14].

4.1.2. Phantom mixture

The tissue-mimicking phantom for either cortical or cancellous bone was fabricated following the production process described by Amiri et al. [7] and Losch et al. [37]. Adjustments to these mixtures were made to add electric additives to mimic the dielectric properties of vertebrae tissue. Amiri et al. [7] stated the concentration NaCl could be used in the phantom ingredient list to adjust the dielectric properties without influencing the optical properties. Luik [38] found that adding NaCl could influence the conductivity and permittivity of phantom tissue. Therefore, the electric additive, NaCl, was used to mimic the dielectric properties of bone. Different concentrations of NaCl were added to the optical mixture for cancellous and cortical bone. Table 4.1 shows the different concentrations of NaCl added to the mixture.

Table 4.1: NaCl concentration added to the vertebrae phantom, i.e. cancellous and cortical bone

Concentration [g/dl _{H₂O}]						
NaCl	0	0.4	0.8	1.2	1.6	

For the optical phantom described by Amiri et al. [7] and Losch et al. [37] ingredients such as Lard, demineralized water, barium sulfate, gelatin, sodium benzoate, and NaCl were used to mimic optical properties. Lard represented fat concentration, barium sulfate served as a scattering agent, gelatin functioned as an emulsifier and gelling agent, and sodium benzoate was added as a preservative [7]. Based on the literature the ingredients shown in Table 4.2 were chosen to mimic to optical properties of vertebrae tissue, i.e. cancellous and cortical bone.

Table 4.2: Ingredient list for the optical phantom of vertebrae tissue, i.e. cancellous and cortical bone, based on 100ml of phantom

	Lard [ml]	Water [ml]	Sodium benzoate [g]	Barium sulfate [g]	Gelatin [g]
Cortical	0	100	0.1	3	15
Cancellous	34	66	0.066	0	9.9

The overview of the phantom preparation is shown in Figure 4.3. First, the NaCl, sodium benzoate and barium sulfate are added to distilled water. The water mixture is heated to 50°C and stirred continuously. At 50°C , gelatin is added and the rpm of the stirrer is increased. AT 70°C the mixture is taken from the heat and the lard is added in one go. The beaker is immersed in cold water and stirred until a temperature between $40^{\circ}\text{C} - 50^{\circ}\text{C}$ is reached. Then the mixture is placed in a mixer and stirred. The lard is blended into the mixture with a mixer. After this step, it is crucial to remove the bubbles as these can alter the measurements. The mixture was poured into a mold and stored in the freezer for one hour. Afterwards, the phantom can be kept in the fridge for approximately two weeks. However, testing is recommended the next day as the phantom dehydrates over time which can influence both the EIS and DRS measurements. Figure 4.4 shows the real setup for producing a phantom and a layered developed phantom.

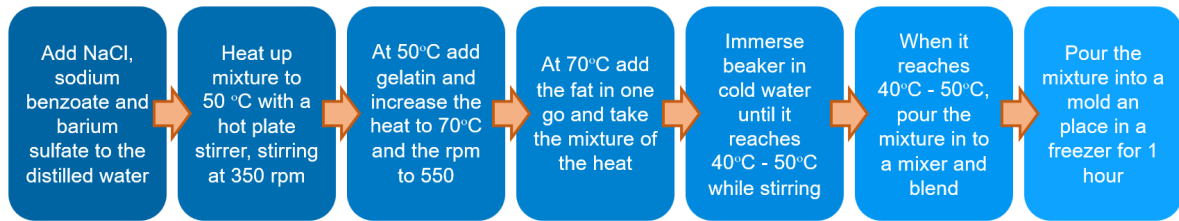


Figure 4.3: Phantom production overview



Figure 4.4: Phantom production setup and phantom example

4.1.3. Measurement Protocol

Measurements were taken the day after the production of the phantom. The phantom was kept cool but not frozen until it arrived at the laboratory. Both steps will limit the dehydration of the tissue. The phantom was then left to rest for about 30 minutes to guarantee room temperature before the experiments.

The impedance analyzer was initiated in advance, enabling a minimum warm-up period of 30 minutes to minimize noise during the process. The probe was cleaned using 96% alcohol and distilled water. To verify the EIS system's operability, a test measurement was conducted by holding the probe still and measuring the impedance of the surrounding air. If no anomalies were detected, EIS measurements could be taken. Subsequently, the calibration for DRS measurements was initiated. The system was calibrated using a Spectralon white reference standard, and an intensity calibration spectrum was acquired to compensate for any wavelength-dependent sensitivities in the setup. The calibration was tested by measuring the intensity factor of a human finger. If no anomalies were detected, DRS measurements could be taken.

The probe was secured by a laboratory stage and manually inserted into the phantom. For both EIS and DRS, three spectra were recorded and averaged at each location. The experiment was replicated three times at different points within each phantom. Between each relocation, both between phantoms and within phantoms, the probe was cleaned with 96% alcohol and distilled water to ensure no residual phantom material remained.

4.1.4. Data Analysis

For the impedance measurements, the measured spectra are compared with the spectra of cancellous and cortical bone. The Mean Squared Error (MSE), see Equation 4.1.4, was chosen as a metric to quantify the similarity between the impedance of vertebrae, i.e. cancellous and cortical bone, and the impedance of phantom.

$$MSE = \sum (Z_{im,cancellous}(w) - Z_{im,phantom}(w))^2 + \sum (Z_{re,cancellous}(w) - Z_{re,phantom}(w))^2 \quad (4.1)$$

The MSE can be calculated over the entire frequency range or a specific frequency. First, the spectrum from $10^3 Hz$ till 10^5 is analyzed. Second, the highlighted frequencies, $10^3 Hz$, found in chapter 3 were used as guiding frequencies. As these frequencies have the highest predictive value, these frequencies will be taken as a classifier between cancellous and cortical bone.

4.2. Results

We measured the susceptance and conductance of the impedance for vertebrae, i.e. cancellous and cortical bone covering the frequency range of $10^3 Hz$ till $10^5 Hz$. Figure 4.5 shows the results for the cortical bone phantom. The graphs show the permittivity or conductivity over the set frequency span. The different plots are the different NaCl concentrations used in the fabrication process of the phantom. For both the permittivity and conductivity it can be seen that an increase in NaCl concentration leads to an increase in permittivity and conductivity. The 1.6 *NaCl* concentration however is an outlier not conforming to the expected pattern. Furthermore, when comparing the found spectra to the IT'is Foundation data [24] and to the data found in chapter 3, the phantom data does not follow the same relationship as bone tissue. The phantom tissue exhibits a more rapid decrease in permittivity and a more rapid increase in conductivity. It can be seen that probably a concentration of 0 *NaCl* fits the data the best, a lower concentration is not possible. Thus a further decrease in permittivity and conductivity should come from other electric additives.

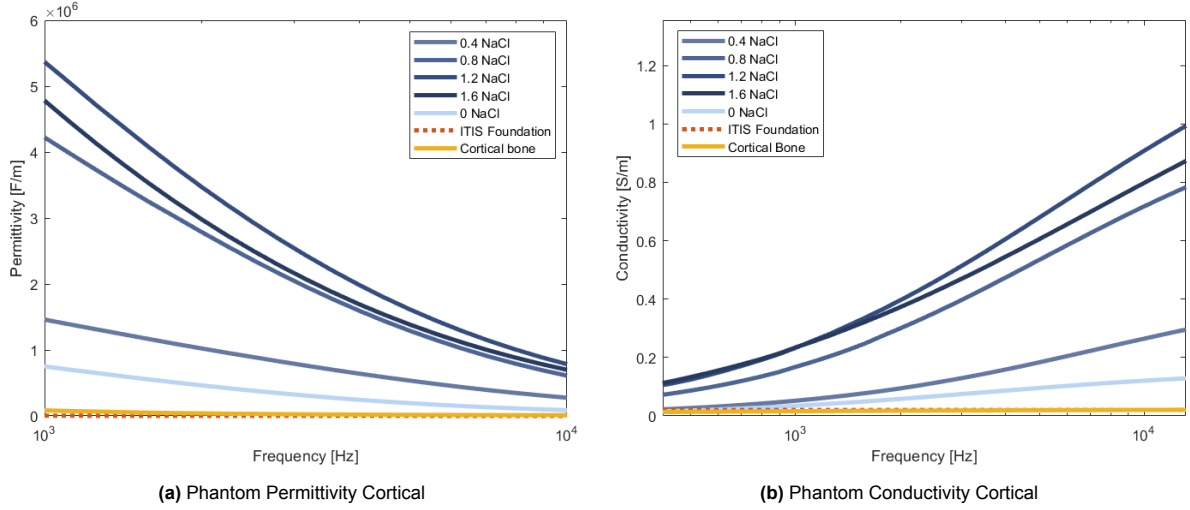


Figure 4.5: Phantom Cortical bone

Figure 4.6 shows the results for the cancellous bone phantom. These graphs also show the permittivity or conductivity over the set frequency span and the different lines represent the different $NaCl$ concentrations. For both the permittivity and conductivity, as with the cortical phantom, it can be seen that an increase in $NaCl$ concentration leads to an increase in permittivity and conductivity. Again the 1.6 $NaCl$ concentration however is an outlier not conforming to the expected pattern. Furthermore, when comparing the found spectra to the IT's Foundation data [24] and to the data found in chapter 3, the phantom data does not follow the same relationship as bone tissue. The phantom tissue exhibits a more rapid decrease in permittivity and a more rapid increase in conductivity. For the cancellous phantom, it is more difficult to determine the best fit, and thus the MSE will be used to determine the best $NaCl$ concentration.

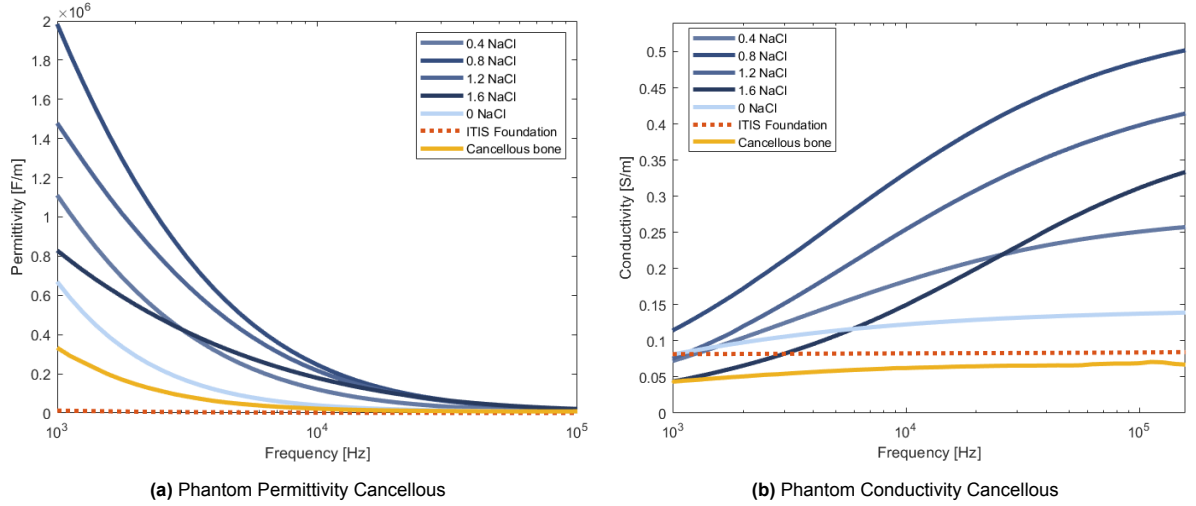


Figure 4.6: Phantom Cancellous bone

The MSE is used to determine the similarity between phantom and vertebrae, i.e. cancellous and cortical bone. The MSE is performed for the entire spectrum and the frequency $10^3 Hz$, see Table 4.3. It was found that a concentration of 0 $NaCl$ would be a good fit for the cortical bone. While a concentration of 1.6 $NaCl$ would suit cancellous bone. Not resulting in the correct spectra, but having correct ratios at $10^3 Hz$.

Table 4.3: Fitting phantom with cancellous and cortical bone and their corresponding MSE

		<i>Cortical</i>				
<i>NaCl Concentration</i>	0	0.4	0.8	1.2	1.6	
MSE_spectra	7.13E+26	1.30E+28	6.22E+30	3.05E+31	3.20E+31	
MSE_1000Hz	1.98E+23	3.59E+24	2.94E+26	7.80E+26	4.87E+26	

		<i>Cancellous</i>				
<i>NaCl Concentration</i>	0	0.4	0.8	1.2	1.6	
MSE_spectra	8.95E+28	2.56E+27	3.07E+29	8.51E+27	2.27E+26	
MSE_1000Hz	1.29E+22	3.66E+23	7.43E+24	1.72E+24	6.06E+22	

4.3. Conclusion

Can we develop a phantom mimicking the dielectric values of spinal tissue, i.e. cancellous and cortical tissue, in the frequency range of 10^3 Hz till 10^5 Hz?

Further research should be performed on developing a phantom with the correct dielectric and electric properties. An attempt was made to find an easy solution. However, this phantom is only sufficient over specific frequencies. A phantom that mimics the entire spectrum is not found and deeper analysis should be done on the influence of dielectric and optical additives on the corresponding impedance or intensity spectrum.

This said, the phantom in specific frequencies gives a sufficient result and shows the expected ratio difference between cortical and cancellous bone. For further analysis of the phantom, these frequencies will be used. Also, assumptions can still be made on the ability for breach detecting even though the spectra do not represent cancellous or cortical tissue as it clearly shows a contrast in impedance measurement and this contrast should also be measured.

Part II

Final Testing

The final testing phase focuses on the comparison between diffuse reflective spectroscopy and electrical impedance spectroscopy. The aim is to assess their usability during spinal surgery by analyzing their performance across various evaluation criteria. Phantom is used to create a controlled environment with spatial awareness.

5

Method

This chapter discusses the methods used to address the research questions presented in chapter 1. The discussion will cover the measurement method, measurement protocol, and data analysis techniques. We will be comparing the Electrical Impedance Model (EIS) model, with the emerging technique, Diffuse Reflective Spectroscopy (DRS). We will be simulating spinal fusion surgery using phantom tissue to compare the performance. Please refer to Figure 5.1 for the experimental setup.

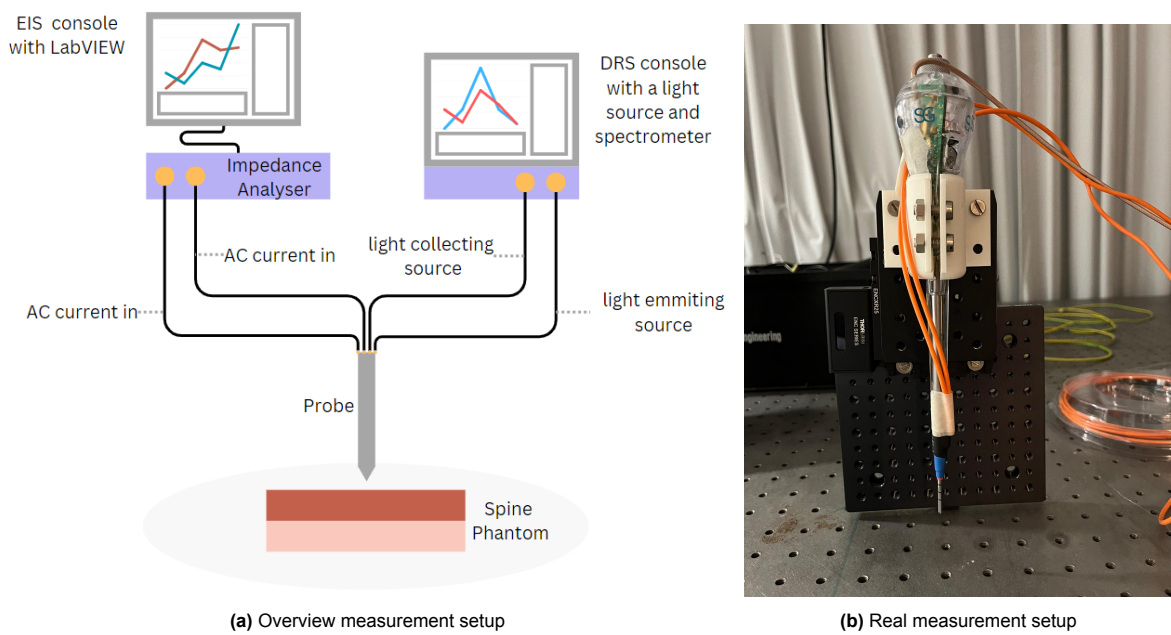


Figure 5.1: Measurement setup for comparing EIS with DRS

5.1. Measurement Method

As can be seen in Figure 5.1, two separate systems are used to take EIS and DRS measurements. The measurement method used in section 4.1 is also employed for the final experiments, the setup will be repeated for the readers who missed the preliminary research. All electrical measurements are performed using a Hewlett Packard 4192A LF HP impedance analyzer connected to a laptop. The impedance analyzer can measure either absolute impedance and phase angle or capacitance and conductance. We use NI LabVIEW 2018 (LabVIEW) to read the data provided by the analyzer. Within LabVIEW, we can specify the frequency range and the number of steps. For this study, we conduct measurements on the absolute impedance and phase angle on a frequency range of 10 Hz to 1 MHz in 101 steps covering the α and β dispersion.

Optical imaging measurements are performed using a DRS console. The light-emitting fiber is connected to a tungsten halogen broadband light source with an integrated shutter, while the light-collecting fiber is connected to a VIS spectrometer (Andor Technology, DU420ABRDD) and a NIR spectrometer (Andor Technology, DU492A-1.7) featuring an InGaAs detector. The spectrometer captures light across 255 distinct wavelengths, ranging from 839.65 nm to 1624.27 nm. To carry out these measurements, we use a custom software named FlexPn developed in-house at Philips using LabView. The measurements generate intensity spectra with a wavelength range from 400 nm to 1400 nm containing both visual and near-infrared.

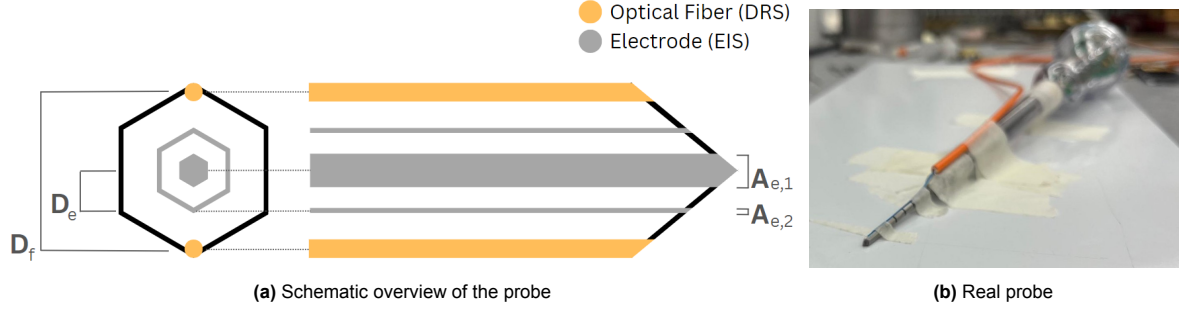


Figure 5.2: Modified PediGuard Probe combining DRS and EIS

Measurements are taken using a modified PediGuard probe, which is illustrated in Figure 5.2. The probe is a modified PediGuard device. The alteration included adding two optical fibers (step-index multimode fiber optic patch cables, core diameter 200 μm , NA = 0.22, low OH, Thorlabs Inc., Newton, NJ, USA) on the sides of the probe positioned at a distance of $D_f = 1.7\text{mm}$. The PediGuard probe uses a coaxial bipolar probe, with respective contact areas of $A_{e,1} = 10\text{mm}^2$ and $A_{e,2} = 4\text{mm}^2$. The distance between the electrodes is $D_e = 1\text{mm}$, as cited by US7580743B2 [14].

5.1.1. Measurement Protocol

The evaluation process involves taking measurements of both electrical impedance and optical intensity in a simulated spinal surgery. To create this simulation, a controlled environment is necessary. For this thesis, phantom tissue made in a mould is used to ensure spatial location at all times. The phantom tissue consists of a double-layer phantom designed to imitate the optical and dielectric properties of bone, see Figure 5.3. This double-layer phantom replicates the conditions leading up to a breach, simulating the interface between cancellous and cortical bone. The phantom has a height of 30mm with both layers being 15mm. The probe is clamped and moved only in the vertical direction to maintain awareness of the distance to the breach. To control the properties of the phantom tissue, it is stored in a fridge for a maximum of one week and cooled until it reaches the laboratory. Then the phantom is left to rest for about 30 minutes at room temperature before the experiments.

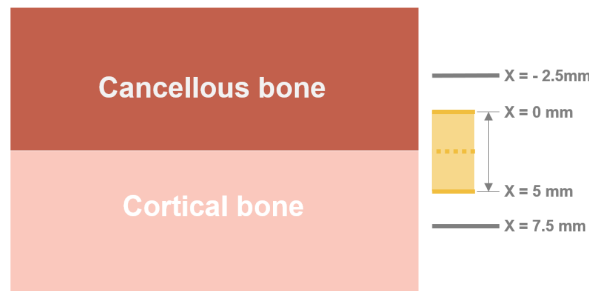


Figure 5.3: Phantom used for mimicking spinal surgery

The process is shown in Figure 5.4. The measurement protocol was validated as shown in Appendix A to ensure that the EIS and DRS measurements would not affect each other. The impedance analyzer was initiated well in advance, enabling a 30-minute warm-up period, similar to the protocol in Part A. During this time, the tissue collected according to the specified protocol reached room temperature. The

probe was carefully cleaned using 96% alcohol and distilled water. Subsequently, the calibration for DRS measurements was initiated. The system was calibrated using a Spectralon white reference standard, and an intensity calibration spectrum was acquired to compensate for any wavelength-dependent sensitivities in the setup. To verify the system's operability concerning EIS, a test measurement was conducted by holding the probe still and measuring the impedance of the surrounding air. If no anomalies were detected, official measurements could be taken. The probe was mounted onto a manual 25mm linear translation stage and slowly guided to the interface with steps of 0.25mm. Impedance, magnitude and phase were measured across a frequency range from 10 Hz to 1 MHz in 101 steps, and light intensity was measured from 400 nm to 1400 nm.

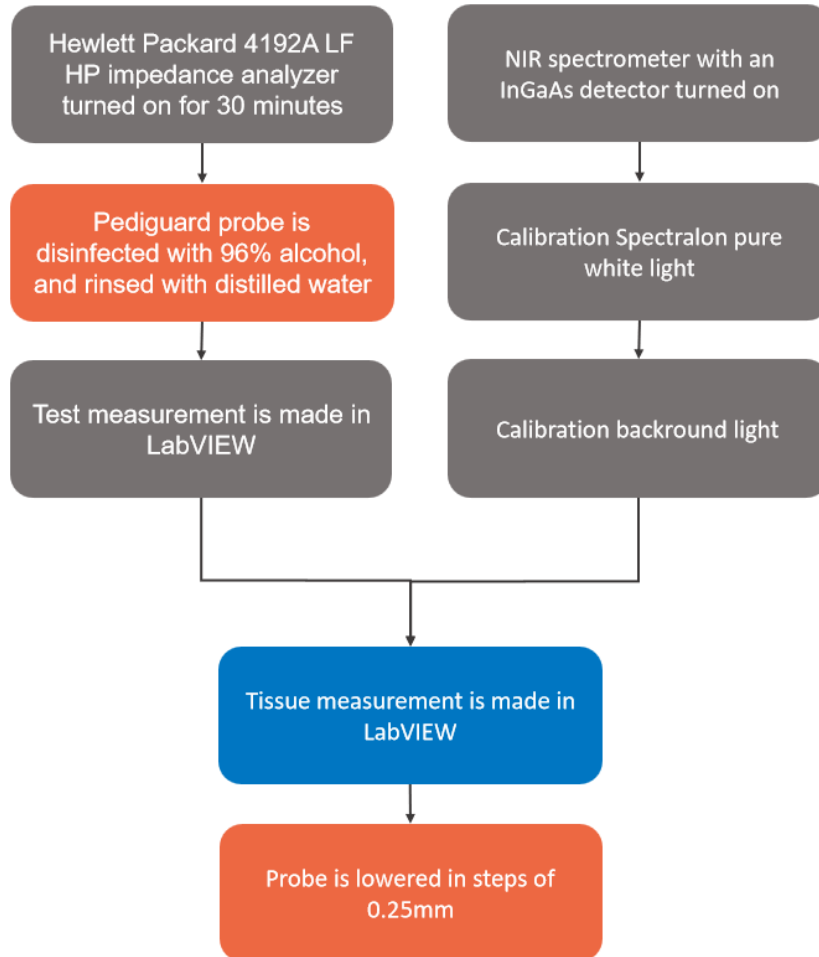


Figure 5.4: Measurement Protocol

5.2. Data Analysis

Diffuse reflection Spectroscopy

For diffuse reflection spectroscopy, processing is done by averaging and through a third-order Savitzky-Golay filter (frame length of 11) to reduce noise. These averaged spectra are plotted against the depth. The discriminatory value found for DRS is the fat absorption peak found at 1210nm. Swamy [58] has found that this fat fraction peak is a good predictor of cancellous and cortical bone. Fat has a high absorption peak at 1210nm and some small peaks at around 900nm and 1400nm. Therefore this study mostly focuses on the light intensity around 1210nm. The intensity at 1210 is then plotted against the depth of the probe.

Electrical Impedance spectroscopy

For electrical impedance spectroscopy, processing is done by averaging the three measurements to reduce noise. These averaged spectra are plotted against the depth. The discriminatory value found for EIS is the magnitude at frequency 10^3 . Signal-frequency analysis performed in chapter 3 shows that the magnitude at this frequency has a high discriminatory value. The magnitude at 10^3 will be plotted against the depth of the probe.

Evaluation Criteria

Further analysis will be the comparison of multiple evaluation criteria. The sensing technique should be able to differentiate between cancellous and cortical bone and should be able to anticipate breach. Therefore the following evaluation criteria are determined.

1. Look-ahead distance

Look-ahead distance is defined as the distance at which breach detection can be anticipated, so the distance at which the signal starts to change. This parameter is found by fitting the Intensity of Magnitude to a sigmoidal function, see below, with the Matlab `fminsearch` method. The resulting parameters will give us insight into the slope and distance giving a good estimation of the look-ahead distance

$$Gompertz = d + (a - d)e^{-e^{-b(x-c)}} \quad (5.1)$$

The sigmoidal is a Gompertz curve in which a stands for the asymptote, b sets the displacement along the x-axis, c is the growth rate and d is the offset from zero. So c and b are important parameters.

2. Capability of tissue detection

Capability of tissue detection is defined as the ratio of measured signal for cancellous and cortical bone. The difference between the signal for both cancellous and cortical bone should be high enough to register. The ratio between the signal at -2.5 mm will be compared to the signal at 7.5 mm assuming that at these locations there is either only cortical bone or cancellous bone.

$$Capability\ of\ tissue\ detection = \frac{Signal_{cancellous}}{Signal_{cancellous}} \quad (5.2)$$

This ratio is compared to the overall variance seen in either technique, to give a better understanding of the detecting potential.

3. Capability of breach detection

Capability of breach detection is defined as the ratio between the measured signal at the cancellous bone and the interface. Again, the difference between the signal for both cancellous bone and the interface should be high enough to register. Also, the surgeon wants to be sure that breach detection is registered. It is computed as the ratio between the signal at -2.5 mm and 2.5 mm. Just as the capability of tissue detection, it is highly dependent on the variances seen in the total system.

$$Capability\ of\ breach\ detection = \frac{Signal_{cancellous}}{Signal_{interface}} \quad (5.3)$$

Measurements and Results

In this chapter, the measurements are discussed for the impedance and absorption data at different depths in the phantom. First, both sensing techniques will be discussed separately, giving a first trend analysis of both techniques. After that, both spectra are analysed against the three evaluation criteria discussed in chapter 5. These evaluation criteria are set to quantify the performance of the sensing technique. By doing so, an answer is given to the research question:

What is the comparative performance between diffuse reflective spectroscopy and electrical impedance in detecting a breach between cancellous and cortical bone in spinal fusion surgery?

6.1. Electrical Impedance Spectroscopy

For the impedance, measurements were taken on the magnitude and phase of the tissue. The current section will use exemplary graphs to show trends seen in the data. The graph demonstrating the five different measurement spots shows similar trends and can be found in Appendix F. Figure 6.1 shows the magnitude of the entire frequency spectra per depth. Every line in the graph represents a specific depth. It can be seen that the data is clustered in two groups. The first group is the data measured before the tissue interface and the second group is the data measured when the interface is passed. The spectrum measured at 2.5mm shows a slight difference from that which passed the 2.5mm interface. This suggests a short transition and an immediate switch between signals at the interface.

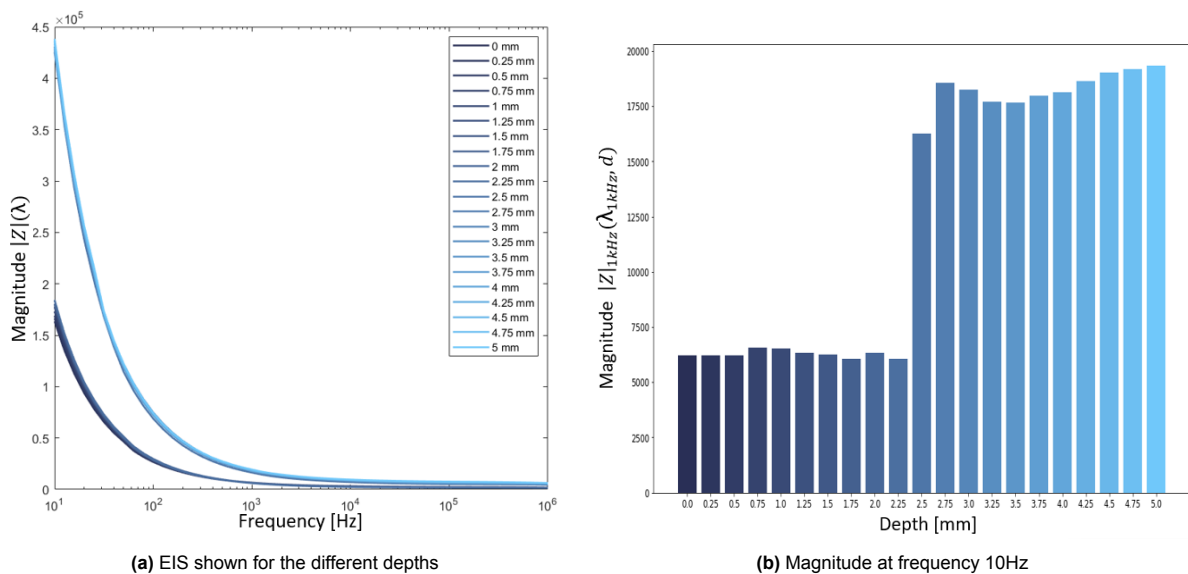


Figure 6.1: Magnitude of the impedance at different depths in the phantom

As discussed in chapter 5 the magnitude at 10^3 is taken as the classification feature between cancellous and cortical tissue. Figure 6.1 shows the magnitude of the impedance at 10^3 at different depths. The trend seen in the entire spectrum is confirmed, the graph seems to be a step function having an immediate switch signal at the interface. A difference is seen between cancellous and cortical bone but this difference is registered exactly at the interface $x = 2.5\text{mm}$. There is no transition seen in the magnitude suggesting a short look ahead distance. The difference in magnitude between 0mm and 5mm is substantially large suggesting effective classification methods. As the signal is a step function the difference in signal at the breach is similar to the difference between both tissues, so at $x = 2.5\text{mm}$ the interface should be detectable.

6.2. Diffuse Reflection Spectroscopy

For the impedance, measurements were taken on the magnitude and phase of the tissue. The current section will use exemplary graphs to show trends seen in the data. The graph at the five different measurement spots shows similar trends and can be found in Appendix G. Figure 6.2a shows the intensity of the received signal for all wavelengths. The different lines represent the different depths at which is measured. It can be seen that the peak at 1210nm gradually decreases when the depth increases, showing a lower intensity in cancellous bone than cortical bone. Just as for the impedance measurements, two clusters can be seen in the data. However, multiple measurements are found in between these clusters, showing a gradual change from one to another cluster. This would suggest a transition period.

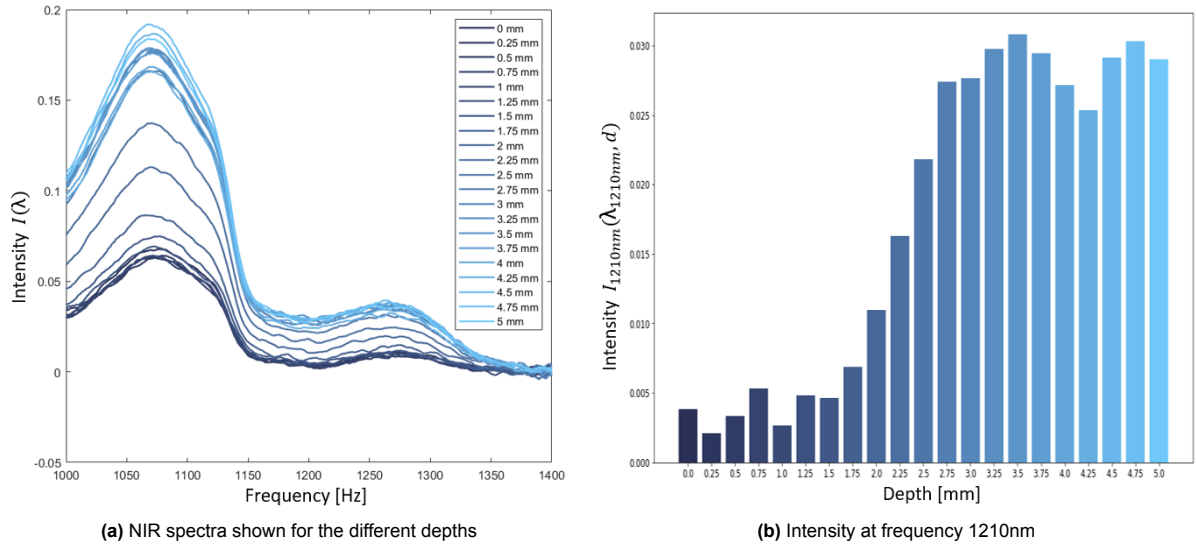


Figure 6.2: Intensity results at different depths in the phantom

Figure 6.2b shows the intensity at 1210nm for different depths. A gradual change can be seen between the intensity at 0mm and the interface at 2.5mm. The transition resembles an exponential function, where the intensity increase becomes higher when the interface is approaching. This increase is first seen at approximately 1.5mm and this increase flattens at 2.75mm. The interface can be found at 2.5mm. This suggests that diffuse reflection spectroscopy has a transition zone and thus a look-ahead distance. This look-ahead distance resembles an exponential function where the change increases when the interface is approached. Both graphs also show a substantial difference between cancellous and cortical tissue when comparing the intensity at 0mm to the intensity at 5mm. At 2.5mm, the intensity does not completely resemble the intensity found for cortical tissue. However, the difference is still significantly large.

6.3. Evaluation Criteria

Evaluation criteria were set to compare the two sensing techniques. These criteria are the look-ahead distance, the capability of breach detection and the capability of tissue detection.

6.3.1. Look-ahead distance

The look-ahead distance is measured by fitting the graph to a Goepertz function. A Goepertz function returns the parameters, a and b , that express the asymptote and displacement of an S curve respectively. The value of the parameters for an ideal function is a high b , as a high displacement on the x-axis shows a longer transition zone, and as high a , as a high asymptote suggests a high difference in value from point 1 to 2. The bar graph of the impedance magnitude at $10^3 Hz$ and the intensity at 1210nm were fitted to a Goepertz function, resulting in the following values Table 6.1

Table 6.1: Fitting results

	c	variation	b	variation
<i>DRS</i>	0.02911	(0.02786, 0.03035)	2.939	(1.989, 3889)
<i>EIS</i>	NaN		NaN	

As can be seen, there is no fit found for the EIS spectra. A step function has a too-hard transition and thus cannot be represented by a Goepertz function. The values of the DRS spectra suggest a transition zone of approximately 3mm. With c , the slope is approximately 0.03mm, showing a relatively long transition zone with a small growth rate.

6.3.2. Capability of tissue detection and breach detection

The capability of tissue detection and breach detection is determined by comparing the ratio in signal between either cancellous and cortical tissue or cancellous tissue and the signal found at the interface. The higher this ratio, the bigger the difference in signal found between the two points. A bigger difference would suggest a higher capability of discrimination. This ratio is however also compared with the variability found in data, as a high variability needs a high ratio and threshold value to guarantee high success rates with a lower variability could be sufficient for lower ratios. Table 6.2 shows the capability ratio for tissue detection and breach detection respectively. The variance is normalized to the mean data to ensure a comparison between the two variances.

Table 6.2: Ratio capability of breach and tissue detection

	Capability of tissue detection	Capability of breach detection	Normalized variance
<i>DRS</i>	10.6	8.6	(0.843, 1.256)
<i>EIS</i>	2.36	2.13	(0.941, 1.181)

It can be seen that the signal is sufficiently different for both EIS and DRS measurements and is mainly dependent on the resolution and noise of the measurement with EIS having relatively low noise. Furthermore, it can also be seen that DRS has a lower prediction score in terms of breach detection. This measurement is not completely fair as the working principle of both principles is not on the same location of the probe. The optical sensors will experience a delay in results as they are mounted on the backside of the needle. When shifting a bit further in the graph it can be seen that DRS also has high capabilities in breach detection.

Discussion

7.1. Highlighted results and limitations

7.1.1. Preliminary testing

Comparison of vertebrae tissue

A significant difference is found in the impedance measurements between cancellous and cortical tissue. At low frequencies, a higher increase in impedance is seen when comparing cortical bone with cancellous bone. The low-frequency region is predominately affected by electrode polarization. After 50 kHz the electrode polarization does not affect the data. This contribution will then overlap the tissue impedance. Low frequencies are thus not suitable for classification features due to the high variability of electrode polarization.

Cancellous bone is expected to have a higher conductivity at low frequencies as the web-like structure of bone increases the space for extracellular fluids. At higher frequencies, cortical bone impedance is still higher than cancellous bone. After 50 kHz the cortical bone shows a decrease in real impedance, suggesting a dispersion area. This dispersion area is also seen in cancellous data, yet it is less pronounced. Wyss Balmer et al. [68] suggested that bone could be modelled as an ideal resistor with a CPE model, however, an ideal resistor does not display a dispersion area. These dispersion areas were also supported by literature [24]. The decrease in impedance could support the flattened curvature of the displacement area. The cause of this flattening is, however, still speculative. The flattening could be caused by macroscopic pathologies of cancellous and cortical tissue. Also, it could be caused by lower tissue hydration, which is an expected difference between cancellous and cortical bone.

Literature supports the findings that cortical bone has a higher impedance than cancellous bone [17, 19, 36, 68]. Almost all current literature measures bone tissue in the kHz frequency range and uses a single-frequency feature as a classifier. None of the papers discuss the reasoning behind the increase in impedance measurements and the dispersion areas seen in the measurements.

High variance is seen across all impedance measurements. Multiple factors could influence this variance. First of all, the measurement technique can influence the data quality. Mulder [44] has found that the freehand technique used in this thesis may introduce noise and inconsistency in the recorded signals. One of the limitations found for EIS is that the sensing technique needs sufficient force contact on the tissue to record meaningful measurements [20, 53]. A freehand technique cannot maintain stable force contact and thus variance can be found using a freehand technique. Another technique where constant force can be guaranteed would be preferred, however, due to the morphology, structure and hard tissue contact of bone this becomes a complex task. A holder or device to ensure stable force contact will limit the mobility of the device, however not all desired points can be measured. Additionally, currently during surgery, a freehand technique is used with possible additional enhancement, therefore, this variability would also be seen during surgery.

Furthermore, bone is a highly anisotropic and heterogeneous material. Factors such as differences in bone density, composition, and micro-architecture among specimens may contribute to this variability. The impedance measurements found per spot are expected to be different and have a high variance [2]. A large dataset is needed to ensure an accurate model. Also, high predictive values are needed

to ensure that tissue can be differentiated with limited overlap. This thesis measured 15 spots for one pig spine. A larger data set would be desirable to ensure a sufficient average.

Moreover, measuring tissue has its limitations. Surrounding tissues, such as muscle or adipose tissue, could influence impedance measurements, leading to inaccuracies in tissue characterization. It is challenging to ensure a homogenous tissue sample to accurately measure the impedance for cancellous and cortical bone [3]. With measuring real tissue, placing probes on tissue boundaries can lead to unbalanced and inaccurate measurements [10]. The spine tissue consists of trabecular bone, which is a web-like structure encapsulated with a relatively thin layer of cortical bone. There are also multiple other tissues surrounding the cortical bone, making it complicated to ensure that measurements only register one tissue.

Discriminatory parameters & parametric model vertebrae

We used both single-frequency and multi-frequency analysis to classify the bone tissue. Our results show that there are significant differences in parameter values among various bone tissues, regardless of whether the single-frequency or multi-frequency analysis was used. This suggests that bone tissue impedance exhibits distinctive characteristics across a wide frequency range, which can be used to differentiate it within the frequency spectrum ranging from 10 to 10^6 Hz.

Especially single-frequency analysis shows high predictive values for the magnitude, phase, real and imaginary impedance, with imaginary impedance and magnitude being the best parameter. In literature, it was found that the classification of bone tissue is often done by single-frequency analysis at a low frequency [17, 19, 36, 68]. Although this thesis shows high discriminatory values for low frequencies, 10Hz, it is also seen that electrode polarization highly influences the impedance measurements at low-frequency increasing the variability and noise on the measurement. Low-frequency analysis is therefore not desirable unless the electrode polarization is well known. The PediGuard is also suggested to use low-frequency analysis [36, 14]. Li et al. [36] uses magnitude at 5Hz as a classifier for cancellous and cortical bone, this is comparable to the working principle stated in the patent of PediGuard [14]. This study would suggest using a higher frequency independent or almost independent of electrode polarization. This study therefore used kHz as a classifier feature, as it shows low p-values and low influence of electrode polarization.

For multi-frequency analysis, discriminatory values can be found in the parameter of R_∞ . However, the data suggests that the current modelling method does not accurately resemble it, as evidenced by the high Mean Squared Error (MSE) values. The complex nature of bone tissue, primarily consisting of an extracellular matrix and bone matrix rather than cellular components, presents challenges in selecting an appropriate impedance model. While the Cole model has been commonly utilized for biological tissue, its applicability to bone tissue remains uncertain. Only two papers were found where a model was used to describe bone tissue. Wyss Balmer et al. [68] and Gabriel, Gabriel, and Corthout [24] respectively use CPE and a resistor or four-pole Cole-Cole model to describe bone tissue. As can be seen by the dispersion found in the data, a CPE with a resistor model is not suitable. A four-pole Cole-Cole model is too extensive for our frequency range, as shown in Appendix B. The unique structural and compositional properties of bone may necessitate the exploration of alternative models that better capture its distinct impedance characteristics. A more extensive data set with more in-depth analysis would contribute to a more precise model of bone. However, the question can also be asked if a more precise model is needed since single-frequency analysis shows high predictive values. Also, a handheld device should ideally have a single-frequency analysis, as it ensures quick and accurate sensing.

Phantom Design

Our research revealed flaws in the design of phantoms used for impedance measurement. The study found that the phantoms developed were not suitable for the full frequency range specified, which limited their usefulness to only a few frequencies within the set range. This emphasizes the limited knowledge of phantom design and additives to ensure complete coverage across the desired frequency range. Phantoms that cover the characteristic over the entire frequency range will enhance the reliability and applicability of impedance measurements. Increasing the accuracy of the phantom will also ensure more realistic results for the single-frequency analysis.

To improve the performance of phantoms, it is necessary to conduct extensive research on the effects of additives on their dielectric and optical properties. It is important to consider the interplay between these two types of additives. Currently, phantoms are manufactured for either dielectric or optical

properties, but not both. Our research highlights the complexity of this relationship and emphasizes the need for further investigation into the effects of additives on phantom performance. To achieve optimal phantom design, it is important to have a deep understanding of how different additives interact with the phantom and how they affect impedance measurements across different frequencies.

7.1.2. Final Test

Electrical Impedance measurements

Through our research, we have discovered that it is possible to distinguish between different types of tissues using impedance measurements. When we visualize the impedance magnitude against the depth at which the measurements were taken, we can differentiate between cancellous and cortical bone, and detect gaps between them. However, the function appears as a step function, the signal changes immediately at the interface indicating that the surgeon had no look-ahead distance. EIS as a sensing technique is susceptible to perturbations and disturbances as it only registers what is right in front of it. This deficiency could potentially impact the system's ability to monitor real-time changes in dynamic surgical environments.

Literature has also suggested this trend [17]. Most literature compares the impedance magnitude versus time. At specific moments in time, the probe transverses from one layer to another. The magnitude either has no transition zone or a short transition zone, suggesting that impedance measurements can only accurately measure tissue when it is in direct contact with that tissue. This is also supported by one of the biggest limitations of EIS, the influence of force contact on the impedance measurements [20, 53]. The PediGuard website, however, does claim that PediGuard shows a transition zone when approaching the cortical zone [55]. This transition zone found in the PediGuard data could be a result of the increase of pure bone in vertebrae when approaching the cortical bone. Therefore, the PediGuard device has no look-ahead distance, however, the morphology of bone makes the transition zone detectable. This hypothesis is not tested with tissue data and more testing is required to support this hypothesis.

These findings support previous findings on the usability of the Pediguard system. The Pediguard system shows high efficiency in everyday spinal fusion surgeries, where no complications are encountered. However, when the surgery becomes complicated, surgeons find the Pediguard system not efficient and not user-friendly [58]. Constant pressure and tissue contact cannot be guaranteed resulting in altered results and feedback, suggesting that the Pediguard system is insufficient in surgeries where feedback and a sensing technique are needed. However, more research should be conducted to support this possible hypothesis.

To summarize our study, although it shows promising abilities in differentiating tissues, there are significant challenges for impedance sensing systems like the Pediguard due to limitations in look-ahead distance and system usability. Overcoming these challenges requires further research and innovation to improve the real-time monitoring capabilities and reliability of impedance sensing in surgical applications.

Diffuse reflection measurements

Our research has demonstrated that the DRS system is effective in distinguishing between different types of tissue. One of the significant findings of our study is the system's ability to predict cortical breach in advance, as shown by the S-curve in chapter 6. This predictive capability is beneficial in surgical procedures, providing surgeons with early warning indicators to prevent potential complications and improve surgical precision.

Our analysis suggests that the DRS system can still detect tissue characteristics even when optimal contact is not achieved. Thereby improving the reliability and usefulness of sensing technologies in clinical settings.

The comparison of dielectric and optical properties

It can be seen that both techniques can discriminate between the two different types of bone. The signal difference for DRS is higher than for EIS. However, the variance found in the measurements of EIS, is lower than for DRS.

Both techniques were also able to detect a cortical breach. For the impedance measurements, when the interface is approached, the measurements resemble the result of cortical bone. The optical measurements show a short delay ($\sim 0.25mm$). Although there is a small delay, the ratio of signal is

still large enough at 2.5mm to detect a breach. This signal delay is, however, not a limitation of the sensing technique but a limitation of the detection device. The impedance measurements were taken at the point of the probe while the optical fibers were installed at the end of the tip. Resulting in a shift in measurements.

The look-ahead distance is only present for DRS. EIS has a step function while DRS has a transition zone. This step function also decreases the usability of the sensing technique. If the sensing technique is highly dependent on the pressure applied and tissue contact at the tip, more disturbances will be found, making the sensing technique more susceptible to surroundings and environmental factors, and limiting the feedback for the surgeon.

Diffuse Reflection Spectroscopy is presumed to be the more robust and more accurate sensing technique for spinal surgery. Even in the current sub-optimal configuration, it could outperform the state-of-the-art, based on phantom experiments.

7.2. Further work

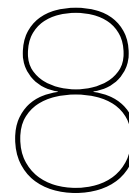
The current study encountered challenges originating from the high variance observed in the dataset. To improve the robustness of our findings, future research could increase the acquisition of data. By increasing the sample size, researchers can potentially capture a more representative range of impedance in the data, thereby enabling more accurate analyses and conclusions.

With this more extensive dataset, a second attempt can be made to model bone tissue. More extensive research should be done on the morphology of bone and how this influences the impedance measurement. With this more comprehensive knowledge of the influence of morphological factors, a more accurate model could be used to decrease the MSE of the model. Furthermore, the more extensive dataset could also increase the model fit which would also decrease the MSE.

The phantom used in the study did not have comparable dielectric properties to bone. Although the phantom was sufficient for this study, adjustments should be made if a more precise analysis is needed when comparing EIS with DRS. The production of the phantom relied on previously utilized methods for optical phantoms to ensure comparability within the research group. However, this dependency limited the options for dielectric additives. Additionally, research on combining electric and optical additives is limited. More research is needed on the combination of both optical and electric additives to ensure the development of a more accurate phantom.

The classification of the tissue is limited by using phantom-specific "zones" that are highlighted and mimicked. Real tissue experiments will expand both techniques to the whole spectrum and could provide different results. Furthermore, real tissue has a gradient which could explain the transition zone found by SpineGuard [55] for the PediGuard. Swamy [58] found that this transition zone influences the measurements found for the optical properties ensuring earlier detection of cortical breach.

To compare diffuse reflection spectroscopy with electrical impedance spectroscopy the probe should also be optimized for the optical measurements. Currently, an easy fix solution has been used to employ DRS on the PediGuard, however, due to the large distance between the fibers and the sharp tip geometry most of the signal is absorbed. Choosing a more optimal design for the DRS measurements could lead to better and more accurate results.



Conclusion

8.1. Part I - Preliminary Testing

What is the basic working principle of the Pediguard with regards to the difference in conductivity of spinal tissue, i.e. cancellous and cortical bone and at what frequency is this measured?

As found in the literature it is suggested that the Pediguard works at a frequency of 5 Hz. Comparing the magnitude, phase, and real and imaginary parts of the impedance, the magnitude at 10Hz was the best discriminatory parameter, which is in line with the research of Li et al. [36]. However, the features have better prediction values at other frequencies, suggesting upping the frequency for better discriminatory values. These low prediction values and high variability are mostly likely caused by electrode polarization. Nonetheless, in vivo experiments could suggest a different outcome. As bone marrow is highly vascular and contains more blood, it could be that the performance for low frequency measured in the extracellular matrix will be highly influenced by the amount of blood. Resulting in better prediction values for lower frequencies, this can however only be taken into account when measured. It is estimated that the decrease in impedance is mostly caused by blood in the α -dispersion.

Furthermore, by analyzing the spectra, it is suggested that the best frequencies to discriminate between cancellous and cortical bone is at around 10^3 to 10^5 . These frequencies show low p-values and no CPE effects. The high variances seen across all frequencies could be also due to the hand-held measuring technique, which causes excessive noise [44]. Also, bone tissue is highly anisotropic and heterogeneous, thus different locations could result in different measurements. Next to this, it is already hard to measure specific tissue exclusively, as "pure" cortical bone is thin and no guarantee can be given that no other tissues are measured at the same time.

Can the impedance of spinal tissue, i.e. cancellous and cortical bone, be modelled and what are the discriminative factors?

An attempt is made to describe bone tissue with a parametric model, the Cole model with CPE. This model shows that CPE highly influences low frequencies below 50 kHz, while the Cole terms influence higher frequencies. This fitting results in parameters to do a discriminatory evaluation on. Only the parameter R_∞ showed the potential to be a discriminatory factor. This, combined with the high MSE resulting from the fit suggests that the modelling approach used in this thesis does not describe bone tissue sufficiently. Signal-frequency analysis shows lower p-values for each frequency, thus a single-frequency approach would be suitable for this application.

Can we develop a phantom mimicking the dielectric values of spinal tissue, i.e. cancellous and cortical tissue, in the frequency range of 10^3 Hz till 10^5 Hz?

Further research should be performed on developing a phantom with the correct dielectric and electric properties. An attempt was made to find an easy solution. However, this phantom is only sufficient over specific frequencies. A phantom that mimics the entire spectrum is not found and deeper analysis should be done on the influence of dielectric and optical additives on the corresponding impedance or intensity spectrum.

This said, the phantom in specific frequencies gives a sufficient result and shows the expected ratio difference between cortical and cancellous bone. For further analysis of the phantom, these frequencies were used. Also, assumptions can still be made on the ability for breach detecting even though

the spectra do not represent cancellous or cortical tissue as it clearly shows a contrast in impedance measurement and this contrast should also be measured.

8.2. Part II - Final Testing

What is the comparative performance between diffuse reflective spectroscopy and electrical impedance in detecting a breach between cancellous and cortical bone in spinal fusion surgery?

This study marks an initial step towards evaluating the usefulness of EIS and DRS in the context of pedicle screw placement. Our findings demonstrate that both methodologies effectively distinguish between the two tissues. Furthermore, distinct graph shapes emerge, with EIS exhibiting a stepper function at the interface and DRS conforming to the expected s-curve pattern. This indicates that DRS possesses the ability to foresee tissue breach, as evidenced by a curve fitting to a sigmoidal model. Consequently, DRS may boost usability, enabling earlier trajectory adjustments and demonstrating greater robustness against perturbations. However, further investigation is needed to determine the effectiveness of both matters. In vivo experiments are suggested to validate these arguments. Additionally, the non-ideal design of the DRS probe needs improvements in for example fiber configuration and tip distance. Nevertheless, in scenarios characterized by less-than-optimal conditions, DRS appears to outperform EIS, positioning itself as the more robust and user-friendly sensing technique.

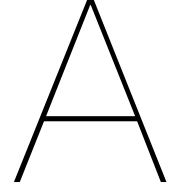
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Conductivity experiments

This appendix discusses the results and main findings of the conductivity experiments. These experiments were performed to gain an understanding of the working principle of PediGuard, to assess the accuracy of the impedance measurements, and to establish the geometry constant of the PediGuard.

A conductivity solution is used to test the PediGuard. A conductivity standard solution is a reference solution with a known conductivity value used for sensor calibration or verification. The expected value can be ensured by using a standard solution and diluting it. In this experiment, ten conductivity solutions were measured. These solutions were created by diluting two NIST-traceable reference solutions EC12.88 and EC1413 of 20ml (AQUAMASTER, the Netherlands). Either 0ml, 10ml, 20ml or 40ml was added to the solution, and the mixture was stirred to ensure homogeneity.

1. Solution 1: 20ml EC12,88 with 0ml Demiwater (100% EC12,88 solution)
2. Solution 2: 20ml EC12,88 with 10ml Demiwater (66.67% EC12,88 solution)
3. Solution 3: 20ml EC12,88 with 20ml Demiwater (50% EC12,88 solution)
4. Solution 4: 20ml EC12,88 with 30ml Demiwater (40% EC12,88 solution)
5. Solution 5: 20ml EC12,88 with 40ml Demiwater (33.33% EC12,88)
6. Solution 6: 20ml EC1431 with 0ml Demiwater (100% EC1431 solution)
7. Solution 7: 20ml EC1431 with 10ml Demiwater (66.67% EC1431 solution)
8. Solution 8: 20ml EC1431 with 20ml Demiwater (50% EC1431 solution)
9. Solution 9: 20ml EC1431 with 30ml Demiwater (40% EC1431 solution)
10. Solution 10: 20ml EC1431 with 40ml Demiwater (33.33% EC1431 solution)

Measurements were made on the conductance and susceptance over a frequency range from 10Hz to 1MHz. The measurement was repeated 5 times to limit the variability in the measurements. The PediGuard was secured to a laboratory stage and the electrodes were submerged in the sample solutions, ensuring proper contact and avoiding air bubbles.

Figure A.1 shows the conductance measured for the different saline solutions. The curvature follows the expected patterns. At low frequencies, there is a significant decrease in conductance. Mulder [44] suggest that the electrode polarization is more pronounced for solutions with higher conductivity. The curve flattens when the frequency increases. The conductance at high frequencies decreases almost linearly as the percentage of conductivity solution in the mixture decreases.

The offset of the conductance with the conductivity is related to the geometry factor. The geometry factor relates the measured electrical signal to the specific geometry of the electrodes and the sample solution. The equation to calculate the geometry factor is discussed in chapter 2 and shown in Equation A.

$$\sigma = \kappa G \quad (\text{A.1})$$

With σ being the conductivity, G the conductance and κ the geometry factor. For the geometry factor, the conductance from solution 1 and solution 6 is used to ensure measurements are taken on

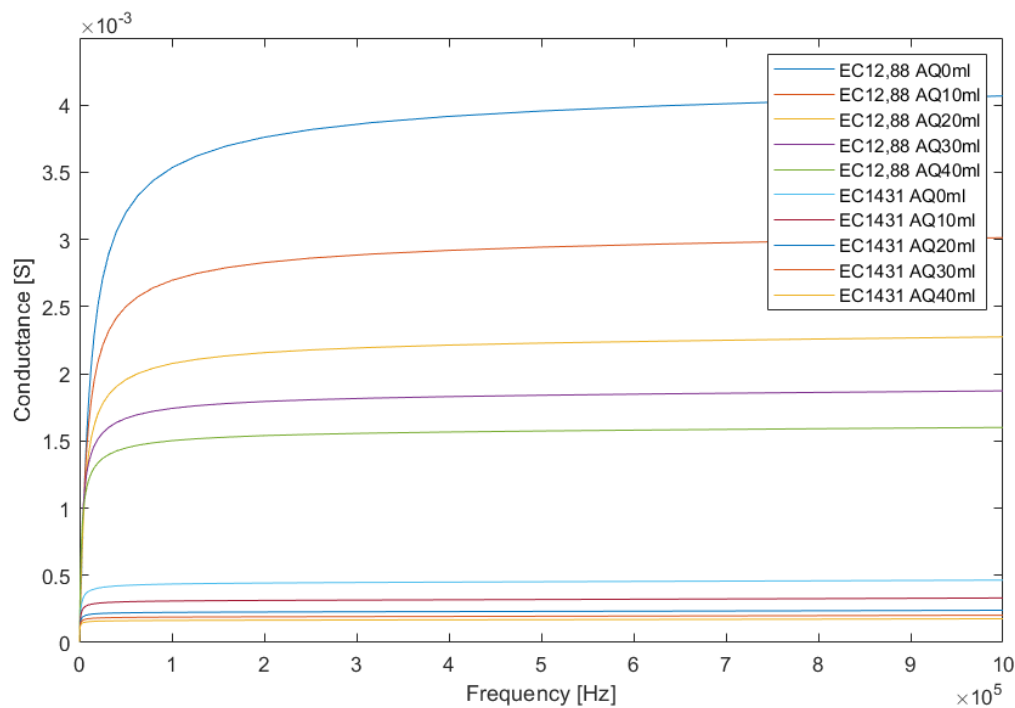


Figure A.1: Conductance for various conductivity solutions

repeatable solutions with homogeneous properties. The flattened frequency range is used, 10^5 till 10^6 , and the statistics are used to calculate the mean value and the variation, Table A.1.

Table A.1: Geometry factor PediGuard Probe

Geometry factor	Variance
300.98	203.4431

The data indicates that the PediGuard is highly sensitive to electrode polarization. When the conductivity increases, polarization effects become more dominant. Furthermore, the expected decrease in saline solution was observed, suggesting accurate measurements. Additionally, the small variation observed in the geometry factor indicates that stable measurements could closely approximate accuracy. The calculated geometry factor will be utilized throughout the study.

B

Benchmark Data & Model

Benchmark Data

The data acquired is compared to Gabriel, Gabriel, and Corthout [24]. Gabriel, Gabriel, and Corthout [24] data is accessible in the IT'is database and is widely used for comparison. Gabriel, Gabriel, and Corthout [24] measured the ovine skull and porcine to find the conductivity and permittivity of cortical and cancellous bone. These measurements were fitted against a four-pole Cole-Cole model to find the result as shown in Figure B.1.

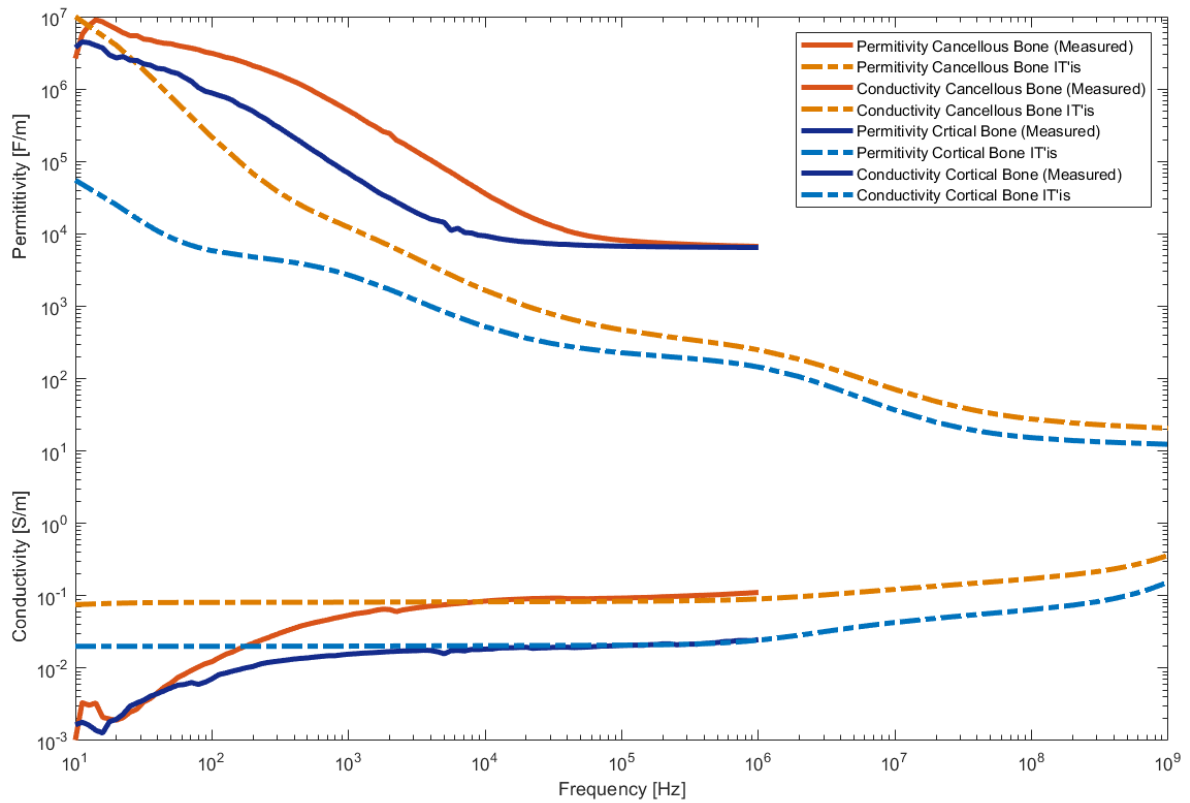


Figure B.1: Comparison measured data and IT'is database [24]

The measured magnitude and phase of vertebrae in this study are transformed to conductivity and permittivity using the equations in chapter 2 and the geometry factor calculated in Appendix A. Figure B.1 shows the permittivity and conductivity of our data in comparison with the IT'is database. The graph suggests that for the conductivity measurements, the data is compatible. The low frequencies

are subjected to electrode polarization. If the data were fitted to a model a similar curvature for the overlapping frequencies would probably be shown. However, for the permittivity, an offset is seen in the data with the measured data being a bit higher than the database. However, Amin et al. [5] suggests that there is a high variability found in the permittivity values for bone, even showing other papers which have a higher permittivity than the IT's database. Furthermore, the permittivity of the IT's database suggests at least two or three dispersion regions for bone tissue. While the data measured will only suggest a maximum of two dispersion regions.

Benchmark Model

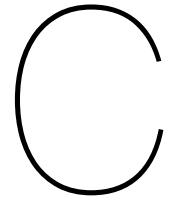
Our fitting method based on the study of Mulder [44] uses Gabriel, Gabriel, and Corthout [24] to benchmark here fitting method. As this study uses a similar method to Mulder [44], the model for cortical and cancellous bone of Gabriel, Gabriel, and Corthout [24] will also be used as a benchmark model.

Gabriel, Gabriel, and Corthout [24] as mentioned above performed measurements on the ovine skull and porcine to find the conductivity and permittivity of cortical and cancellous bone. These measurements were performed over a frequency range of $10Hz$ to $100GHz$ and are fitted against a four-pole Cole-Cole model [24]. Four poles are used while there are only three main dispersions as these provide a better fit. The formula for the Cole-Cole model is shown in Equation B.

$$\varepsilon = \varepsilon_{\infty} + \sum \frac{\delta\varepsilon_n}{1 + (j\omega\tau_n)^{(1 - \alpha_n)}} + \frac{\sigma_i}{j\omega\varepsilon_0} \quad (B.1)$$

Gabriel (1996) states that the fit with the Cole-Cole model is suitable for the high-frequency range with high certainty. However, it should be used with caution in the low-frequency range below 1 MHz. Factors such as electrode polarization and stray impedance are taken into consideration as follows: The capacitance and conductance are first normalized against the parameters of the probe measured in salt concentrations of similar conductivity. The electrode polarization effect is known to be significant below 100 Hz and plays a role below 1 kHz. However, even with the EP correction method, it cannot be concluded that it is eliminated.

As shown in Figure B.1 there is an overlap in data from $10Hz$ until 10^6Hz . The curvature shows two dispersion curves so it is expected that a two or three-pole method would be sufficient Mulder [44].



Single-frequency Predictive Value

P-value magnitude and phase of the impedance

Table C.1:

Frequency [kHz]	Feature Magnitude			Phase		
	<i>Cancellous</i>	<i>Cortical</i>	p [$\cdot 10^{-5}$]	<i>Cancellous</i>	<i>Cortical</i>	p [$\cdot 10^{-5}$]
0.010	85300	120000	3.0	-68	-57.9	947
0.011	66300	114000	3.1	-67.3	-59.5	7785
0.013	65000	110000	1.6	-67.3	-63	34919
0.014	56800	113300	0.48	-65.1	-63.7	38786
0.016	52700	89000	0.25	-65.8	-61.2	8273
0.018	49700	89600	0.22	-64.7	-59	2845
0.020	45500	83900	0.18	-64.3	-57.3	275
0.022	40500	72300	0.17	-62.1	-58.6	3999
0.025	35500	65000	0.11	-61.3	-53.9	258
0.028	33500	62400	0.25	-61.3	-57	1250
0.032	29200	59600	0.26	-59.6	-54.7	615
0.035	28000	56600	0.23	-59	-53.2	174
0.040	26200	53600	0.17	-57.5	-53.4	362
0.045	24500	50200	0.23	-57.4	-52.3	428
0.050	22400	47300	0.17	-55.4	-50.8	530
0.056	21700	44600	0.22	-55.3	-48.7	113
0.063	19300	43600	0.15	-54.4	-46.9	108
0.071	18500	40200	0.19	-52.4	-46.7	132
0.079	17400	38000	0.18	-51.2	-44.1	121
0.089	16100	37000	0.20	-50.1	-43	251
0.10	15700	34400	0.25	-48.7	-42.2	194

Continued on next page

Table C.1: (Continued)

0.11	14800	32800	0.39	-47.1	-40.6	258
0.13	14100	32100	0.33	-45.8	-39.1	244
0.14	13200	30300	0.38	-44	-37.8	348
0.16	12300	28500	0.53	-41.7	-35.8	412
0.18	11800	27000	0.47	-40.3	-33.8	456
0.20	11100	26300	0.49	-38.6	-33.8	622
0.22	10440	25900	0.54	-37	-32.2	456
0.25	9840	25000	0.62	-35.3	-29.8	523
0.28	9440	24500	0.70	-33.6	-28.7	480
0.32	9030	23700	0.72	-32.2	-27.2	498
0.35	8690	22800	0.78	-30.8	-25.7	557
0.40	8230	22100	0.78	-29.1	-24.7	662
0.45	7810	21700	0.86	-27.7	-22.9	585
0.50	7470	21100	0.89	-26.5	-22.3	686
0.56	7170	20800	0.92	-25.3	-21.2	712
0.63	6980	20100	0.91	-24.1	-20.1	720
0.71	6830	19600	0.96	-23.1	-19.1	600
0.79	6680	19300	1.0	-22.1	-18.5	925
0.89	6450	18800	1.1	-21.1	-17.8	1089
1.00	6300	18400	1.1	-20.2	-17	1208
1.12	6130	18000	1.3	-19.3	-16.3	1547
1.26	6000	17700	1.4	-18.6	-15.7	2145
1.41	5900	17300	1.4	-17.8	-15.1	1618
1.58	5780	17100	1.7	-17.2	-14.8	2409
1.78	5650	16800	1.6	-16.5	-14.1	3148
2.00	5580	16500	1.9	-15.8	-14.1	4800
2.24	5490	16400	2.0	-15.2	-14.4	7850
2.51	5380	16100	2.0	-14.7	-14.2	16753
2.82	5330	15900	2.1	-14.4	-13.9	25851
3.16	5240	15700	2.4	-14	-13.7	50035
3.55	5170	15600	2.4	-13.7	-13.3	81176
3.98	5100	15300	2.4	-13.6	-13.1	78377
4.47	5030	15100	2.4	-13.2	-14.1	32673
5.01	4980	14900	2.3	-12.8	-14.7	9083
5.62	4920	15000	2.4	-12.6	-14	3730
6.31	4870	14700	2.1	-12.5	-14.8	523
7.08	4830	14600	2.2	-12.5	-15.1	82
7.94	4780	14400	2.5	-12.6	-15.4	11
8.91	4720	14200	2.4	-12.5	-15.4	4.3
10.0	4710	14000	2.7	-12.2	-15.8	0.61

Continued on next page

Table C.1: (Continued)

11.2	4670	14000	2.8	-11.9	-16.9	0.39
12.6	4650	13700	2.7	-11.8	-17.2	0.23
14.1	4620	13600	3.4	-11.9	-18.4	0.16
15.8	4580	13400	3.4	-12.1	-19.7	0.18
17.8	4550	13400	3.2	-12.3	-21.1	0.16
20.0	4530	13000	2.7	-12.7	-22.8	0.26
22.4	4490	12700	3.2	-13.1	-24.5	0.47
25.1	4460	12500	4.3	-13.6	-26.9	0.87
28.2	4430	12200	4.1	-14.1	-28.7	1.1
31.6	4420	12000	3.7	-14.8	-31.2	1.4
35.5	4410	11700	3.6	-15.7	-33.4	2.1
39.8	4350	11200	3.5	-16.9	-36.2	2.8
44.7	4300	10760	2.8	-18.3	-39	2.7
50.1	4260	10240	2.3	-19.8	-41.8	2.8
56.2	4210	9720	2.1	-21.4	-44.6	2.6
63.1	4130	9160	2.0	-23.3	-47.6	2.7
70.8	4060	8600	2.3	-25.2	-50.4	2.9
79.4	3940	8020	2.1	-27.4	-53.3	2.9
89.1	3860	7430	2.1	-29.9	-56	3.2
100	3790	6860	2.4	-32.5	-58.8	3.1
112	3630	6310	2.0	-35	-61.4	3.1
126	3480	5780	1.7	-37.5	-63.7	3.3
141	3350	5250	1.7	-40.9	-66.1	3.4
158	3180	4770	1.8	-44	-68.2	4.0
178	2980	4310	1.4	-46.8	-70.3	3.9
200	2820	3890	0.97	-49.9	-72.2	4.2
224	2630	3510	0.63	-52.6	-74.1	4.0
251	2440	3160	0.50	-55.2	-75.4	4.3
282	2260	2840	0.34	-57.9	-76.8	4.4
316	2090	2550	0.24	-60.4	-78.1	4.4
355	1920	2290	0.17	-62.7	-79.2	3.9
398	1750	2050	0.093	-65	-80.2	3.9
447	1590	1840	0.064	-67.1	-81.1	3.5
501	1440	1640	0.051	-69	-82	3.6
562	1310	1470	0.021	-70.8	-82.7	4.1
631	1180	1320	0.015	-72.4	-83.3	3.4
708	1067	1170	0.0093	-73.9	-83.9	3.5
794	963	1049	0.0051	-75.3	-84.5	2.6
891	868	936	0.0011	-76.5	-85	2.3
1000	782	837	0.0007	-77.6	-85.5	2.3

P-value real and imaginary impedance

Table C.2:

Frequency [kHz]	Feature		p [$\cdot 10^{-5}$]	Imaginary		p [$\cdot 10^{-5}$]
	Real			Cancellous	Cortical	
	<i>Cancellous</i>	<i>Cortical</i>				
0.010	57881	27300	25	-72244	-93258	318
0.011	55934	27283	298	-59882	-96568	33
0.013	52387	26748	130	-57826	-98112	0.20
0.014	40083	23433	211	-49034	-77882	0.16
0.016	40702	20941	8.2	-45744	-80792	0.072
0.018	42830	20559	3.1	-43793	-72355	0.079
0.020	41595	20876	1.1	-40024	-64338	0.24
0.022	35999	19382	6.1	-37177	-57873	0.097
0.025	38516	17762	2.5	-32497	-53279	0.10
0.028	34550	16257	3.4	-30508	-50737	0.29
0.032	35206	15646	2.8	-26403	-45654	0.25
0.035	34504	13543	2.4	-24780	-43358	0.25
0.040	32687	13906	2.2	-22959	-39306	0.12
0.045	30412	12618	2.5	-21605	-36486	0.089
0.050	31183	12429	1.4	-19529	-33792	0.12
0.056	31594	11265	1.1	-17306	-31467	0.10
0.063	28662	10916	0.84	-15945	-28179	0.064
0.071	28283	10848	0.78	-14625	-26383	0.072
0.079	28284	10365	0.91	-13244	-25378	0.059
0.089	27884	10144	1.1	-12077	-23084	0.050
0.10	26280	9787	0.70	-11102	-21745	0.093
0.11	25650	9662	0.94	-10128	-19779	0.13
0.13	25075	9103	0.81	-9471	-17463	0.13
0.14	24350	8824	0.94	-8520	-16872	0.11
0.16	23905	8578	1.0	-7801	-15745	0.16
0.18	23011	8181	0.94	-7195	-14625	0.16
0.20	22800	7843	0.94	-6692	-13958	0.11
0.22	22348	7798	1.0	-6255	-11997	0.16
0.25	21543	7463	1.0	-5747	-11080	0.18
0.28	21218	7328	1.1	-5375	-10471	0.24
0.32	20788	7144	1.0	-4891	-9363	0.28
0.35	20358	7016	1.2	-4576	-8858	0.31
0.40	20038	6922	1.2	-4334	-8198	0.24
0.45	19619	6756	1.5	-3947	-7695	0.33

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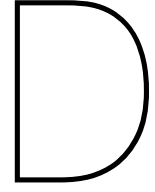
Table C.2: (Continued)

0.50	19155	6603	1.5	-3684	-7199	0.36
0.56	19003	6445	1.6	-3440	-6762	0.28
0.63	18583	6285	1.6	-3219	-6280	0.36
0.71	18323	6176	1.6	-3029	-5950	0.41
0.79	17925	6057	1.6	-2817	-5775	0.31
0.89	17644	5966	1.8	-2662	-5348	0.32
1.00	17340	5842	1.9	-2487	-5077	0.31
1.12	17072	5742	2.3	-2322	-4782	0.32
1.26	16834	5651	2.4	-2230	-4599	0.36
1.41	16544	5554	2.3	-2086	-4332	0.32
1.58	16413	5493	2.4	-1951	-4122	0.29
1.78	16265	5415	2.4	-1832	-3941	0.38
2.00	15930	5357	2.6	-1734	-3867	0.42
2.24	15870	5279	2.9	-1626	-3729	0.51
2.51	15608	5197	2.6	-1535	-3660	0.51
2.82	15434	5172	2.6	-1451	-3504	0.75
3.16	15266	5095	2.7	-1369	-3529	0.71
3.55	15188	5035	2.8	-1289	-3441	0.70
3.98	14937	4989	2.4	-1206	-3371	0.60
4.47	14736	4925	2.5	-1146	-3297	0.70
5.01	14530	4882	2.5	-1099	-3301	0.65
5.62	14604	4823	2.4	-1058	-3364	0.70
6.31	14300	4784	2.4	-1010	-3405	0.62
7.08	14203	4743	2.7	-984	-3451	0.58
7.94	13966	4701	2.9	-957	-3605	0.84
8.91	13735	4636	2.7	-933	-3656	0.87
10.0	13491	4630	2.7	-917	-3826	0.87
11.2	13444	4589	2.7	-907	-3945	0.83
12.6	13094	4569	2.5	-893	-4146	0.87
14.1	12905	4538	2.8	-903	-4419	1.1
15.8	12631	4493	3.2	-903	-4629	1.8
17.8	12425	4462	2.6	-918	-4896	1.8
20.0	12019	4434	2.3	-949	-5171	1.8
22.4	11575	4389	2.0	-982	-5432	2.1
25.1	11216	4347	4.0	-1023	-5641	3.2
28.2	10732	4308	3.4	-1067	-5940	3.4
31.6	10178	4273	2.4	-1124	-6148	3.1
35.5	9440	4233	1.7	-1193	-6441	3.1
39.8	8698	4171	1.7	-1270	-6618	3.0
44.7	7563	4094	2.3	-1360	-6728	2.5

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Table C.2: (Continued)

50.1	6530	4023	2.5	-1464	-6839	2.4
56.2	6062	3929	3.0	-1540	-6825	2.5
63.1	5641	3719	9.7	-1635	-6753	2.4
70.8	5042	3563	21	-1735	-6588	2.5
79.4	4405	3401	86	-1821	-6430	2.1
89.1	3790	3248	578	-1918	-6151	2.3
100	3326	2941	7193	-2036	-5859	2.0
112	2858	2537	41505	-2077	-5524	2.0
126	2390	2406	92286	-2118	-5168	2.0
141	2002	2141	33691	-2202	-4811	2.6
158	1660	1882	5685	-2209	-4441	2.4
178	1372	1766	585	-2172	-4073	2.1
200	1133	1632	72	-2157	-3714	2.0
224	964	1475	12	-2089	-3385	1.6
251	797	1371	2.5	-2004	-3063	1.4
282	649	1190	1.1	-1906	-2771	0.98
316	526	1022	0.87	-1800	-2499	0.81
355	429	887	1.5	-1688	-2247	0.60
398	349	746	1.8	-1568	-2022	0.35
447	285	621	2.4	-1459	-1817	0.22
501	228	515	3.5	-1343	-1624	0.18
562	187	429	5.5	-1238	-1458	0.093
631	153	355	4.4	-1127	-1302	0.077
708	124	294	5.2	-1022	-1165	0.043
794	101	242	4.1	-927	-1043	0.021
891	82	200	4.0	-839	-934	0.007
1000	66	165	3.7	-760	-834	0.004



Multiple-frequency Modelling

The objective of this chapter is to develop a parametric model that accurately fits the impedance spectra of vertebrae tissue, specifically cancellous and cortical bone. According to Mulder [44], these spectra consist of an electrode polarization component and a tissue component. If the specific electrode polarization and the affected frequency range are unknown, modelling the electrode polarization impedance and tissue impedance in series could be a solution. Tissue modelling is conducted using a Cole model, and the polarization is modelled with a CPE model. First, a Cole model is analyzed, then this Cole model is expanded with a CPE model, and finally, a two-pole Cole model is analyzed. For the fitting of the model, the mean impedance for both cortical and cancellous bone is used, a representation of this data can be found Appendix E. The most promising model will be utilized in chapter 3.

Cole Model

The data was fitted to a Cole model. The Cole impedance model describes a single ideal dispersion, by the following formula.

$$Z = R_{\infty} + \frac{(R_0 - R_{\infty})}{1 + (jF/F_c)^{(1-\alpha)}} \quad (D.1)$$

Wherein Z is the impedance, R_{∞} is the resistance at a very high frequency, R_0 is the resistance at a very low frequency, F_c is the frequency at which the impedance spectra has its maximum gradient, F is the frequency and α is a constant [3].

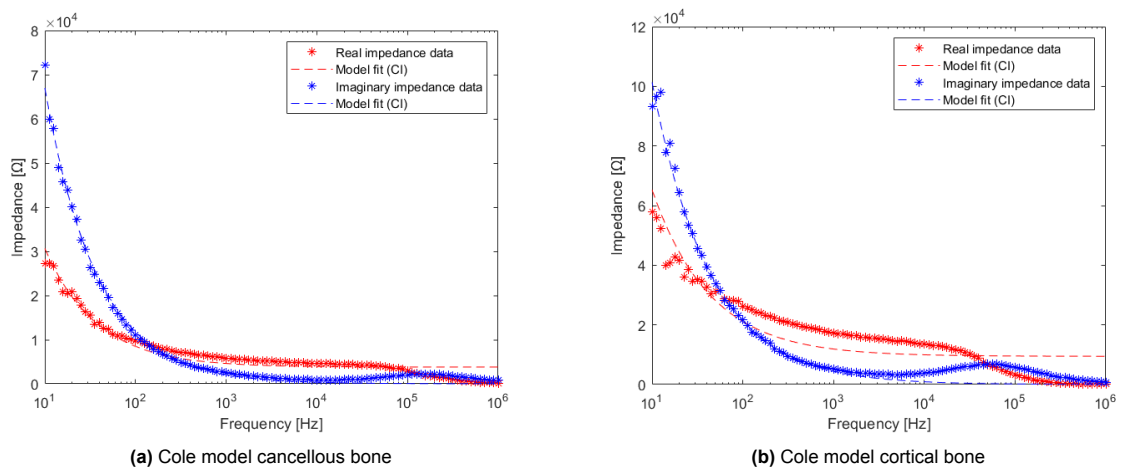


Figure D.1: Fitted curve for (a) cancellous bone and (b) cortical bone to a Cole model

Figure D.1 shows the fitted data. A single Cole model can describe tissue in one dispersion area with electrode polarization. However, no differentiation can be found between the amount affected by

the tissue and the electrode polarization. As can be seen, the impedance of bone tissue is described by more dispersion area, showing that the Cole model does not sufficiently describe the measured tissue for the entire frequency range. The MSE values for the Cole model are high being $3.88\text{e}8$ and $4.55\text{e}9$ respectively for cancellous and cortical tissue. To purely describe the tissue impedance, the fit should be accurate for the high-frequency range where the electrode polarization impedance has disappeared. As the single pole Cole model mostly describes the electrode polarization it is not subjected to be a good fit.

Cole Model with CPE

The CPE model is frequently mentioned in articles for modelling electrode polarization, primarily in the context of blood. The CPE model is a frequency-dependent component that combines a resistor and a capacitor. The parameter K represents the ion concentration at the electrode-tissue contact, while the parameter m is associated with the surface roughness of the electrodes [44]. The Cole model can be modelled in series with the CPE model to separate the influence of electrode polarization and tissue, this is done by the following Equation 3.3

$$Z = R_{\infty} + \frac{(R_0 - R_{\infty})}{1 + (jF/F_c)(1 - \alpha)} + K(j\omega)^{-m} \quad (\text{D.2})$$

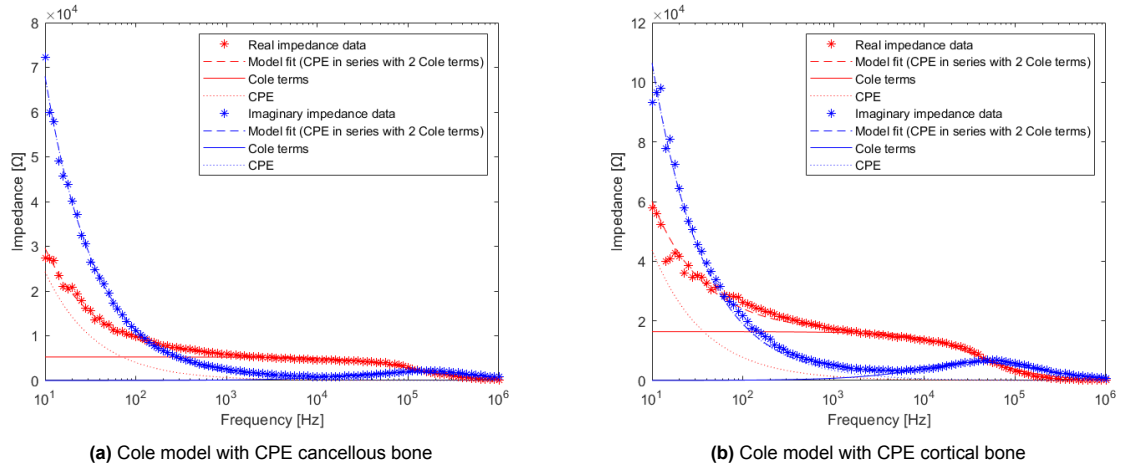


Figure D.2: Fitted curve for (a) cancellous bone and (b) cortical bone to a one-pole Cole model with CPE

Figure D.2 shows the fitted data to a one-pole Cole model with CPE. As can be seen in comparison to the single Cole model, the contributions of the electrode polarization are modelled by the CPE terms and the Cole terms describe the electric properties of tissue from 10^3 to 10^5 . However, it can be seen that the impedance includes more than one dispersion area. So the Cole model with CPE is a better fit than the singular Cole model, yet, as more dispersion areas are seen a more extensive model could be ideal. The MSE values for the Cole model with CPE are high being $6.71\text{e}7$ and $7.07\text{e}8$ respectively for cancellous and cortical tissue.

Two-pole Cole model with CPE

To include two dispersion areas the Cole model with CPE can be expanded to a two-pole Cole model with CPE. This is done by adding two Cole elements in series with a CPE element as seen in Equation D.3.

$$Z = R_{\infty} + \frac{(R_0 - R_{\infty})}{1 + (jF/F_c)(1 - \alpha)} + \frac{(R_0 - R_{\infty})}{1 + (jF/F_c)(1 - \alpha)} + K(j\omega)^{-m} \quad (\text{D.3})$$

Figure D.2 shows the fitted data to a twp-pole Cole model with CPE. As can be seen in comparison to the one-pole Cole model with CPE, the contributions of the electrode polarization are modelled by the CPE terms and the two Cole terms describe the electric properties of tissue from 10^3 to 10^5 and

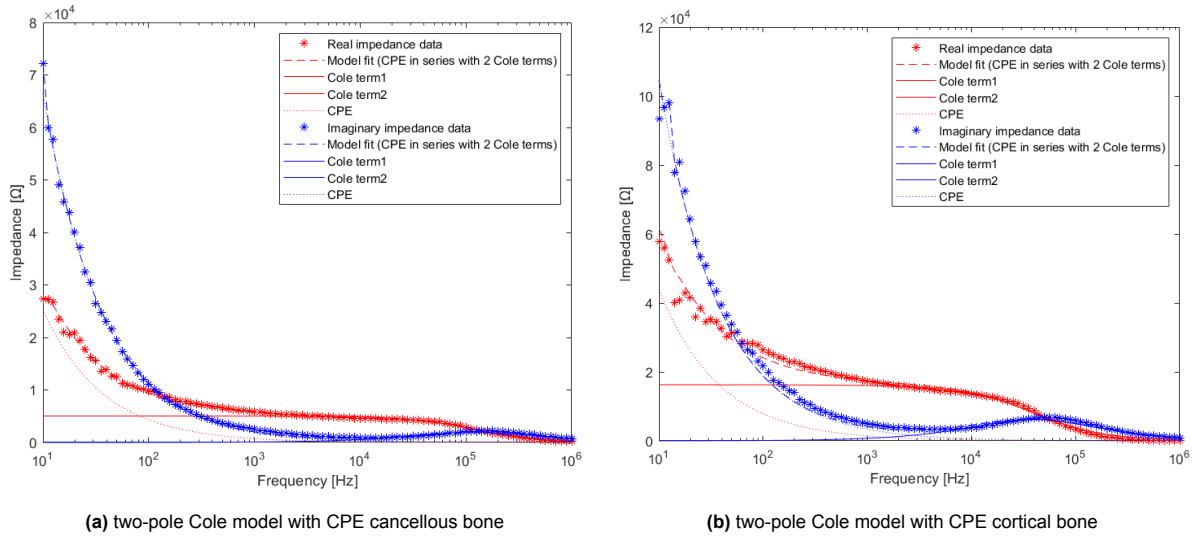
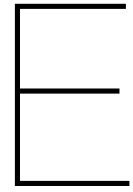


Figure D.3: Fitted curve for (a) cancellous bone and (b) cortical bone to a two-pole Cole model with CPE

past 10^5 . Although the fitted model seems to resemble the measured data the MSE values for the Cole model with CPE are high being $6.71\text{e}7$ and $7.07\text{e}8$ respectively for cancellous and cortical tissue.

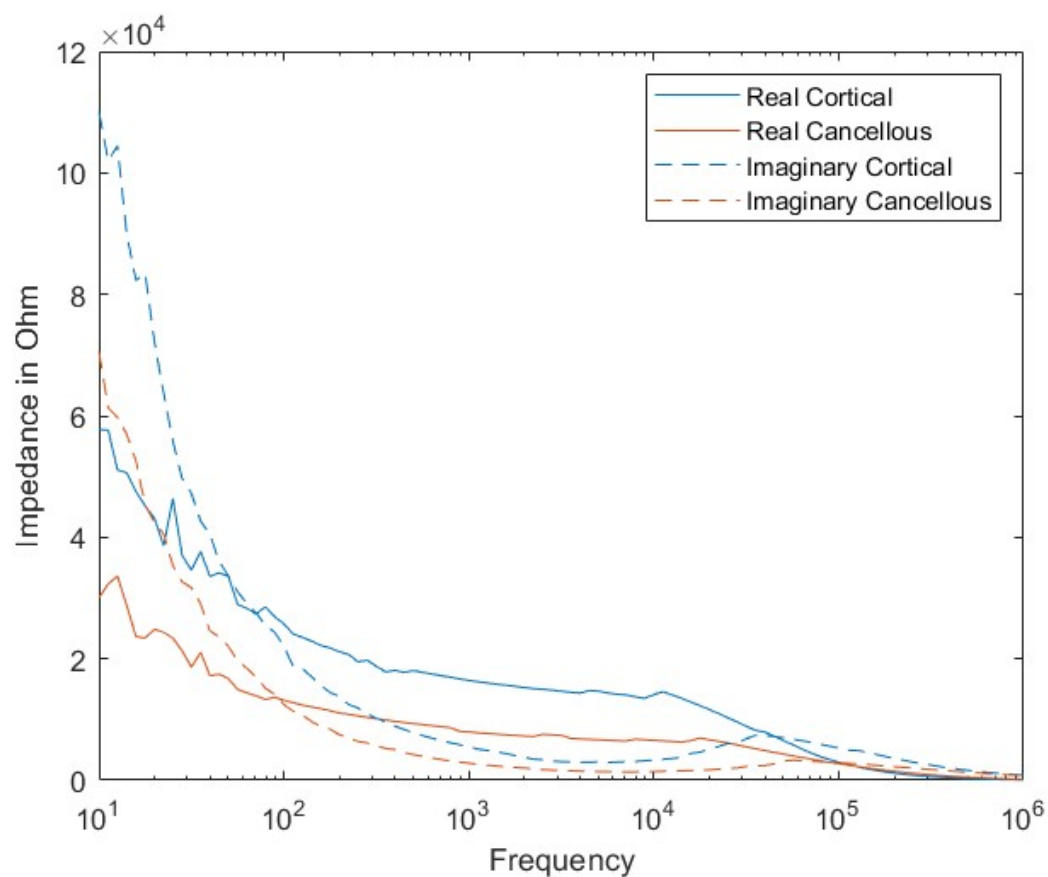
Table D.1: MSE for Cole, Cole with CPE and two-Cole with CPE model

			MSE re	MSE im	MSE tot
Cole	<i>Cancellous</i>	1st	2.46E+08	1.42E+08	3.88E+08
		2nd	2.46E+08	1.42E+08	3.88E+08
	<i>Cortical</i>	1st	3.44E+09	1.10E+09	4.55E+09
		2nd	3.44E+09	1.10E+09	4.55E+09
Cole with CPE	<i>Cancellous</i>	1st	2.05E+07	4.66E+07	6.71E+07
		2nd	2.05E+07	4.66E+07	6.71E+07
	<i>Cortical</i>	1st	3.44E+09	1.10E+09	4.55E+09
		2nd	2.81E+08	4.27E+08	7.07E+08
Two-pole Cole with CPE	<i>Cancellous</i>	1st	4.40E+07	6.89E+07	1.13E+08
		2nd	1.35E+07	2.22E+07	3.57E+07
	<i>Cortical</i>	1st	2.76E+08	3.59E+08	6.35E+08
		2nd	2.72E+08	3.42E+08	6.14E+08



References impedance spectra for cancellous and cortical bone

This appendix shows the mean impedance spectra for vertebrae tissue, i.e. cancellous and cortical bone.



F

Electrical Impedance Spectroscopy Results

Point 1

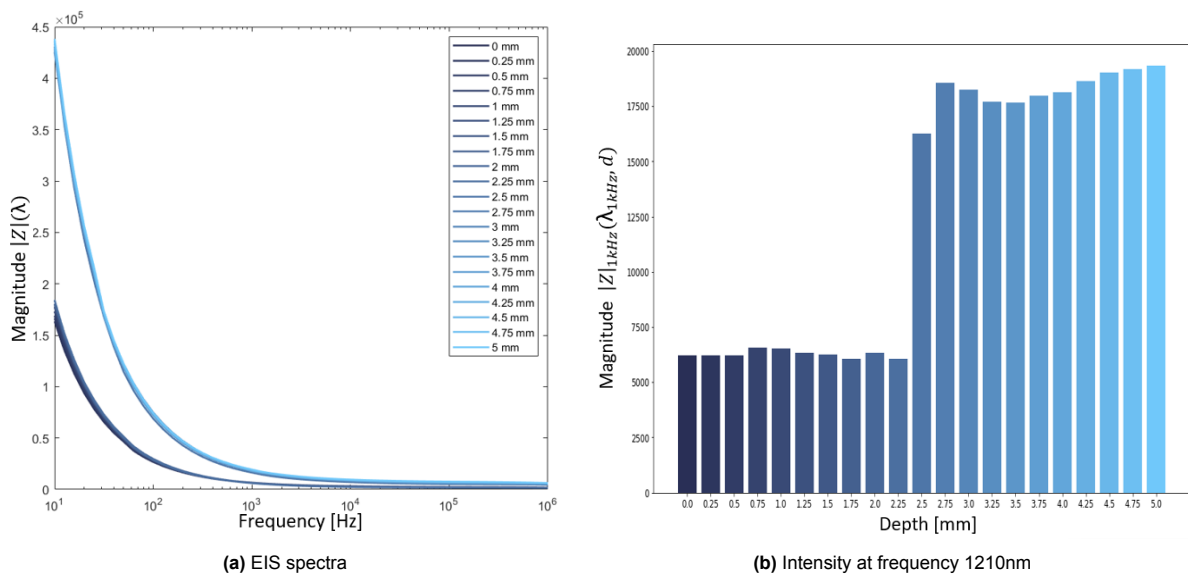


Figure F.1: EIS measurements at point 1

Point 2

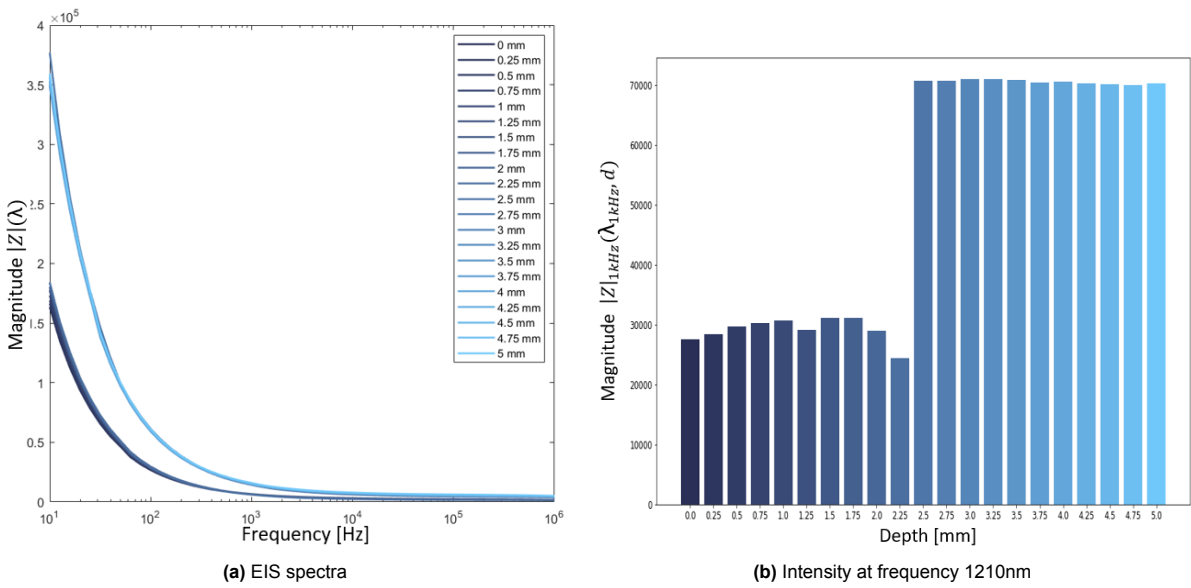


Figure F.2: EIS measurements at point 2

Point 3

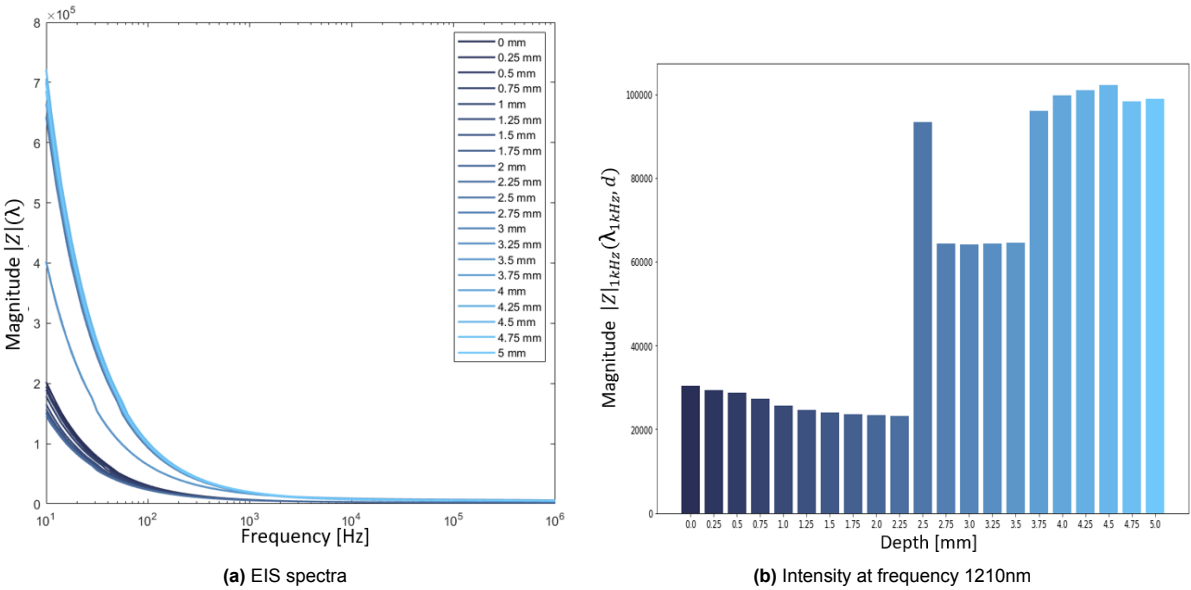


Figure F.3: EIS measurements at point 3

Point 4

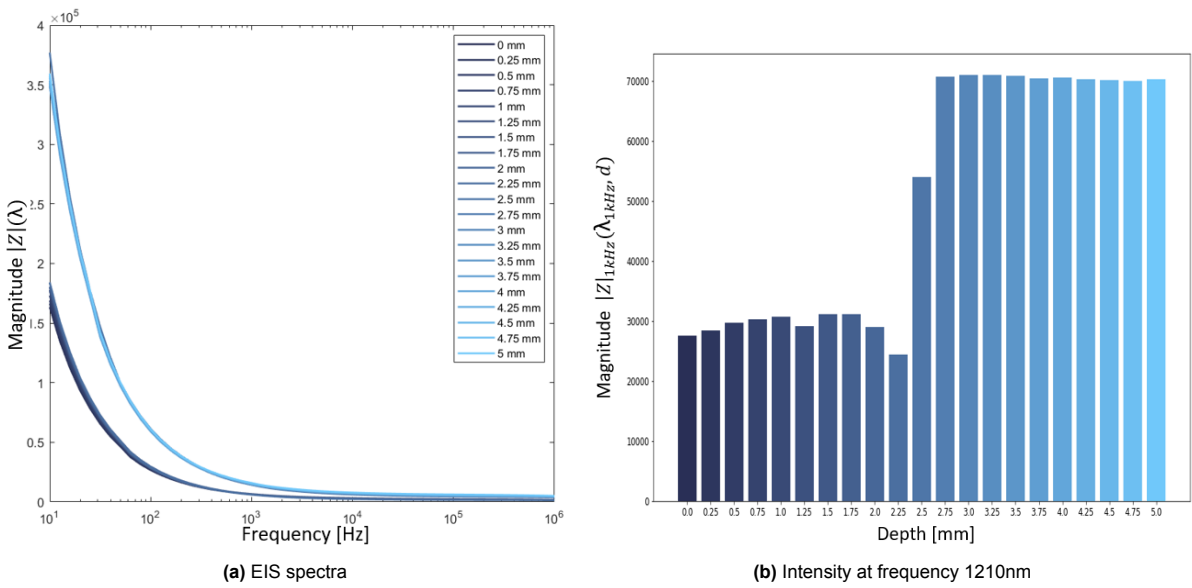


Figure F.4: EIS measurements at point 4

Point 5

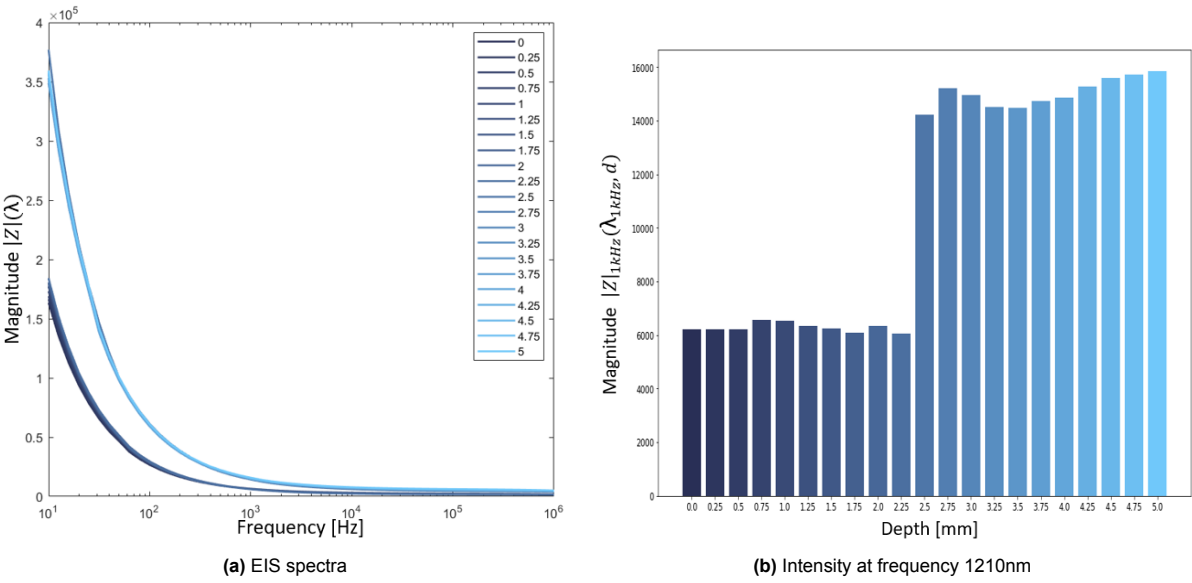


Figure F.5: EIS measurements at point 5

G

Diffuse Reflection Spectroscopy Results

Point 1

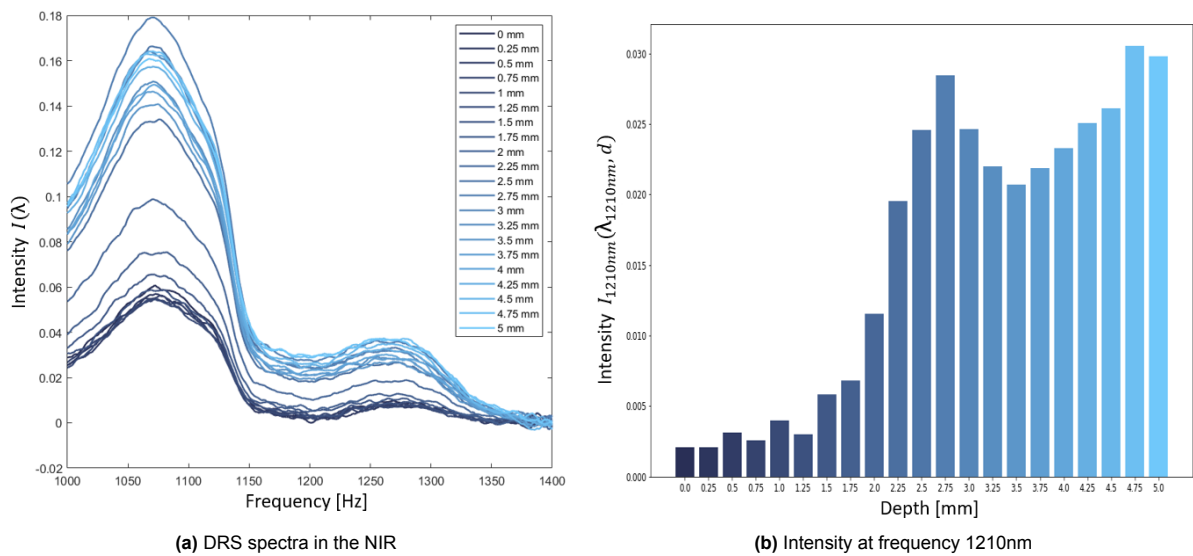


Figure G.1: DRS measurements at point 1

Point 2

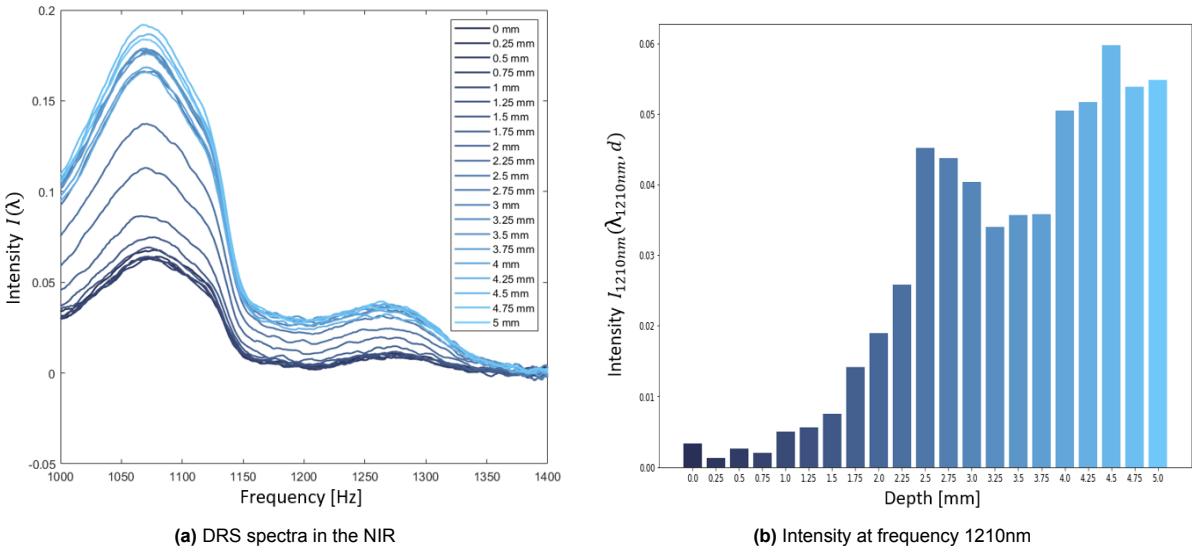


Figure G.2: DRS measurements at point 2

Point 3

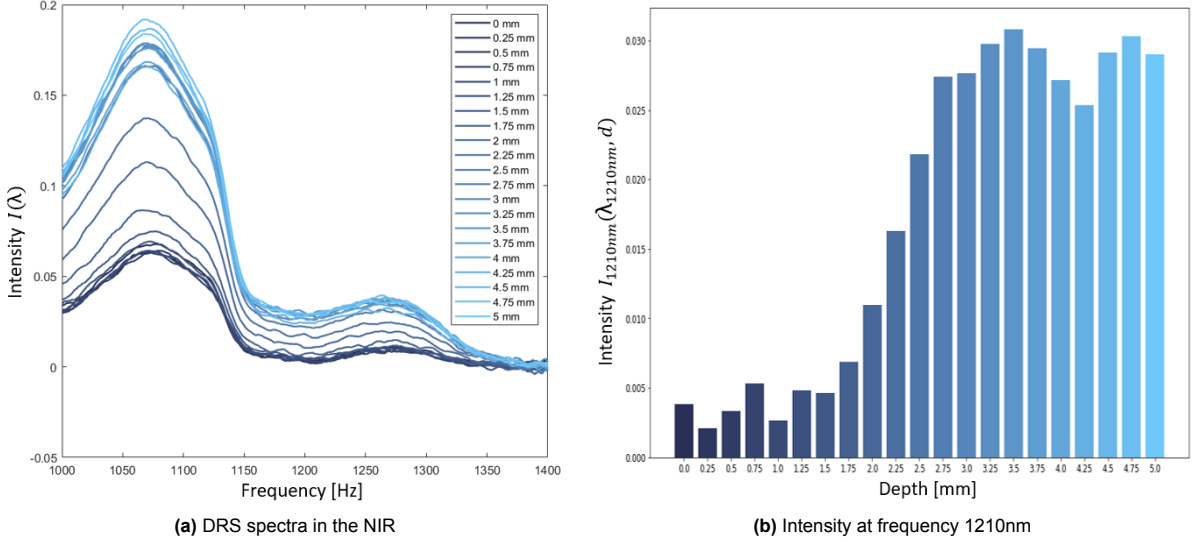


Figure G.3: DRS measurements at point 3

Point 4

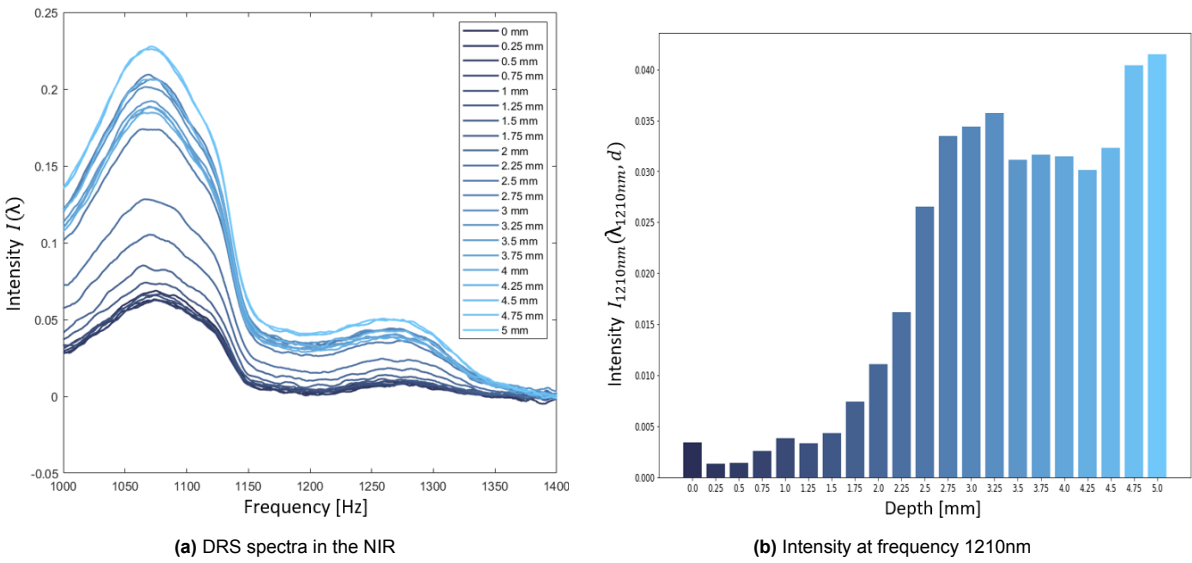


Figure G.4: DRS measurements at point 4

Point 5

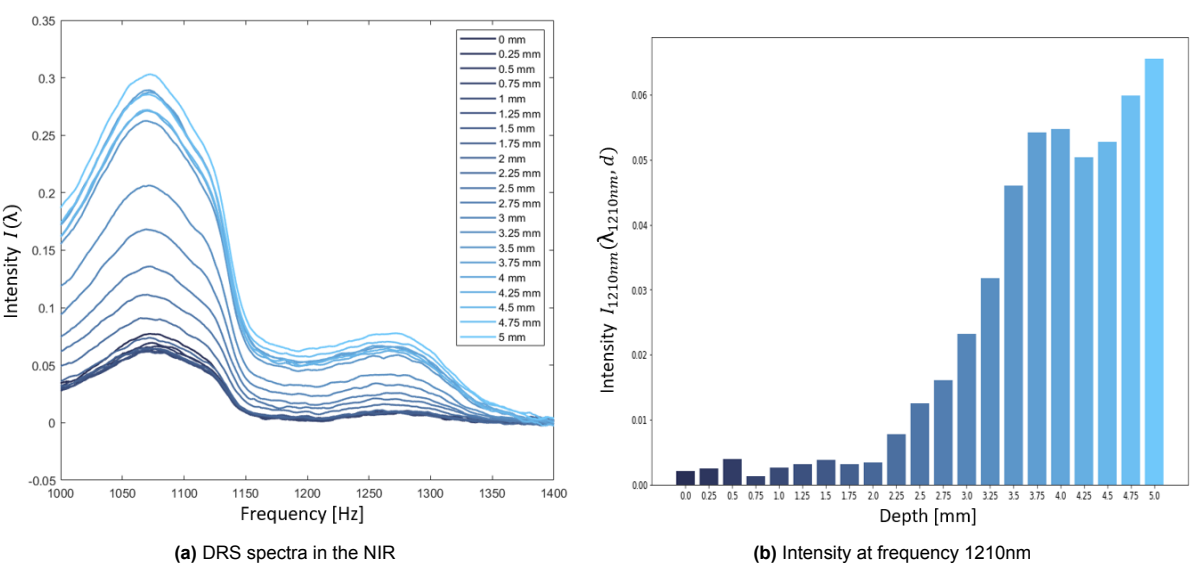


Figure G.5: DRS measurements at point 5