

REPUCLIC OF TURKEY
MUĞLA SITKI KOÇMAN UNIVERSITY
GRADUATE SCHOOL OF NATURAL AND APPLIED
SCIENCES

ELECTRICAL ELECTRONICS ENGINEERING
DEPARTMENT

MULTI-WAVELENGTH OXIMETER DESIGN

MASTER OF SCIENCE

ÖZGE TAYLAN MORAL

DECEMBER 2020

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APPROVAL OF THE THESIS

The thesis submitted by **ÖZGE TAYLAN MORAL** with the title of **“MULTIWAVELENGTH OXIMETER DESIGN”** has been unanimously accepted by jury members on the 14th of December, 2020 to fulfill the requirements for the degree of Master of Science in the Department of Electrical Electronics Engineering.

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I hereby declare that all information in this document has been obtained and presented in accordance with academic rules and ethical conduct. I also declare that, as required by these rules and conduct, I have fully cited and referenced all material and results that are not original to this work.

Özge Taylan MORAL

14 /12/2020

ÖZET

ÇOKLU DALGABOYLU OKSİMETRE TASARIMI

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Yüksek Lisans Tezi

Fen Bilimleri Enstitüsü

Elektrik Elektronik Mühendisliği Anabilim Dalı

Danışman: Doç. Dr. Ufuk BAL

Aralık 2020, 108 sayfa

Ağır enfeksiyon, travma, hemolitik hastalıklar ile özellikle Türk toplumunda sık görülen Favizm gibi hastalıklar hemoglobin ile ilişkilidir. Özellikle karbonmonoksit zehirlenmesinden kaynaklanan mortalitelerde hemoglobinin bazı çeşitleri etkilidir. Hemoglobin değerlerinin hızlıca değerlendirilmesi özellikle acil servislerde hayati bir önem taşımaktadır. Bu parametrelerin monitorizasyonu verimliliği artırmakta ve ölümcül hastalıklara müdahale zamanını azaltmaktadır.

Bu çalışmada, çeşitli hastalıkların tanısında önemi olan hemoglobin konsantrasyon değerlerinin ölçümünü yapan özgün bir temassız cihaz tasarımı hedeflenmiştir. Mevcut hemoglobin ölçümleri invaziv kan alımını ve kan tahlilini gerektirmektedir. Bu, zaman alıcı ve süreksiz bir yöntemdir. Hemoglobin değerlerinin belirlenmesi oksijen saturasyonu tespitini sağlar. Oksijen saturasyonu, doku oksijenasyonu hakkında bilgi verir. Oksijen saturasyonu, nabız gibi parametrelerin ölçüm ve görüntülenmesini sağlayan cihazlara oksimetre adı verilir. Son çalışmalar oksijen saturasyonu ölçümünü iyileştirmenin yanısıra hemoglobin çeşitlerinin ölçümünü sağlama üzerinedir. Halihazırda hemoglobin ölçümü yapabilen ticari oksimetrelerin doğrulukları açısından yeterlilikleri tartışılmaktadır. Bu çalışma ile mevcut ticari oksimetrelerin sahip olduğu dezavantajlar giderilmeye çalışılmış ve mevcut olmayan temassız hemoglobin ölçümü cihazı tasarlanmıştır. Hemoglobin ölçümünde kritik öneme sahip saçılma

ve soğurulma katsayıları optik fantomlar kullanılarak frekans domenli çoklu uzaklık yöntemi ile hesaplanmış, ve tasarlanan cihazın kalibrasyonu yapılmıştır. Cihaz ile alınan ölçümlerden oluşan veri kümesine regresyon yöntemi uygulanarak toplam hemoglobin ve üç farklı hemoglobin çeşidi kestirimi yapılmış ve daha sonra derin öğrenme yöntemleri uygulanarak toplam hemoglobin kestirimi yapılmıştır.

Bu tasarım sayesinde noninvaziv, sürekli ve temassız ölçüm yapılacaktır. Kanda az bulunan hemoglobin çeşitlerinin neden olduğu oksijen saturasyonu hatası tasarımda iyileştirme yapılarak çözümlenebilir.

Anahtar Kelimeler: Hemoglobin, Temassız Ölçüm, Spektroskopi, Frekans Domenli Çoklu Uzaklık, Yapay Zeka



ABSTRACT

MULTI-WAVELENGTH OXIMETER DESIGN

Özge Taylan MORAL

Master of Science (M.Sc.)

Graduate School of Natural and Applied Sciences

Department of Electrical Electronics Engineering

Supervisor: Assoc. Prof. Dr. Ufuk BAL

December 2020, 108 pages

The determination of serious infections, trauma, hemolytic diseases, and favism, a common disease in Turkey, is related to hemoglobin. Some species of hemoglobin are effective especially in mortality caused by carbon monoxide poisoning. A quick evaluation of total hemoglobin and hemoglobin species is vital, especially in emergency situations. Monitorization of hemoglobin value will increase efficiency and decrease response time in treated deadly diseases.

A non-contact device design that measures hemoglobin concentration values, which is important in the diagnosis of various diseases, is proposed in this study. Current hemoglobin measurements require drawing blood invasively, it is a time-consuming and non-continuous blood gas analysis. The determination of hemoglobin values provides to detect oxygen saturation. The oxygen saturation gives information on a patient's tissue oxygenation. The devices that measure and display the parameters such as oxygen saturation and heart rate are called oximeters. Recent studies have focused on improving the measurement of oxygen saturation as well as providing the measurement of hemoglobin types. The accuracy of current oximeters with a hemoglobin measurement capability is being discussed. With this study, the disadvantages of existing commercial oximeters were tried to be overcome by designing a novel non-contact hemoglobin measurements device. The absorption and reduced scattering coefficients, which are critical in hemoglobin measurement were calculated by

the frequency domain multiple distance method using optical phantoms, and the designed device was calibrated. Total hemoglobin and three different types of hemoglobin were estimated by applying the regression method to the dataset consisting of the measurements taken with the device, and then the total hemoglobin was estimated by applying deep learning methods.

This design allows noninvasive, continuous, and non-contact measurement will be made. Oxygen saturation error caused by hemoglobin species that are scarce in the blood can be resolved by making improvements in design.

Keywords: Hemoglobin, Noncontact Measurement, Spectroscopy, Frequency Domain Multiple Distance, Artificial Intelligence





To my dear family

ACKNOWLEDGMENTS

Firstly, I would like to thank my advisor Assoc. Prof. Dr. Ufuk BAL for the continuous support of my M. Sc. study and related research, for his motivation and knowledge.

The most appreciated help was from my parent Nurcihan and Aydın, and especially my brother Özgür Taylan. I would like to thank for their never-ending support, patience, encouragement, respect, and love.

This thesis has been granted by the Muğla Sıtkı Koçman University Research Projects Coordination Office through Project Grant Number 19/079/08/2/1 and TUBITAK by grant number 115E245.

I would like to thank TUBITAK for supporting my thesis under “2210-C Yurt İçi Öncelikli Alanlar Yüksek Lisans Burs Programı” by grant 1649B021803281.

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LIST OF SYMBOLS AND ABBREVIATIONS

π	Pi
ω	Modulation frequency
v	The speed of light in the medium
φ	The phase shift
ψ	Wavelet
λ	Lambda, wavelength
ε	Extinction coefficient
μ_a	Absorption coefficient
μ_s	Scattering coefficient
μ'_s	Reduced scattering coefficient
Δl	Optical path length
cm	Centimeter
cm^{-1}	1/centimeter
dB	Decibel
E	Entropy
EU	Entropy unit
Hz	Hertz
k Ω	Kiloohm
mm	Milimeter
nm	Nanometer
MHz	Megahertz
mA	Miliampere
mmol	Milimolar

GHz	Gigahertz
1-D	One-dimensional
2-D	Second-dimensional
AC	Alternating Current
Adam	Adaptive Moment Optimization
ANN	Artificial Neural Network
BP-ANN	Backpropagation ANN
CNN	Convolutional Neural Network
CO	Carbon monoxide
CW	Continuous Wave
CWT	Continuous Wavelet Transform
DAQ	Data Acquisition Card
c	Concentration
DC	Direct current
EEG	Electroencephalogram
FDMD	Frequency domain multiple distance
FTIR	Fourier Transform Infrared Spectroscopy
GPIO	General Purpose Interface Bus
GPR	Gaussian Process Regression
Hb	Hemoglobin
HbCO	Carboxyhemoglobin
HHb	Deoxyhemoglobin
HbMet	Methemoglobin
HbO_2	Oxyhemoglobin
I	Transmitted intensity

InGaAs	Indium gallium arsenide
kS/s	Kilo sample/second
l	The optical path length
LED	Light Emitting Diode
MAE	Mean Absolute Error
MSE	Mean Square Error
MMIC	Monolithic microwave integrated circuit
NI USB	National Instrument
PCA	Principal Component Analysis
PCB	Printed Circuit Board
PLS	Partial Least Square
PMT	Photomultiplier Tube
PPG	Photoplethysmogram
PSD	Power Spectral Density
r	Fiber distance
RF	Radio Frequency
RGB	Red Green Blue
RMS	Root Mean Square
R_{dc}	the mean of the measured intensity
R_{ac}	the modulation amplitude
RMSE	Root mean square error
rmsprop	RMS propagation
Sgdm	Stochastic Gradient Descent Method
SpCO	The percentage of HbCO
SpMet	The percentage of HbMet

SVM	Support Vector Machine
SaO ₂	Arterial Oxygen Saturation
SpO ₂	Pulse oximeter Oxygen Saturation
SO ₂	Oxygenation
SO _{2 fr}	Fractional oxygenation
S	Slope
tHb	Total Hemoglobin
TIA	Transimpedance Amplifier
V	Volt
VGG(16-19)	Visual Genome Group (16 or 19 layer)
VI	Virtual Instrument
U(t)	The energy intensity over time
UV	Ultraviolet

1. INTRODUCTION

1.1. Motivation

Hemoglobin is a protein-based component of red blood cells and transfers oxygen throughout the body (Alam, K.A., 2011). The determination of oxygen saturation provides information on a patient's tissue oxygenation, and hemoglobin is relevant in cases of serious infections, trauma, hemolytic diseases, and favism (a very common disease in Turkey) (Bal, U. et al., 2020). A quick assessment of those parameters is vital, especially in emergencies (Bal, U. et al., 2020). Determination of these values in a quick and non-invasive manner, as soon as the emergency services get involved, and before a clinical examination by a physician, will increase efficiency and decrease response time in treated deadly diseases (Bal, U. et al., 2020).

Tissue oxygenation can be described as a multiple staged process where respiratory and cardiovascular systems cooperate to supply oxygen and eliminate carbon dioxide in the body. Oxygen is mostly transported in a chemical combination with hemoglobin in the red blood cells. Adult blood contains four species of hemoglobin. These are oxyhemoglobin (HbO_2), deoxyhemoglobin (HHb), methemoglobin (HbMet), and carboxyhemoglobin (HbCO).

HbCO has increased the result as the interaction of carbon monoxide (CO) with blood (Kozlova, E. et al., 2020). This hemoglobin cannot bind to oxygen and does not carry oxygen and affects the organisms (Kinoshita, H. et al., 2020), therefore they cause hypoxia (Cantürk, G., 2003). The concentration of HbCO is less than 1-2% in healthy blood. If HbCO levels are higher than 10%, neurological symptoms as dizziness, nausea, headache can be observed (Kinoshita, H. et al., 2020). Some kind of symptoms are observed such as syncope and increases in respiratory and heart rates at an HbCO level of 30-50%.

HbCO may lead to chest pain at concentrations of 1-9% (Kinoshita, H. et al., 2020). Generally, when the HbCO level goes up to 60% and above, mortality occurs (Vural, N., and Kahraman, R., 1994). It is critical to developing quantitative methods for the measurement of the HbCO level in the blood with accuracy for the evaluation of clinical cases due to CO-poisoning in forensic medicine (Kozlova, E. et al., 2020). The diagnosis of CO- poisoning relies on a measurement of blood HbCO via venous or arterial blood gas analysis (Sebbane, M. et al., 2013).

Nitrate poisoning causes HbMet formation. Also, MetHb can be formed through direct or indirect oxidizers that react with hemoglobin (Hb) (Zaouter, C., and Zavorsky, GS., 2012). The heme iron atom is in the ferric state (Fe^{+3}) rather than the normal ferrous (Fe^{+2}) in the HbMet prevents normal oxygen binding to hemoglobin. When HbMet is above 20-30%, neurologic and cardiovascular symptoms (dizziness, headache, anxiety, dyspnea, drowsiness, and seizures) present (Zaouter, C., and Zavorsky, GS., 2012). Methemoglobin can be found in concentrations up to approximately 70%, above which it can be fatal (Reynolds, K.J. et al., 1993). Methemoglobinemia is a rare disease in which methemoglobin increase in the blood. It can cause cyanosis, respiratory failure, and mortality (Hanedan Onan, S. et al., 2007).

Current hemoglobin measurements require an invasive blood draw and blood analysis. This is a time consuming and non-continuous method (Bal, U. et al., 2020). Current commercial oximeters are incapable to measure the oxygen delivery capacity of blood in the presence of carboxyhemoglobin or methemoglobin, or at low total hemoglobin concentration (Urpalainen, K., 2011). Oximeters with a hemoglobin measurement capability offer a noninvasive method that requires contact between the sensor and the skin (Wolf, M., Ferrari, M., and Quaresima, V., 2007; Lin, P. et al., 2009; Scholkmann, F. et al., 2014). These oximeters have drawbacks when measuring child patients with asthma, bronchiolitis, bronchopneumonia, patients with an extremely high risk of mortality, and patients with mental confusion (Bal, U. et al., 2020). In such cases, either measurement is not possible, or the results are not accurate. In addition, if

there is a problem with the patient's blood supply, e.g., a cold finger, measurement with probes will not be possible (Chan, E. D. et al., 2013). Also, if the patient's tissue integrity is impaired, current oximeters will not work. Currently, it is not possible to assess oxygenation in open wounds like diabetic foot ulcers or other chronic wounds (Bal, U. et al., 2020). For all these reasons, it is worth developing and testing a fast non-contact and oximeter (Bal, U. et al., 2020).

A multi-wavelength oximeter will be a noninvasive and continuous method to measure total hemoglobin (tHb), HbO₂, HbCO, and HbMet. Besides, it would increase the accuracy of oxygen saturation measurement.

Noninvasive, continuous, and non-contact measurement can be done using this thesis study. Also, oxygen saturation errors caused by hemoglobin species that are present in the blood can be resolved. Diseases that have similar symptoms with common diseases and diseases that reach a critical level can be monitored without performing a blood test, it is also important for forensic medicine. Hemoglobin measurement is significant in detecting anemia during blood donation, and effective and rapid measurements can be made with this design.

1.2. Related Work

1.2.1. Non-contact measurement of hemoglobin based on near infrared spectroscopy

Hemoglobin is a protein-based component of red blood cells and transfers oxygen throughout the body (Alam, K. A., 2011). The red blood cells of the body contain hemoglobin molecules (Alam, K. A., 2011). Oxygen is transported from the lungs to tissue by hemoglobin and carbon dioxide is transported from the tissues to the lungs in this way. The form of hemoglobin is called oxyhemoglobin

if it is saturated with oxygen molecules, whereas it is called deoxyhemoglobin (or reduced hemoglobin) if it is desaturated with oxygen molecules (Alam, K.A., 2011). HbO_2 has a higher affinity for oxygen than HHb, therefore oxygen is transported through to tissues by binding to HbO_2 , in the lungs. Carbon dioxide is transported with deoxyhemoglobin to the lungs (Alam, K.A. 2011).

Hemoglobin can be in the form of dysfunctional hemoglobin that does not support the transport of oxygen to the tissues. Two common dyshemoglobins such as HbMet and HbCO are introduced here. Current hemoglobin measurements require invasively blood gas analysis. Radiometer ABL-90 Flex CO-oximeter is a multiwavelength optical blood gas analyzer for analyzing arterial blood. A laboratory CO-oximeter or hemoximeter is the standard for measuring the presence of HbCO or HbMet in the blood (Bickler, M. P., and Rhodes, L. J. 2018).

Pulse oximeters use measure tissue light at two wavelengths to estimate arterial Hb saturation, but these pulse oximeters assume the presence of only two light absorbers in the blood: HbO_2 and HHb (Barker, S. J. et al., 2006). If the blood has HbMet and HbCO, they affect the readings of oxygen saturation (SpO_2) (Barker, S. J. et al., 2006). Most of the current commercial oximeters are based on red and near Infrared (NIR) continuous wave (CW) light sources combined with a finger- or ear-lobe probe that is applied to the patients (Bal, U. et al., 2020).

Several oximeters are designed to solve the measurement of low oxygen saturation problem with the presence of HbCO and HbMet. An inexpensive pocket infrared spectrometer and smartphone system (SCiO Pocket Molecular Sensor) is designed to detect HbCO and HbMet in single drops of blood by Consumer Physics Ltd., Israel (Bickler, M. P., and Rhodes, L. J., 2018). Masimo (Irvine, CA) designed a device RAD-57 pulse CO-oximeter that allows noninvasive measurement of blood HbCO through a fingertip sensor has been approved for use in clinical practice (Barker, S. J. et al., 2013). This device uses 8 wavelengths of light and measures more than two species of Hb. In addition, this device estimates HbCO and HbMet in addition to the usual (SpO_2) (Barker, S. J.

et al., 2006) with good sensitivity and specificity. Another pulse oximeter by Masimo is introduced as Radical-7 that used five to 12 wavelengths of light. When SaO_2 is approximately less than 87%, detecting HbCO is still not possible in addition to improved accuracy in volunteer studies and a more robust tolerance for hypoxic oxygen levels (Kulcke, A. et al., 2016). Feiner, J. R., and Bickler, P. E., (2010) presented that this pulse oximeter demonstrated a high level of accuracy for measuring the percent of HbMet up to 14.4%, which did not decrease during hypoxia. Methemoglobinemia does not affect the ability of this device to detect hypoxemia.

Another company (Senspec, Germany) designed a LED-based device, named V-Spec Monitoring System, allowing measurement of oxygen saturation, HbMet, and HbCO, and detection of hypoxemia with probes on the forehead and fingers with a high level of accuracy up to 11% (Kulcke, A. et al., 2016).

These oximeters use contact probes, so they cannot measure oxygenation in open wounds (Bal, U. et al., 2020). CW oximeters measure intensity changes but not phase changes induced by attenuation and scattering in the tissue (Bal, U. et al., 2020). Since the phase is not measured, they must make assumptions regarding the path length the light travels in the tissue. Therefore, most systems measure only relative changes and require calibration (Bal, U. et al., 2020).

1.2.2. Total hemoglobin estimation using artificial intelligence methods

Recent studies on noninvasive solutions for estimating hemoglobin levels use different approaches in feature collection and image analysis techniques. Hb measurement using principal component analysis (PCA) and artificial neural networks (ANNs) from photoplethysmogram (PPG) signal was developed in studies of Lakshmi, M., and Manimegalai, P., (2019). They also applied to generalize linear regression techniques for monitoring the non-invasive measurement of Hb among pregnant women (Lakshmi, M., Manimegalai, P., and

Bhavani, S., 2020). A real-time total hemoglobin monitoring system was developed and Hb was predicted using an algorithm based on partial least square (PLS) as well as backpropagation artificial neural network (BP-ANN) models by extracting features of PPG signals (Liu, H. et al., 2020). Jingze, Y. et al., (2015) constructed a near-infrared spectrophotometric system with InGaAs detector array and Hb was detected non-invasively using methods based on PLS. Kavsaoğlu, A.R., Polat, K., and Hariharan, M., (2015) represented a non-invasive method for the prediction of Hb using PPG signals and different machine learning algorithms. A smartphone camera and white flash is used to measure Hb noninvasively in Wang, E.J. et al., (2017)'s study. Linear regression algorithm calculated hemoglobin value from a video collected from the smartphone camera in this study. Noor, N.B., Anwar, M.S., and Dey, M., (2019) used to image processing method and machine learning techniques such as multivariate linear regression, decision tree, and linear support vector regression to screening Hb level. The images are taken with a smartphone camera. Hasan, M. K. et al., (2018) developed a smartphone-based system that predicts hemoglobin levels using an ANN with processing videos taken from patients' fingertip. Hb value using hematological parameters is estimated with machine learning algorithms: random forest, linear regression, and ANN (El-kenawy, E., 2019), after that the estimated values are used to classify anemia. Ding, H. et al., (2014) represented that a developed spectrophotometric system using LED and photodiode detects Hb levels with the BP-ANN method combined with PCA. A frequency-domain diffuse optics system with five frequency-multiplexed wavelengths was developed and a deep neural network (DNN) algorithm was used to calculate optical properties. A real-time molar concentration of HbO_2 and HHb was provided non-invasively (Zhao, Y. et al., 2018). DePaoli, D. T. et al., (2019) developed a convolutional neural network (CNN) based spectroscopic analysis for multiwavelength retinal oximetry and showed the improved performance in measurement of oxygenation (SO_2) and fractional oxygenation ($\text{SO}_{2\text{fr}}$). Hb is quantified using noninvasive fundus of eye images and deep learning methods in Mitani, A. et al., (2020). The fundus images were used as an input to a deep CNN with Inception-v4 architecture. Türk, Ö., and Özerdem, M. S., (2019) developed

an epilepsy detection system by using scalogram based CNN from electroencephalogram (EEG) signals. Another scalogram based intelligent deep model using electrocardiogram signals was developed for biometrics (Byeon, Y. H., Pan, S. B., and Kwak, K. C., 2019).

1.3. Research Objective

The main objective of this thesis is to measure the total hemoglobin concentration in a non-contact manner and develop a device for determining the HbO₂, HHb, HbCO, and HbMet.

The tasks to achieve this objective are as follows:

- To develop a non-contact measurement device using a frequency domain multiple distance method
- To design the transimpedance amplifier that is suitable for optical systems
- To design an interface for controlling the non-contact measurement device
- To apply the artificial intelligence methods

1.4. Thesis Outline

This thesis includes four chapters organized as follows: Section 1 discusses the introduction, related works, and research objectives. Section 2 proposes a non-contact measurement of absorption and reduced scattering coefficients of optical phantoms and four hemoglobin species. Data is collected from two optical phantoms and 24 healthy volunteers. Then, the frequency domain multi-distance (FDMD) method is employed to develop non-contact measurement. Single-stage and four-layer multi-stage transimpedance amplifiers are designed to amplify the signal. Section 3 explains the applications of regression models to estimate three species of hemoglobin and total hemoglobin and six deep learning architectures to classify the measurements. Section 4 summarized the results of previous sections and gives ideas for future works.

2. THE DETERMINATION OF ABSORPTION AND REDUCED SCATTERING COEFFICIENTS OF OPTICAL PHANTOMS USING A FREQUENCY DOMAIN MULTI DISTANCE METHOD IN A NON-CONTACT MANNER

2.1. Light-Tissue Interaction

The light propagates inside biological tissues as the flow of photons. Photons can experience different processes, such as absorption, scattering, and fluorescence (Figure 2.1.). HbO_2 , HHb and water are the main absorbers of NIR light in blood-perfused tissue. Their absorption spectra are between 300 and 1500 nm (Figure 2.2) (Fantini, S., and Franceschini, M.A., 2002).

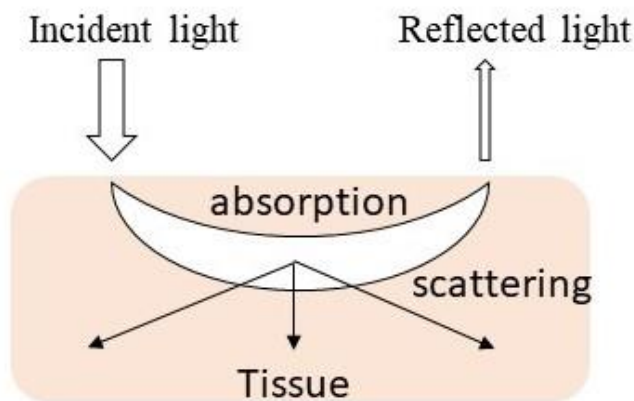


Figure 2.1. The light propagation in a tissue

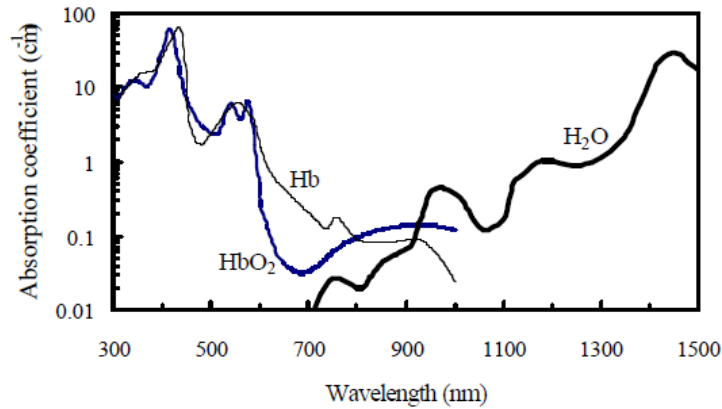


Figure 2.2. Absorption spectra of the three dominant near-infrared chromophores in tissues (Fantini, S., and Franceschini, M.A., 2002).

The absorption of light shows a minimum of 700 to 900 nm, and it is called a “medical spectral window”. The light penetrates deeply into tissues in this window. The depth of optical penetration is limited by hemoglobin absorption at shorter wavelengths and by water absorption at longer wavelengths into tissues (Fantini, S., and Franceschini, M.A., 2002). The absorption coefficient (μ_a) describes the absorption properties of tissue. It refers to the inverse of the average photon path length before absorption. μ_a is typically in the range from 0.02 to 0.30 cm^{-1} in the NIR (Fantini, S., and Franceschini, M.A., 2002).

The size of the scattering particles relative to the wavelength of the light and the refractive index mismatch between the scattering particles and the surrounding medium determines the scattering properties of tissue (Fantini, S., and Franceschini, M.A., 2002). The scattering coefficient (μ_s) is defined as the average photon path length between successive scattering events. The reduced scattering coefficient (μ'_s) is introduced as the inverse of the average distance over which the direction of propagation of a photon is randomized. (μ'_s) is typically in the range from 2 to 20 cm^{-1} in biological tissues (Fantini, S., and Franceschini, M.A., 2002).

2.2. Oximeter Basics and Hemoglobin Measurement

Pulse oximetry is a well-established monitoring oxygen saturation system in medicine (Jubran, A., 1999). Pulse oximeters may lead to a quicker treatment of serious hypoxemia and avoid complications (Jubran, A., 1999). These oximeters may reduce the number of arterial blood gas samples. The oxygenated blood (oxyhemoglobin) and the deoxygenated blood (deoxyhemoglobin) have different absorption spectra (Jubran, A. 1999). Pulse oximetry measures oxygen saturation by illuminating the skin and measuring changes in light absorption of HHb and HbO₂ using red (660 nm) and infrared (940 nm) light wavelengths using the spectrophotometric methodology. The ratio of absorbance is calculated against direct measurements of arterial oxygen saturation (SaO₂) to establish the pulse oximeter's measure of arterial saturation (SpO₂) at these wavelengths (Jubran, A., 2015). In the red region, HbO₂ absorbs less light than HHb, whereas the reverse occurs in the infrared region (Jubran, A., 1999). Intravenous dyes used for diagnostic purposes, low perfusion states (e.g., low cardiac output, and hypothermia), pigmented subjects, in patients with sickle cell anemia, and motion artifacts cause inaccurate readings (Jubran, A., 2015). Pulse oximeters employ only two wavelengths of light, thus, can distinguish only two substances, HHb and HbO₂. Four wavelengths are required to determine the fractional arterial oxygen saturation in the presence of HbCO and HbMet (Jubran, A., 1999). Studies represented that the presence of elevated levels of HbCO and HbMet could affect the accuracy of SpO₂ (the percentage of HbO₂) readings (Jubran A., 2015). The light absorption characteristics of HbCO and HbO₂ are near each other, this causes inaccuracy of traditional two-wavelength pulse oximeter in the presence of HbCO. An elevated HbCO falsely elevates oxygen saturation by an amount less than the HbCO but which can result in an extreme overestimation of HbO₂ (Hess, D. R., 2016). HbMet, body temperature and blood pressure also influence the SpCO (the percentage of HbCO) accuracy (Hess, D. R., 2016). There is crosstalk between SpMet and SpCO measurement in the conventional pulse oximeter with two wavelengths. A falsely elevated SpCO when it displays a correct SpMet (the percentage of HbMet) in the presence of HbMet (Hess, D.

R., 2016). Newer pulse oximetry technology that uses multiple wavelengths of light is available for more than two forms of hemoglobin (Hess, D. R., 2016).

Pulse oximeters must assume that all light absorbances in the arterial blood are caused by HHb and HbO₂. These pulse oximeters calculate and display their values of oxygen saturation, which are estimates of “functional arterial hemoglobin saturation” (Barker, S. J. et al., 2006):

$$SaO_2 = \frac{HbO_2}{HHb + HbO_2} \quad (2.1)$$

Another important definition is the fractional arterial hemoglobin saturation, given by (Barker, S. J. et al., 2006),

$$HbO_2 (\%) = \frac{HbO_2}{HHb + HbO_2 + HbMet + HbCO} = \frac{HbO_2}{tHb} \quad (2.2)$$

The absorbances are in the same region of the spectrum (e.g., HHb and HbMet are spectrally similar in the region of 600 to 700 nm), therefore crosstalk between the detection of multiple Hb can be reduced by the spectroscopic approach (Kulcke, A. et al., 2016). The extinction coefficient can be graphed at various wavelengths as a spectrum and this spectrum is specific for each substance (Figure 2.3) (Alam, K.A., 2011).

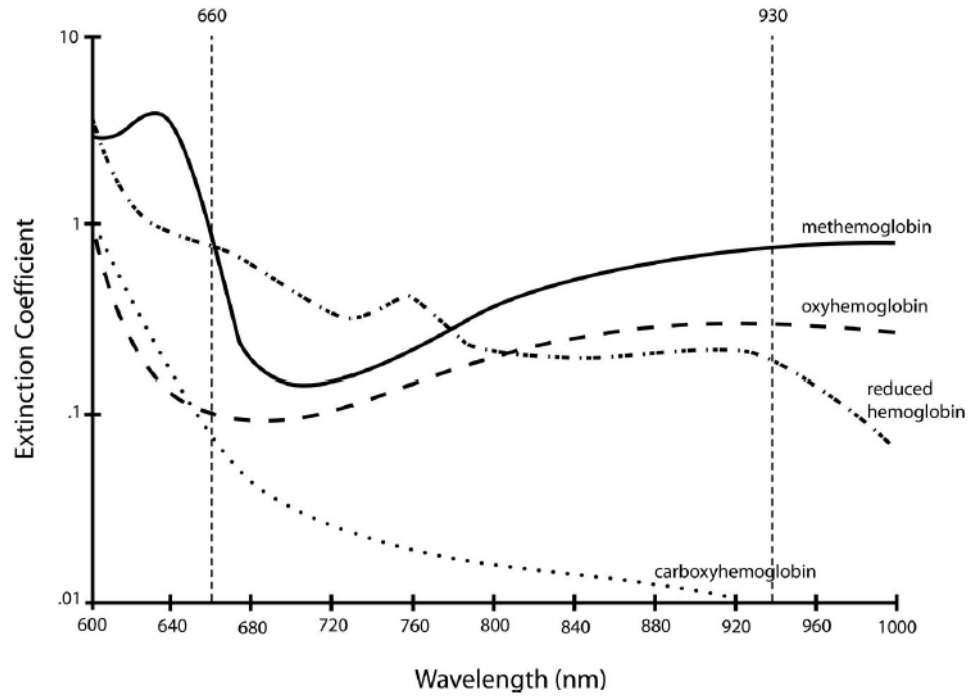


Figure 2.3. Light absorbance versus wavelength for four hemoglobin species. Vertical lines indicate two wavelengths used by conventional pulse oximeters (Barker, S. J. et al., 2006).

The methods to determine the concentration of a light-absorbing substance in a medium using a spectrophotometer are based on Beer Lambert's law (Alam, K.A., 2011).

Beer Lambert law (Figure 2.4) describes light attenuation through a sample of homogeneous non-scattering media. The measurement principle of continuous wave (CW) oximeters is based on this law.

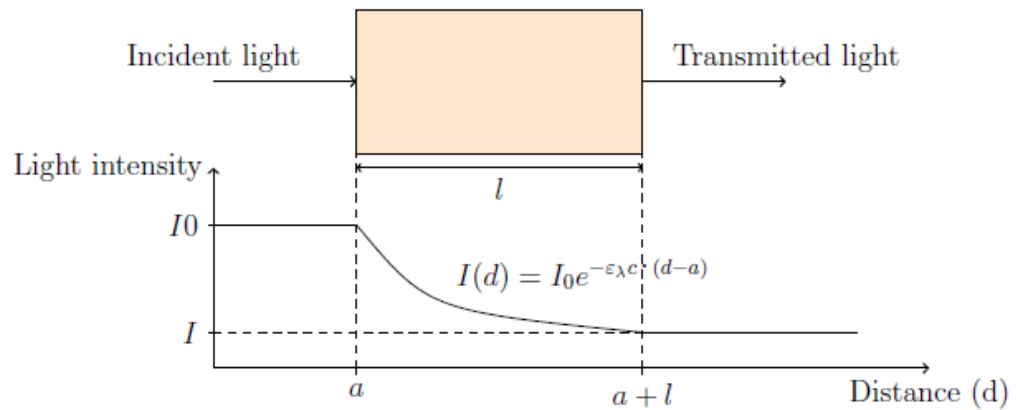


Figure 2.4. Illustration of Beer Lambert law

Mathematically law is expressed as

$$I = I_0 e^{-\varepsilon_\lambda c l} \quad (2.3)$$

where I is the transmitted intensity of the light, I_0 is the incident intensity, ε is the extinction coefficient or absorptivity of the absorbent at wavelength λ , c is the concentration of the absorbent, and l is the optical path-length of the sample. In the case where the sample consists of layers of absorbents, the total intensity of transmitted light is a linear superposition of intensities of each absorbent. The absorbance can be written in the form,

$$A_\lambda = -\ln(T) = -\ln\left(\frac{I}{I_0}\right) = \sum_a \varepsilon_{\lambda,a} c_a l_a \quad (2.4)$$

where represents all tissue components such as arterial blood, venous blood, skin, and bones in the sample, T represents a sample called transmission.

Currently available two-wavelength oximeters use ratio R for the calculation of oxygen saturation via LED and photodetector:

$$R = \frac{dA_{\text{red}}}{dA_{\text{ired}}} = \frac{(\varepsilon_{\text{HbO}_2,\text{red}} c_{\text{HbO}_2,\text{red}} + \varepsilon_{\text{HHb},\text{red}} c_{\text{HHb},\text{red}}) \Delta I}{(\varepsilon_{\text{HbO}_2,\text{ired}} c_{\text{HbO}_2,\text{ired}} + \varepsilon_{\text{HHb},\text{ired}} c_{\text{HHb},\text{ired}}) \Delta I} \quad (2.5)$$

$$dA_\lambda = \frac{I_{\text{max}} - I_{\text{min}}}{I_{\text{min}}} \quad (2.6)$$

After optical path lengths are simplified, the oxygen saturation is calculated by the following equation.

$$SpO_2 \frac{c_{HbO_2}}{c_{HbO_2} + c_{HHb}} = \frac{\epsilon_{HbO_2,red} - R\epsilon_{HHb,red}}{(\epsilon_{HbO_2,ired} - \epsilon_{HHb,red}) - R(\epsilon_{HbO_2,ired} - \epsilon_{HHb,ired})} \quad (2.7)$$

In this equation, the optical path length Δl is calculated to be equal for two different wavelengths. But the optical path of light at different wavelengths is different in tissue and this is not a line. There are some assumptions for optical path length in the continuous wave approach. Continuous-wave oximeters have to do calibration for Beer Lambert law deviation. In addition to calibration, the continuous wave approach does not allow to calculate phase information, it causes relative results. Optical path length can be calculated with frequency and time domain approaches, so absolute values of absorption and scattering coefficients can be found.

2.3. Near Infrared Spectroscopy

There are three basic techniques for near-infrared spectroscopy in the published literature: continuous wave (CW), frequency domain (FD), and time domain (TD) approaches (Figure 2.5 (Scholkmann, F. et al., 2014; Bal, U. et al., 2020)).

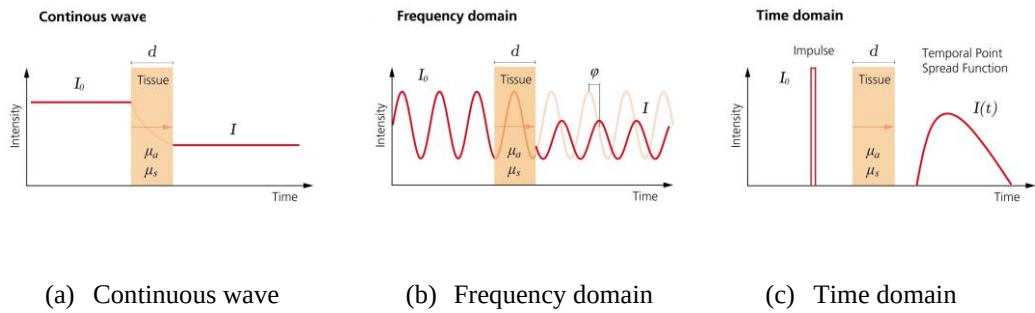


Figure 2.5 NIRS techniques

CW methodology measures the intensity of the light sent into the tissue and the reflected light (Scholkmann, F. et al., 2014; Bal, U. et al., 2020). The optical path of the light is different in tissue and light does not follow a direct path according

to Modified Beer-Lambert Law (Figure 2.6 (Bozkurt A. et al., 2015; Bal, U. et al., 2020)).

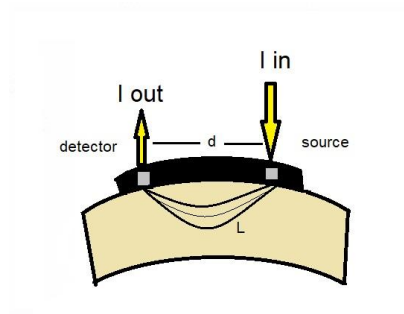


Figure 2.6. Parameters for Modified Beer-Lambert law

The CW methodology must make assumptions regarding the pathlength of the light in tissue (Bal, U. et al., 2020). Therefore, most systems measure only relative changes and require calibration (Bal, U. et al., 2020).

The FD methodology modulates the signal sent to the tissue and measures the intensity and the phase of the emerging light (Bal, U. et al., 2020). Frequency modulated light and the detector-source are separated at fixed distances (Figure 2.7).

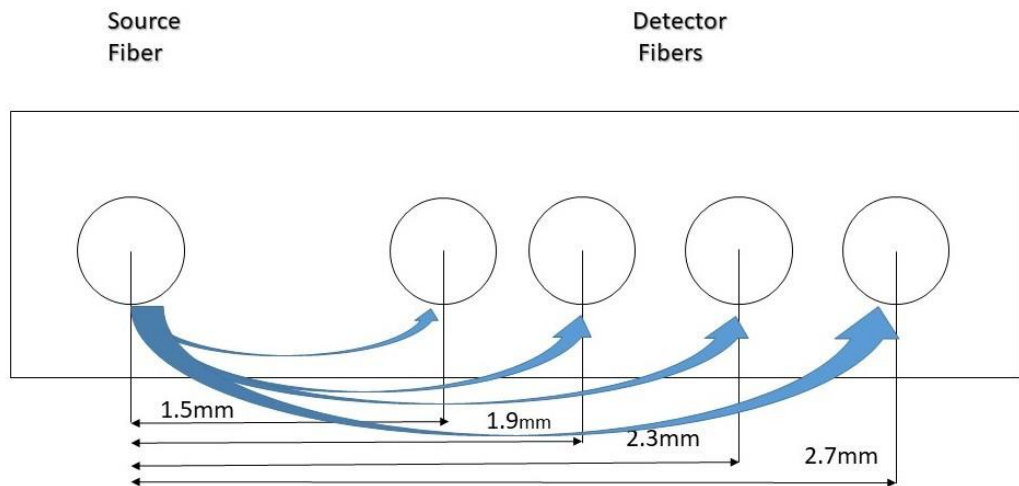


Figure 2.7. Source and detector distances

This approach allows calculation of the absolute absorption and reduced scattering coefficients by measuring intensity modulation and phase changes at known distances (Bal, U. et al., 2020). The TD methodology sends a very short pulse of light and measures the time of arrival of photons emitted from the tissue (Bal, U. et al., 2020). The TD approach is the most complicated and expensive system, although it contains the most information. Since the optical path length can be determined in the frequency domain and time domain approaches, absolute values can be obtained (Bal, U. et al., 2020).

A comparison of different approaches is given in Table 2.1. (Wolf, M., Ferrari M., and Quaresima, V., 2007; Lin, P. et al., 2009; Chan, E. D. et al., 2013; Bal, U. et al., 2020).

Table 2.1. Comparison of different approaches

Properties	Continuous Wave	Frequency Domain	Time Domain
Parameters (HbO ₂) (Hb) (tHb – total hemoglobin)	Yes, relative.	Yes absolute.	Yes, absolute.
Absorption and scattering coefficients, optical path length	No.	Yes.	Yes.
Penetration depth (4 cm source-detector distance)	Low.	Deep.	Low.
Sampling rate (Hz)	Fastest (~100)	Middle (~50)	Slowest (~1)
Signal to noise ratio	Largest	Middle	Least
Price	Low to high	Middle	High
Dimensions	Small	Portable	Big
Commercial applicability	Yes. (Masimo)	Yes. (Oxiplex)	Yes (Hamamatsu)

In the current published literature, the FDMD approach is applied in a contact manner by using multiple light sources at several wavelengths and locations with one detector. However, it is known that due to probe pressure, contact

measurements may distort the hemodynamic responses of the tissue (Lim, L. et al., 2011; Mourant J.R. et al., 2014; Bal, U. et al., 2020). Although new sensors are being developed by Masimo, they are not suitable for open wounds. For instance, some publications show an underestimation of hemoglobin that can reach 20% (Ruderman, S. et al., 2010; Bal, U. et al., 2020). In addition, contact probes may increase the risk of infections and deformation of the soft tissues (Li, T. et al., 2020). Li reported a novel non-contact, diffuse correlation spectroscopy flow oximeter for simultaneous quantification of relative changes in oxygenation. Monte Carlo simulations and phantom experiments revealed that the angle of the arm resulted in approximately a -20% change non-contact measurements in of oxygenation (Li, T. et al., 2020).

The most important step for the determination of hemoglobin concentration is the measurement of the absorption and reduced scattering coefficients. There are several methods to determine the absorption and reduced scattering coefficients. In the published literature, the inverse adding doubling technique – typically with an integrating sphere - or Monte Carlo simulation are mostly used to measure those properties (Dimofte, A., Finlay, J. C., and Zhu, T. C., 2005; Akarçay, G.H. et al., 2012; Hlavac, M., 2013; Spinelli, L. et al., 2014; Bal, U. et al., 2020). These methods are available for determining the optical properties but not four species of hemoglobin because of their set up (Angelo, J. P. et al., 2015; Chen, W. et al., 2017; Kono, T., and Yamada, J., 2019). There are also some studies on the estimation of the absorption and reduced scattering coefficients by using near-infrared frequency-domain, time-domain, and continuous wave measurements using a contact method (Fishkin, J. B. et al., 1995; Tahir, K., and Dainty, C., 2005; Xu, H. and Patterson, M.S., 2006; Zhang, X., and Webb, A., 2013; Bal, U. et al., 2020). A study has shown that the brain optical absorption could be retrieved with an error between 8 to 24% in newborns and infants, while the error increased to 19 to 44% in adults' overall source-detector distances by using the FDMD technique with a contact method (Dehaes, M. et al., 2011; Bal, U. et al., 2020).

2.4. Frequency Domain Multi Distance

For this study, the frequency-domain multi-distance approach has been extended with non-contact measurements. In frequency-domain multi-distance spectroscopy, light is modulated at a single frequency and the backscattered light is measured at different source-detector distances (Spichtig, S., Wolf, M. P. and Rudin, M., 2010; Bal, U. et al., 2020). Radiated energy in a highly scattering medium with intensity U decreases exponentially as a function of the distance from the source. The rate of energy intensity depends on the optical properties of the medium (Bal, U. et al., 2020).

Light is modulated sinusoidally. The change of energy intensity with respect to time is given by:

$$U(t) = U_{AC}(2\pi ft + \phi_t) + U_{DC} \quad (2.8)$$

where U_{DC} is the mean intensity of the backscattered light, U_{AC} the modulation amplitude and ϕ_t the phase shift between the emitted and detected light. The solution of this equation for a semi-infinite medium supposed by Fantini is given below (Fantini, S., Franceschini, M. A., and Gratton, E., 1994; Bal, U. et al., 2020). The change in modulated light intensity with source-detector distance r is given by:

$$\ln(R_{dc}r^2) = rS_{dc}(\mu_a, \mu'_s) + I'_{dc}(D, K_{dc}) \quad (2.9)$$

$$R_\phi = rS_\phi(\mu_a, \mu'_s, \omega, \nu) + I'_\phi(K_\phi) \quad (2.10)$$

$$\ln(R_{ac}r^2) = rS_{ac}(\mu_a, \mu'_s, \omega, \nu) + I'_{dc}(D, K_{dc}) \quad (2.11)$$

where R_{dc} is the mean of the measured intensity, R_{ac} is the modulation amplitude and ϕ is the phase shift of the modulated light. The terms μ_a and μ'_s are the

absorption and reduced scattering coefficients, respectively.

$$S_{dc} = -\left(\frac{\mu_a}{D}\right)^{1/2} \quad (2.12)$$

$$S_{\phi} = \left(\frac{\mu_a}{2D}\right)^{1/2} \left\{ \left[1 + \left(\frac{\omega}{v\mu_a} \right)^2 \right]^{1/2} - 1 \right\} \quad (2.13)$$

$$S_{ac} = \left(\frac{\mu_a}{2D}\right)^{1/2} \left\{ \left[1 + \left(\frac{\omega}{v\mu_a} \right)^2 \right]^{1/2} + 1 \right\} \quad (2.14)$$

and where v is the speed of light in medium, ω is the modulation frequency and D is the diffusion coefficient:

$$D = \frac{1}{3\mu_a + 3\mu'_s} \cong \frac{1}{3\mu'_s} \quad (2.15)$$

and S_{dc} , S_{ac} , and R are the slopes of $\ln(R_{dc}r^2)$, $\ln(R_{ac}r^2)$, R_{ϕ} with respect to r , respectively. Finally, μ_a and μ'_s can be calculated by using equations four above.

Once absorption coefficients are determined for four wavelengths, they can be used to quantify hemoglobin using below equation (Spichtig, S., Wolf, M. P. and Rudin, M., 2010; Bal, U. et al., 2020)):

$$\mu_a^{\lambda} = \epsilon_{HbO_2}^{\lambda} c_{HbO_2} + \epsilon_{HHb}^{\lambda} c_{HHb} + \epsilon_{HbCO}^{\lambda} c_{HbCO} + \epsilon_{HbMet}^{\lambda} c_{HbMet} \quad (2.16)$$

and Table 2.2 (Zijlstra, W. G., Buursma, A., and Meeuwse-van der Roest, W.P., 1991) given below:

Table 2.2. Millimolar absorptivity of hemoglobin species

Wavelength (nm)	HbO ₂ (L.cm ⁻¹ /mmol)	HHb (L.cm ⁻¹ /mmol)	HbCO (L.cm ⁻¹ /mmol)	HbMet (L.cm ⁻¹ /mmol)
658	0.08	0.81	0.06	0.81
705	0.09	0.44	0.02	0.2
785	0.17	0.29	0.01	0.31
833	0.25	0.19	0.01	0.51

2.5. Wavelength Selection

Light can propagate deeply into biological tissue in the optical window (650 to 900 nm), depending on the medium (Scholkmann, F. et al., 2014). The first demonstration of the spectroscopic determination of HbO₂ and HHb in human tissue used two wavelengths, one in the red and the other in the near-infrared region (Bal, U. et al., 2020). The wavelength range from 600 to 700 nm is used for the measurement of hemoglobin in the earlobe or fingertip in this oximeter (Bal, U. et al., 2020). The light within the near-infrared region (around 800 nm) is suitable for non-invasive measurement of the brain (Bal, U. et al., 2020). A large difference in the absorption coefficients between two wavelengths results in a more sensitive and precise measurement. (Yamashita Y., Maki, A., and Koizumi, H., 2011).

The selection of an optimal wavelength is important for minimizing cross-talk and the influence of noise in calculating the chromophore concentration (Correia, T. M., Gibson, A. P. and Hebden, J.C., 2010; Bal, U. et al., 2020). The wavelengths are critical for the number of chromophores to be determined (Correia, T. M., Gibson, A. P. and Hebden, J.C., 2010). The optimal wavelength also depends on the optical properties in the measurement area that affect the strength of the attenuation data (Sato, H. et al., 2003; Bal, U. et al., 2020). Correia, T. M., Gibson, A. P. and Hebden, J.C., (2010) revealed that one

wavelength should be in the range from 650 to 750 nm and the other one is greater than 820 nm. The optimal values for distributing three wavelengths are 680 ± 5 , 725 ± 10 , and 876 ± 12 nm, and for four wavelengths these values are 685 ± 7 , 719 ± 8 , 731 ± 8 , and 873 ± 9 nm. The wavelength of 692 nm and 830 nm provided the highest SNR according to Sato, H. et al., (2003). An analysis by Correia, T. M., Gibson, A. P. and Hebden, J.C., (2010) revealed that the optimum wavelength pair is 704 ± 7 and 887 ± 12 nm. Another approach for optimal wavelength selection was presented by Arifler, D. et al., (2015) for three wavelengths at 785, 833, and 885 nm, and for four wavelengths at 785, 809, 849 and 889 nm. Increasing the number of wavelengths reduces mean errors.

Four different wavelengths (658 nm, 705 nm, 785 nm, and 833 nm) were chosen based on the absorption spectrum of the hemoglobin in this thesis (Bal, U. et al., 2020).

2.6. Materials

In this section, the components of the proposed design given in Bal, U. et al., (2020) were explained. The design is built on an optical breadboard. The setup is similar to Şahin, T., (2003) but designed to measure in a non-contact manner. The laser diode driver (LDX-3220, Newport), three RF switches (PE42020, Peregrine), four Photomultiplier Tube (PMT) modules (H9305-13, Hamamatsu), and a function generator (DG4162, RIGOL) are controlled by a data acquisition card (DAQ, USB-6343, National Instruments) combined with LabVIEW software installed on the computer. The laser diodes were driven by a constant DC source and mixed through a Bias-Tee (ZX85-12G-S+, Mini-Circuits) with the output of an RF signal generator. An RF switch sequentially selected between the four laser diodes (658, 705, 785, and 833 nm, Thorlabs). The output of the four laser diodes was collimated and redirected with dichroic mirrors onto a single fiber collimation package. Four laser diodes with different wavelengths can be modulated up to 100 MHz by using our laser diode driver and RF signal generator. The wavelengths were chosen to match the absorption spectrum of

hemoglobin species. A fiber optic probe was used to guide the light to an imaging system for collection and illumination (FiberTech Optica). The fiber probe consisted of an illumination fiber and several collection fibers. Several collection fibers were at distances of 1.5 mm, 1.9 mm, 2.3 mm, and 2.7 mm, respectively. Re-emitted light from the tissue was imaged to the input of the fiberoptic probe with a camera objective lens (MVL75M1 - 75 mm, Thorlabs). Six source-detector separations were created that after magnification through a camera lens, corresponded to distances of between 5 and 20 mm on the tissue. Each source-detector separation was measured on individual photomultiplier tubes (PMTs). The shortest distances were not used for this study. Initially, the illumination fiber at the center of the fiber optic probe was used to illuminate the tissue. After experiments, it was decided to separate collection and illumination paths with a second fiber probe using a single illumination fiber. The single camera lens was replaced with two objective lenses (Nikkor AF 50mm f/1.4, Nikon) to provide a separate path for illumination and collection of the signals. The alignment of the two systems was accomplished by ensuring that the image from the illumination fiber in the collection of fiber optic cable overlaid the illumination spot in the illumination fiber bundle.

Light from four detector locations was guided by a fiber bundle to four photomultiplier tubes (PMTs). Custom transimpedance amplifiers (TIAs) designed using OPA657 (Texas Inst.) operational amplifiers converted the current output to voltage, which was then further amplified by an RF amplifier (ZFL-500LN+, Mini Circuits). Frequency modulators mixed the modulated signal to a lower frequency that was passed through low pass filters and recorded through analog inputs of the USB-DAQ board.

Each components' properties were briefly explained in the following sections.

2.6.1. Optical components

Laser diodes, dichroic mirrors, collimation lens, fiber probes, photomultiplier tubes, and camera lens are used as optical components in this design.

Laser diode is used as a light source. Laser diode has fast response time, and they can modulate at frequencies up to the GHz range (Fantini, S., and Franceschini, M.A., 2002). Four laser diodes with different wavelengths can be modulated up to 15, 20, and 50 MHz by using our laser diode driver and RF signal generator (Bal, U. et al., 2020). RF switches are used for sequential drive. Four wavelengths (658 nm, 705 nm, 785 nm, and 833 nm, Thorlabs) are chosen for measuring hemoglobin species. The properties of laser diodes are given below (Figure 2.8).



Figure 2.8. Laser diode

Table 2.3. Driving current of laser diodes

Type	Wavelength (nm)	Power	Typical/Max Drive Current
L658P040	658	40	75 mA/110 mA
HL7001MG	705	40	75 mA/110 mA
L785P090	785	90	120 mA/160 mA
HL833MG	830	50	75 mA/100 mA

Laser diodes are driven with 30 and 35 mA using a laser diode driver. The laser diode driver is used for driving laser diodes as a constant DC source (Table 2.3.).

It is controlled from the computer by a GPIB card. The GPIB card makes it possible for the user to change the outputs of these devices, by the LabVIEW software control program. The laser diodes' signals are modulated by 15 MHz, 20 MHz, and 50 MHz AC from a function generator. This instrument is also controlled by GPIB.

Dichroic mirrors are a kind of filter that separates light by transmitting and reflecting light as a function of wavelength. These mirrors have a transmission and reflection band that is divided by a cut-on wavelength. It means the dichroic mirror is highly reflective below the cut-on wavelength and highly transmissive above it.

Dichroic mirrors (FF685, FF757, and FF801, Semrock) are used to adjust for different wavelength light sources in this thesis. The transmission and reflection graphics of FF685-Di02 are given below (Figure 2.9 and Figure 2.10).

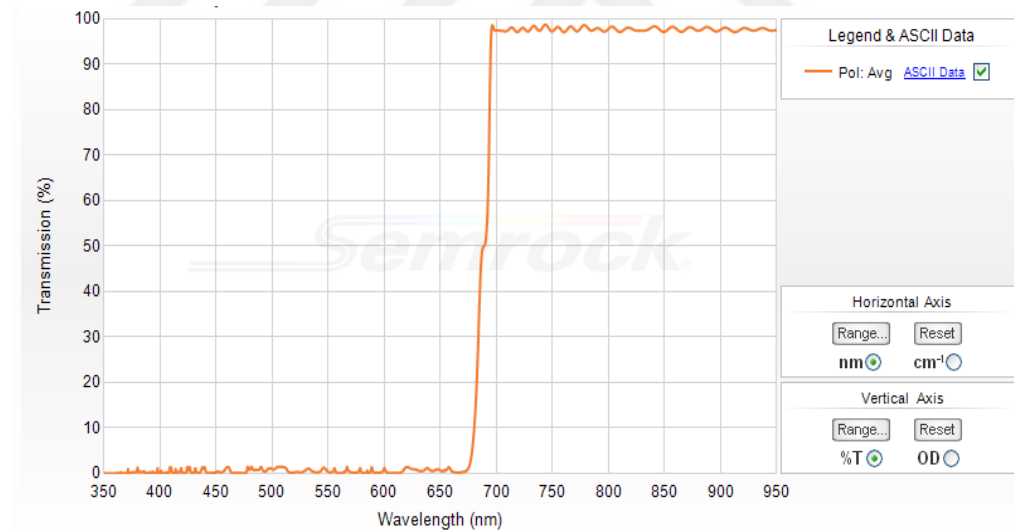


Figure 2.9. Transmission versus wavelength

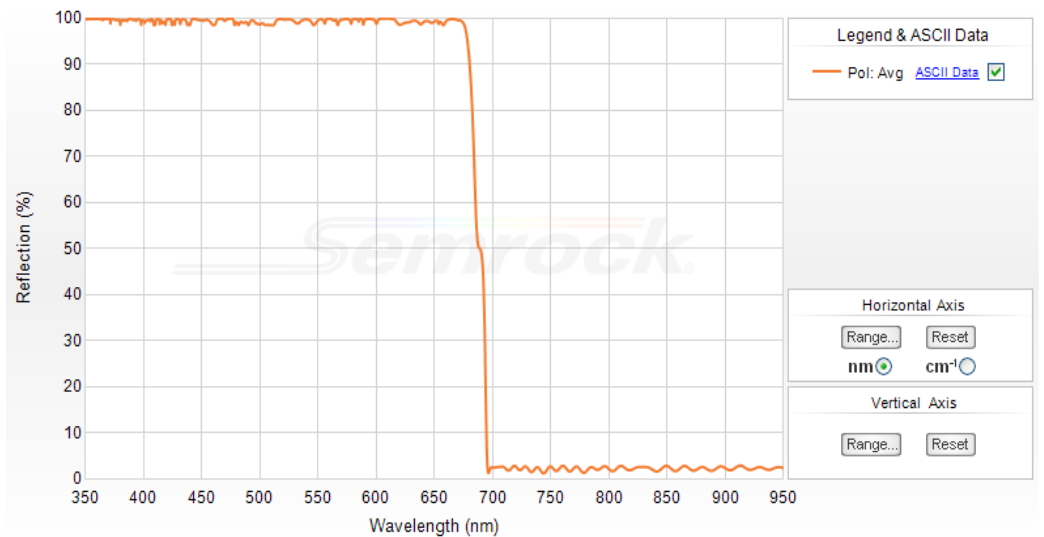


Figure 2.10. Reflectance versus wavelength

The schematic of the working mechanism of our laser diodes and dichroic mirrors are given below (Figure 2.11).

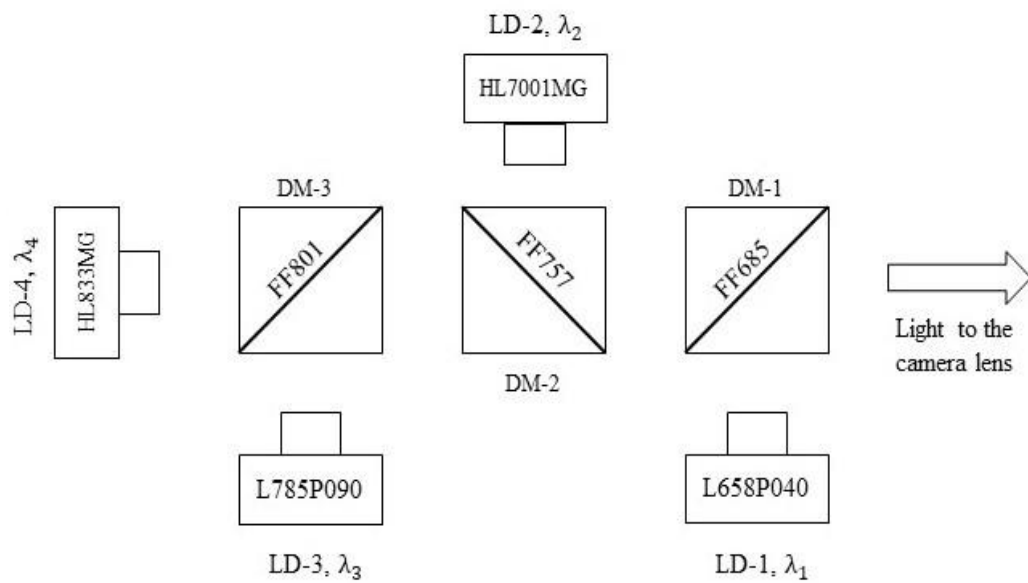


Figure 2.11. Dichroic mirrors

The implemented design of laser diodes and dichroic mirrors are given below (Figure 2.12).

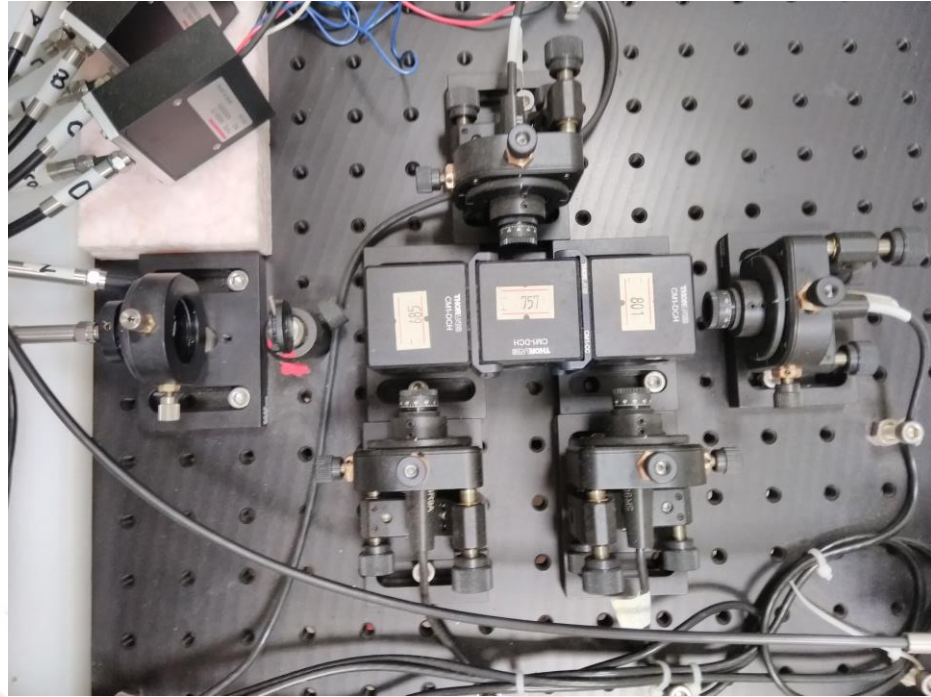


Figure 2.12. Set up for laser diode and dichroic mirrors

A fiber optic probe (Figure 2.13) is designed to guide the light to an imaging system for collection and illumination. The center of this fiber optic probe was used to illuminate the laser diodes' light in the first trials. Several probes at A, B, C, and D were used to collect the light. After several experiments, the center fiber was canceled, and a newer single fiber was used to illuminate the light.

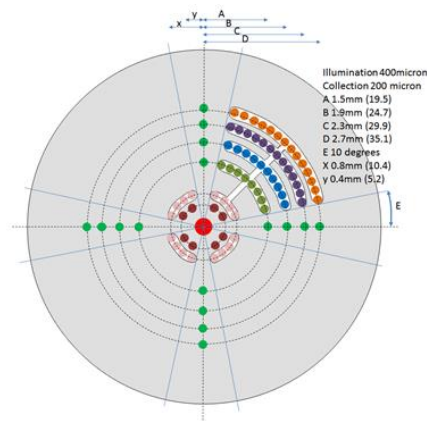


Figure 2.13. The structure of fiber probe

PMT is used as a light detector. Light from four detector locations was guided by a fiber bundle to four PMTs (Figure 2.14) (Hamamatsu H9305-13 PMT). This

PMT has a wide spectral response between 185 nm and 900 nm. This detector has 1.4 ns rise time and the slower rise time provides the smaller bandwidth. The inputs of PMTs are the carrier 15.001 MHz (20.001 MHz or 50.001 MHz) signal and the detection fiber with light modulated at 15 MHz (20 MHz or 50 MHz). The gain of the PMT is controlled with a DC signal of 0.25 - 1.8 V from the PMT gain driver. The voltage is generated at the DAQ card by software control.

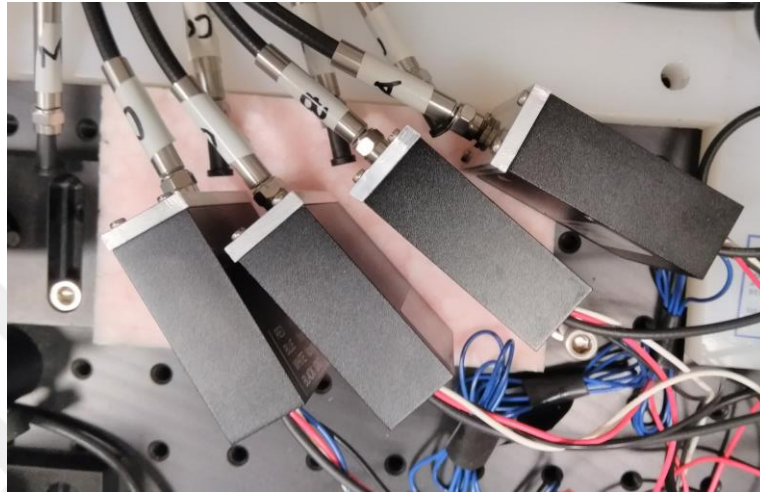


Figure 2.14. The implementation of PMT's

Camera lenses are used to collect re-emitted light from the tissue. First, a single camera objective lens with a focal length is 75 mm. The illumination fiber at the center of the fiber probe was used to illuminate the tissue. However, back reflections of the camera lens from the center of the fiber optic probe caused an unexpected light distribution. The intensity and phase of the reflected light with respect to distance should decrease but this did not happen as expected (Bal, U. et al., 2020). It was decided to separate collection and illumination paths with a second fiber probe using a single illumination fiber.

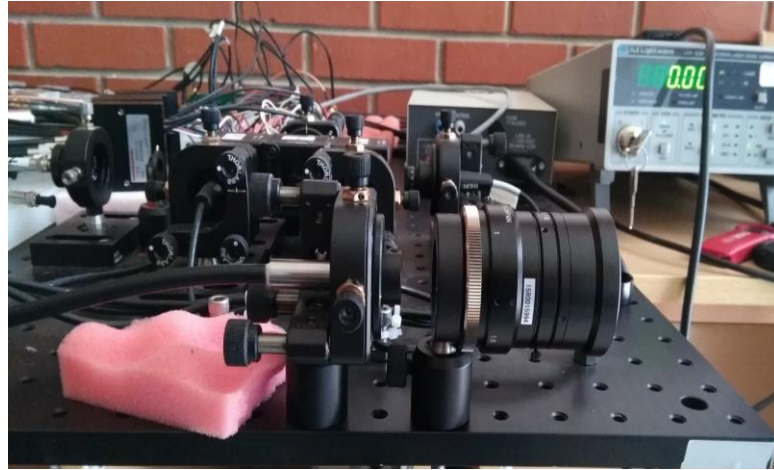


Figure 2.15. The implementation of a single camera

The single camera lens (Figure 2.15) was replaced with two objective lenses (Nikkor AF 50mm f/1.4, Nikon) to provide a separate path for illumination and collection of the signals (Bal, U. et al., 2020). The alignment of the two systems was accomplished by ensuring that the image from the illumination fiber in the collection of fiber optic cable overlayed the illumination spot in the illumination fiber bundle (Bal, U. et al., 2020). Two fiber optic probes for illumination and collection are imaged with camera objective lenses onto the tissue. The illumination channel is aligned with the center of the collection fiber probe (Figure 2.16).

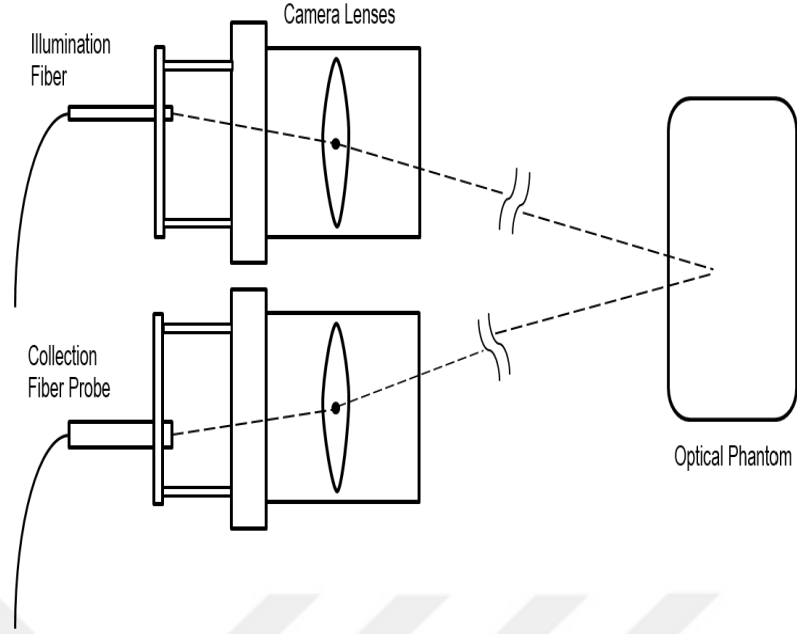


Figure 2.16. Two fiber optic probes for illumination and collection

All experiments were performed at 45 cm (Figure 2.17) (Bal, U. et al., 2020). Therefore the source-detector distances after magnification through the camera lens, corresponded to distances from 13 to 24 mm of tissue. The magnification factor is 9.

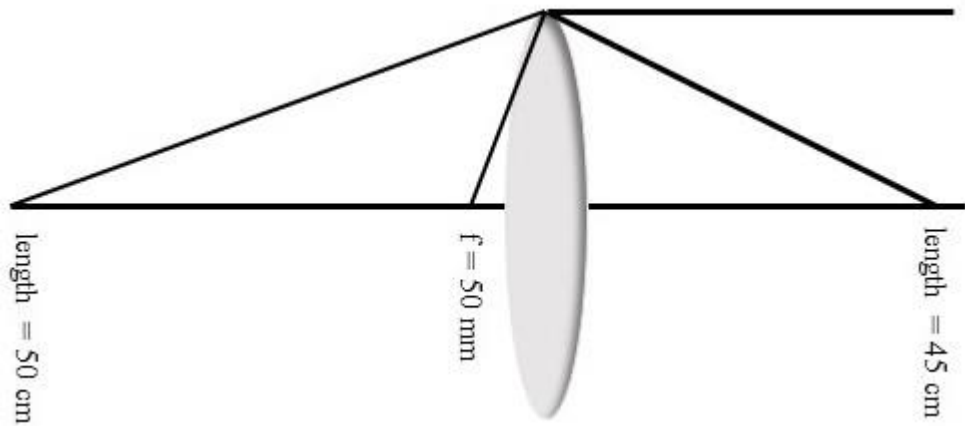


Figure 2.17. Light path from lens

The implementation of double-camera lens is given below (Figure 2.18).

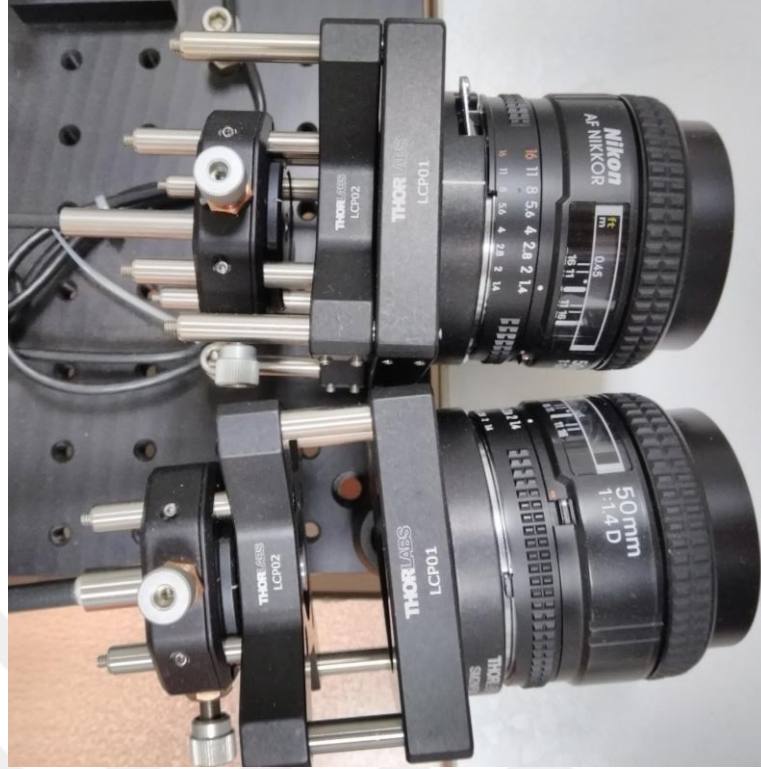


Figure 2.18. The implementation of double-camera lens

2.6.2. Electronic components

RF switch, bias-tee, frequency mixers, low pass filters, RF amplifiers, and transimpedance amplifiers are used as electronic components in this thesis.

Three RF switches (PE42020, Peregrine) are used to driving laser diodes sequentially. The RF switch sequentially selected between the four laser diodes. This RF switch operates from zero Hz to 8 GHz with integrated RF, analog, and digital functions. It can accommodate up to $\pm 10\text{V}$ input DC voltage on the RF ports. The positive supply voltage is 11-15 V and -3.8-3.9 mA. It is chosen as 0 12V in this thesis.

LS (Logic select), CTRL (digital control logic input), LZ (high impedance mode) pins are controlled from DAQ to switch the laser diodes. RF1 refers to RF port 1,

RF2 refers to RF port 2 and RFC refers to RF common. The control logic truth table is given below (Table 2.4).

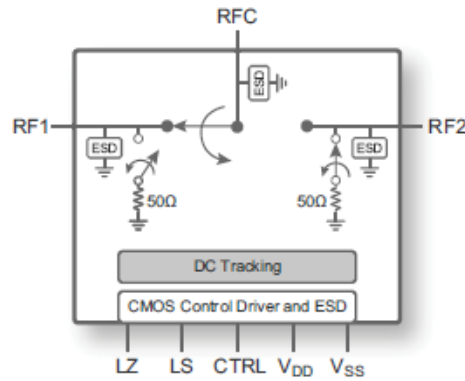


Figure 2.19. The functional diagram of RF switch

Table 2.4. The truth table for control the RF switch

LS	CTRL	LZ	RFC – RF1	RFC - RF2
0	0	0	OFF	ON
0	0	1	OFF	ON
0	1	0	ON	OFF
0	1	1	ON	OFF
1	0	0	ON	OFF
1	0	1	ON	OFF
1	1	0	OFF	ON
1	1	1	OFF	ON

The state of control pins determines the outputs. Using the software, the inputs are adjusted to drive the laser diodes sequentially. The first schematic (Figure 2.20) represents the working schematic of the RF switch for wavelength 658 nm and the control pins must be in true, false, and false, respectively. The second and third RF switches are not given here. The second schematic (Figure 2.21) represents the working schematic of the RF switch for wavelength 705 nm and the control pins must be in false, false, and false, respectively. The third RF

switch is not given here. The third schematic (Figure 2.22) represents the working schematic of the RF switch for wavelength 785 nm and the control pins must be in false, true, and true, respectively. The fourth schematic (Figure 2.23) represents the working schematic of the RF switch for wavelength 833 nm and the control pins must be in false, true, and false, respectively.

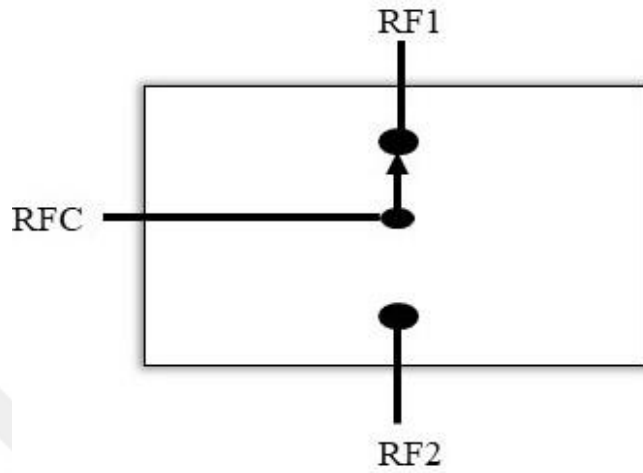


Figure 2.20. RF switch position for 658 nm

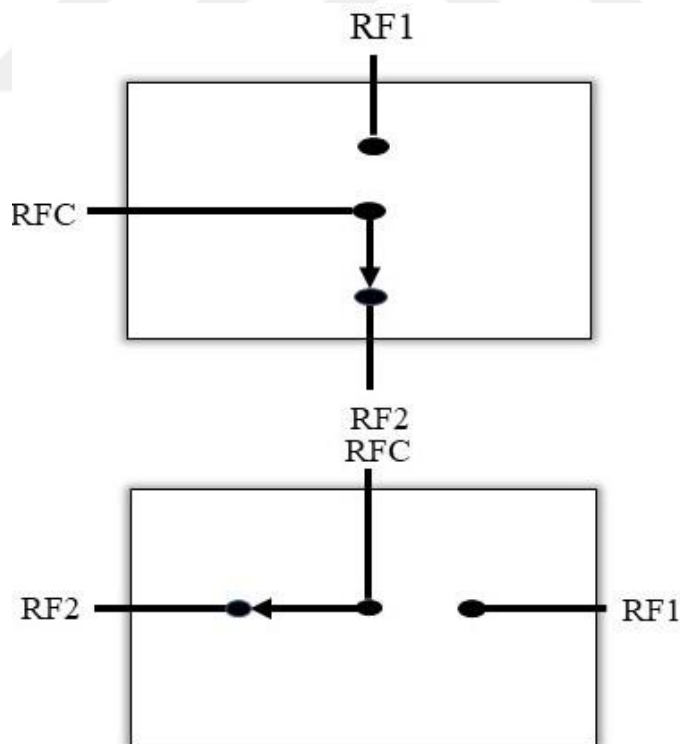


Figure 2.21. RF switch position for 705 nm

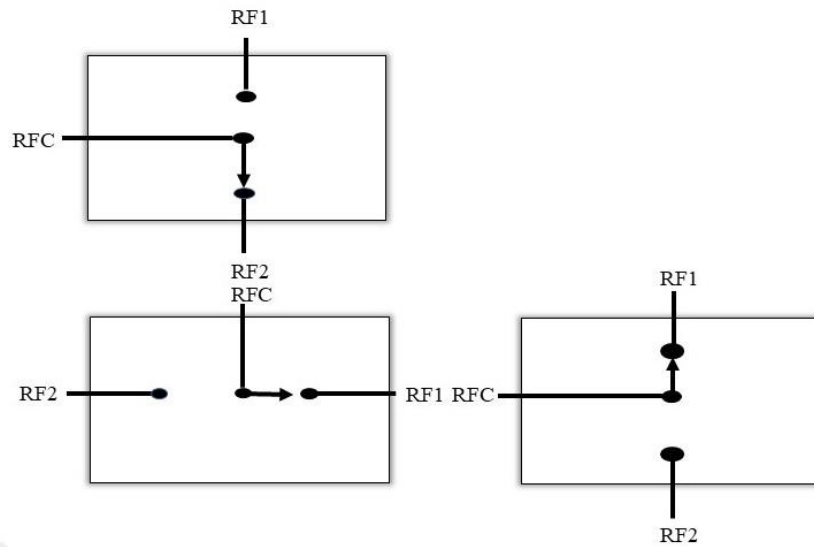


Figure 2.22. RF switch position for 785 nm

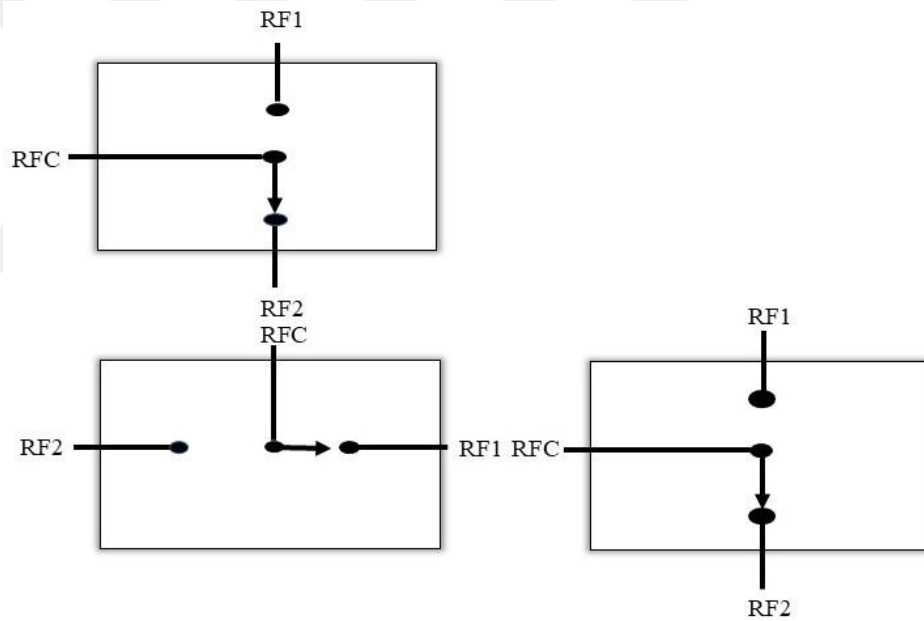


Figure 2.23. RF switch position for 833 nm

Bias-Tee is a 3-port device which allow DC bias to be added to RF signal line without affecting the RF signal. ZX85-12G-S+ is used for adding DC source from laser diode driver and AC source from function generator. The electrical schematic is given as below (Figure 2.24) (<https://www.minicircuits.com/>):

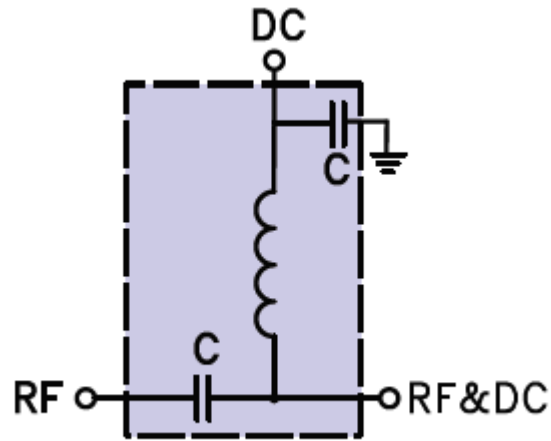


Figure 2.24. The structure of Bias-Tee

The implementation of RF switches and bias-T is given below (Figure 2.25).

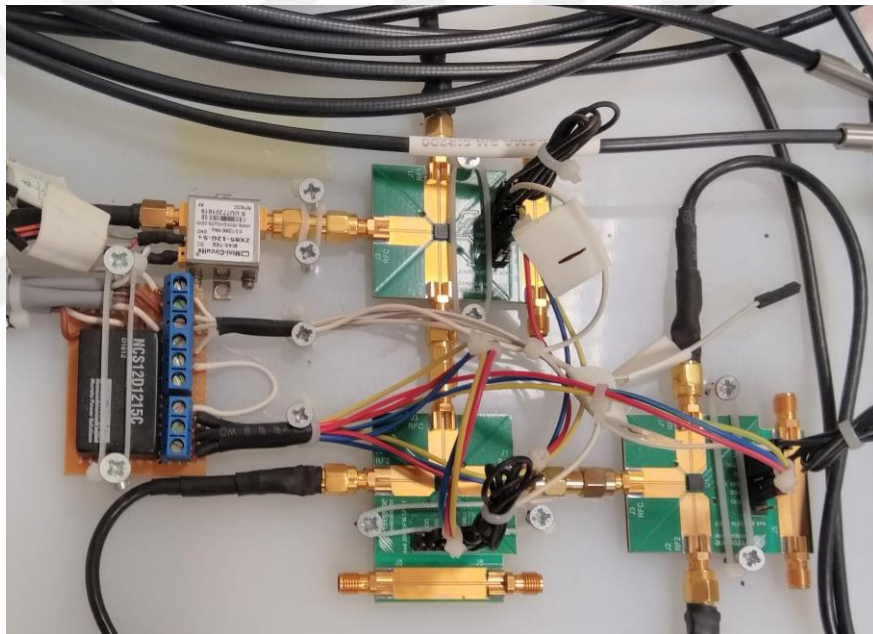


Figure 2.25. The implementation of RF switches and Bias-Tee

Radiofrequency (RF) amplifier (ZFL-500LN+, Mini Circuits) with frequency 0.1 to 500 MHz is used to amplify the output of the TIAs. Frequency mixers (ZFM-3-S+, Mini Circuits) are a nonlinear circuit that takes two applied signals and creates signals equal to the sum and difference of the originating frequencies. This circuit is used to mix the modulated signal to a lower frequency that was

passed through low pass filter in this thesis (Bal, U. et al., 2020). The electrical schematic is given as below (Figure 2.26) (<https://www.minicircuits.com/>):

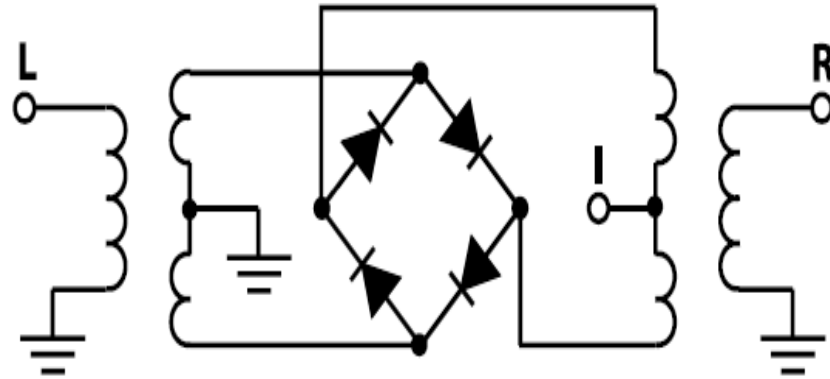


Figure 2.26. The structure of the RF amplifier

The amplified signal from the RF amplifier fed to R input and the signal from the function generator fed to L input. The output of the mixer, I, fed to a low pass filter. It mixes two high-frequency signals 15 MHz (also 20 and 50 MHz) and 15.001 (20.001 and 50.001 MHz). The product is used as the reference signal and is fed to the DAQ card. The reference signal is used to compare the amplitude and phase, and to extract the information from them.

Low pass filters filter unwanted signals and noise with 1 dB passband rejection. The frequency response of the used filter is given below (Figure 2.27) (<https://www.thorlabs.com/>).

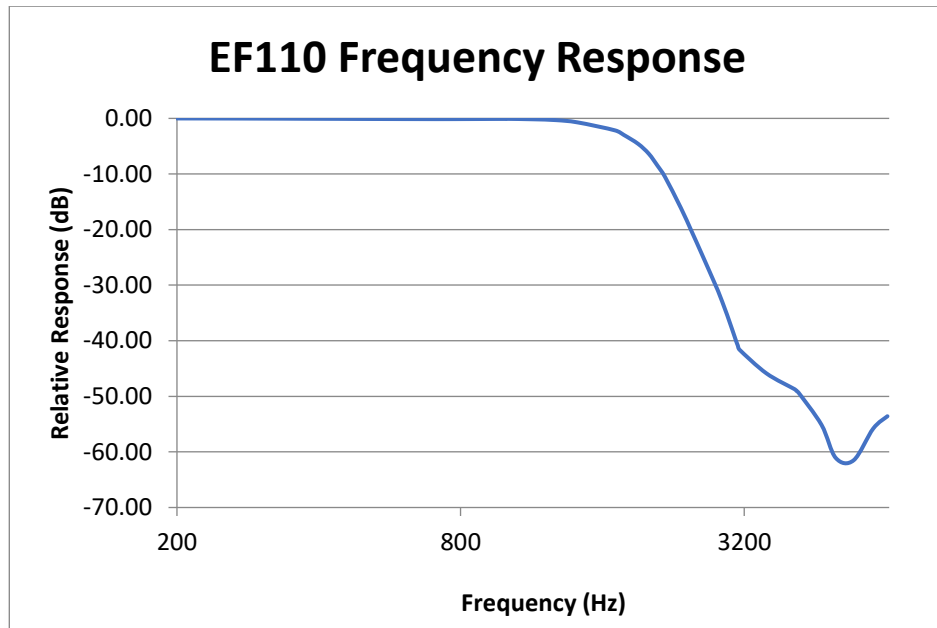


Figure 2.27. The frequency response of LPF

Transimpedance amplifiers is a current to voltage amplifier. These devices convert the current signal into an amplified voltage signal for data processing. Different operational amplifiers such as LT1226, OPA857, LTC6268-69, and OPA657 are tried in designing TIA because of their work with low signals and high frequencies.

Single-stage and multi-stage amplifiers are designed using OPA657. The bandwidth decreased with a three-stage amplifier design. The single-stage amplifier has more advantages than two-stage amplifiers. A single-stage amplifier is combined with an RF amplifier. Different resistor values are tried. 10 k Ω is used as a final design (Figure 2.28). OPA657 amplifier is used for amplifying the signal from PMT. It converts the PMT current signal to a voltage signal.

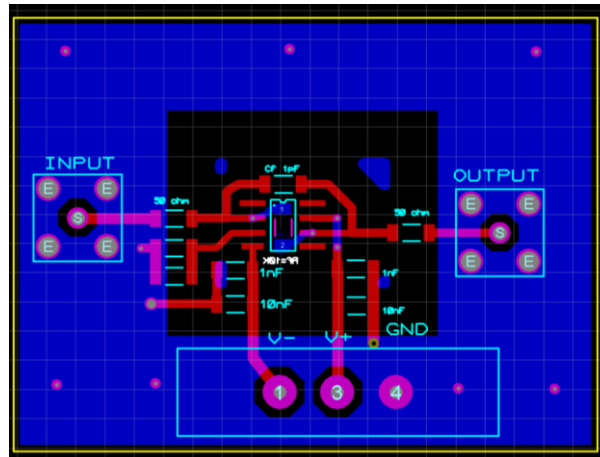


Figure 2.28. PCB schematic of custom single-stage TIA

Unwanted oscillations and very low signals are observed in our experiments above 15 MHz. The first results are taken at 15 MHz.

TIA is critical to amplifying the output signal at the output of the PMT signal. A four-layer multi-stage TIA is designed to decrease noise and increase bandwidth. The four-layer multi-stage TIA (Figure 2.29) includes an operational amplifier based current to voltage converter part and MMIC part.

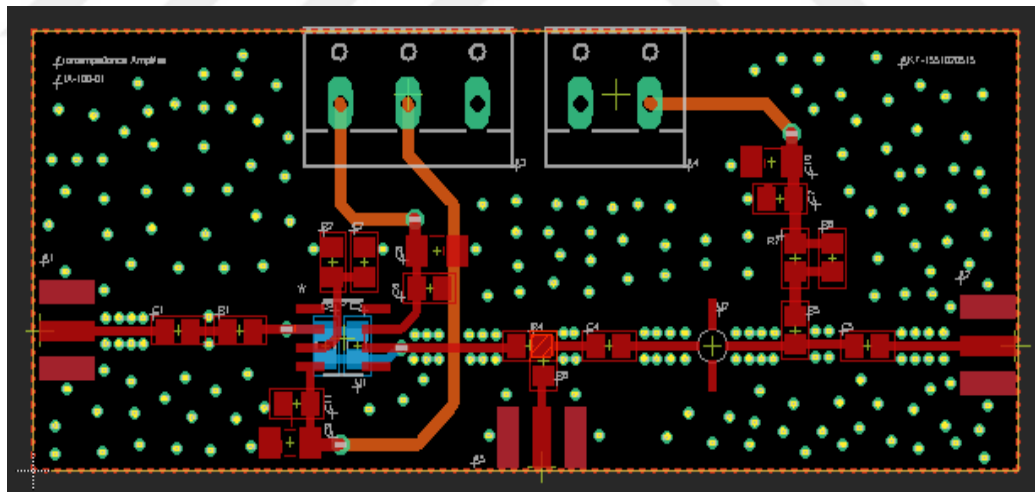


Figure 2.29. PCB schematic of custom four-layer multi-stage TIA

2.6.3. Software

Data are taken and processed from the proposed non-contact design by NI USB 6343 DAQ and, all pieces of equipment are controlled via the computer. The NI USB 6343 offers 32 analog output (16-bit, 500 kS/s), analog output (900 kS/s), 48 digital input/output, and four 32-bit counters/timers for PWM. DAQ creates on/off signals and analog signals with low power-low frequency and reads these signals. DAQ is controlled via software that is developed on NI LabVIEW. The developed software has six different sections such as main, function generator, laser diode driver, analog input, digital output, and analog output. The main section includes a real-time representation of data, processing, and recording the data (Figure 2.30).

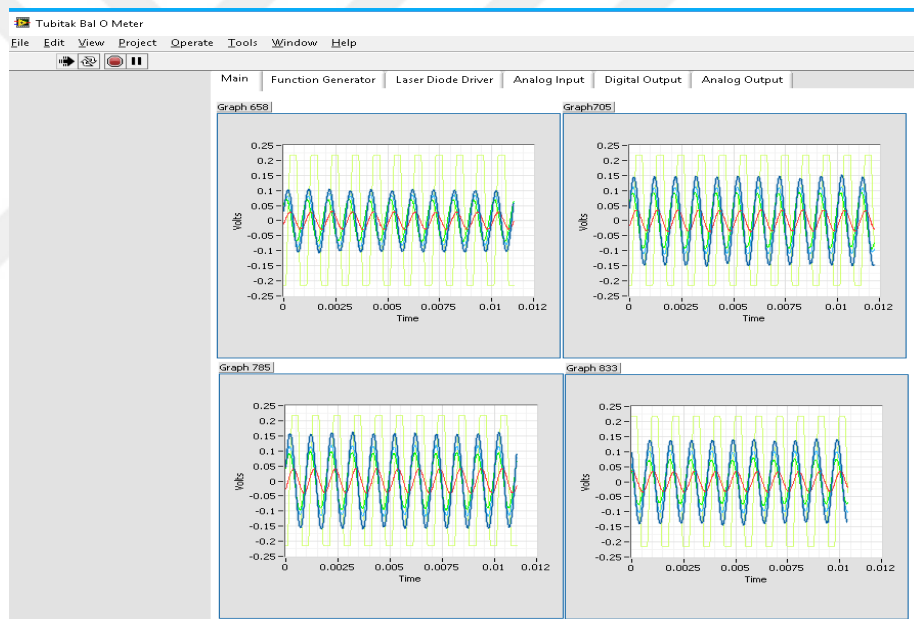


Figure 2.30. The main section of the developed software

The function generator section (Figure 2.31) provides on/off control of the function generator. The reference signal at the first channel of the function generator, the amplitude, and frequency of frequency mixers' signal at the second channel of the function generator, and the desired amplitude and frequency of laser diodes' AC signals are controlled in this section.

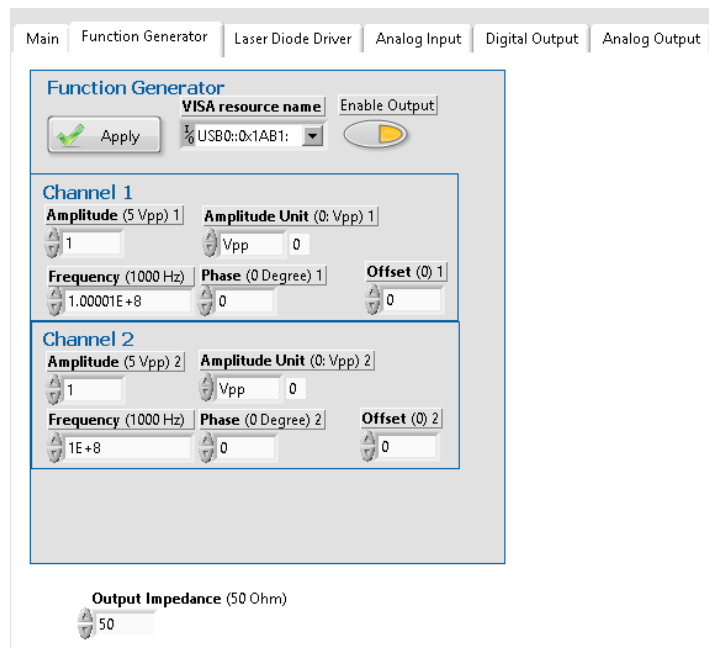


Figure 2.31. The function generator section

The laser diode driver section (Figure 2.32) controls the on/off of the laser diode driver and adjusts the DC current.

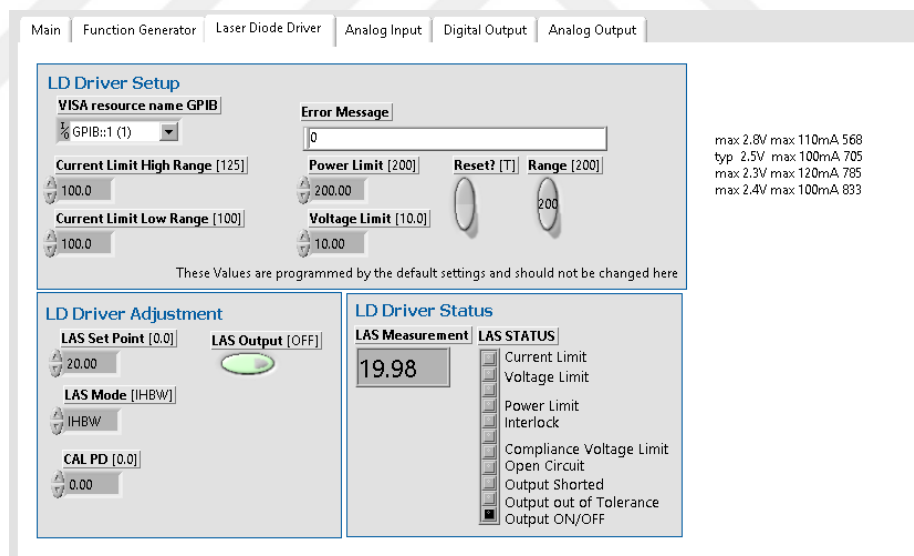


Figure 2.32. Laser diode driver control section

The analog input section (Figure 2.33) includes timing and trigger settings. The reflected light signal is read via analog input of DAQ.

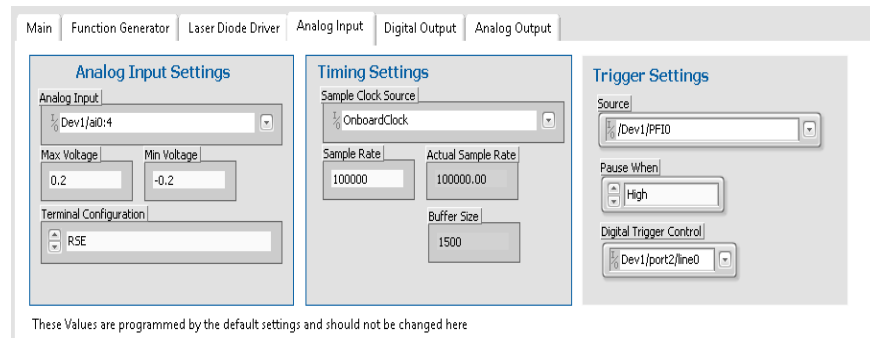


Figure 2.33. Analog input section

The digital output section (Figure 2.34) produces a digital signal for driving sequentially each of the four laser diodes. The combinations of the digital outputs drive the different outputs of the RF switch.

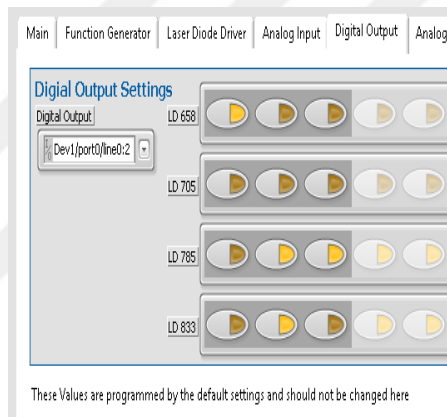


Figure 2.34. Digital output section

The analog output section (Figure 2.35) adjusts the gain of each PMT signal. Analog outputs produce the voltage between 0.25 and 1.00V.

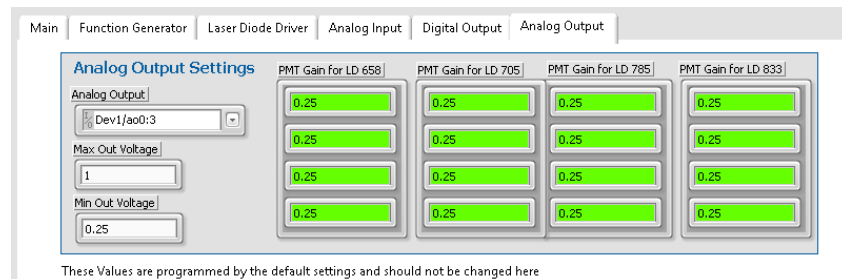


Figure 2.35. Analog output section

The voltage adjusted the according to the given graph of the gain versus control voltage of H9305-13 (Figure 2.36) (<https://www.hamamatsu.com/jp/en/product/type/H9305-13/index.html>).

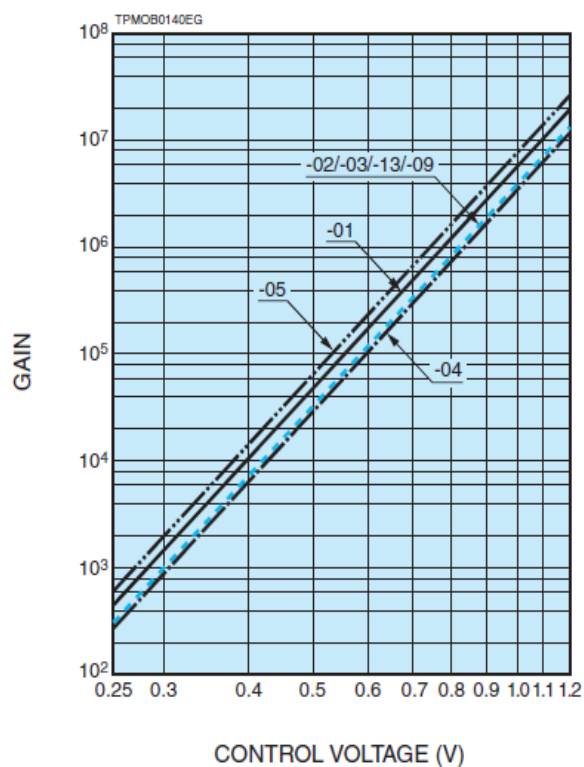


Figure 2.36. The gain versus control voltage

The measurement of the signal is recorded using the TDMS file. The recording section and the recorded data are given in Figure 2.37 and Figure 2.38, respectively.

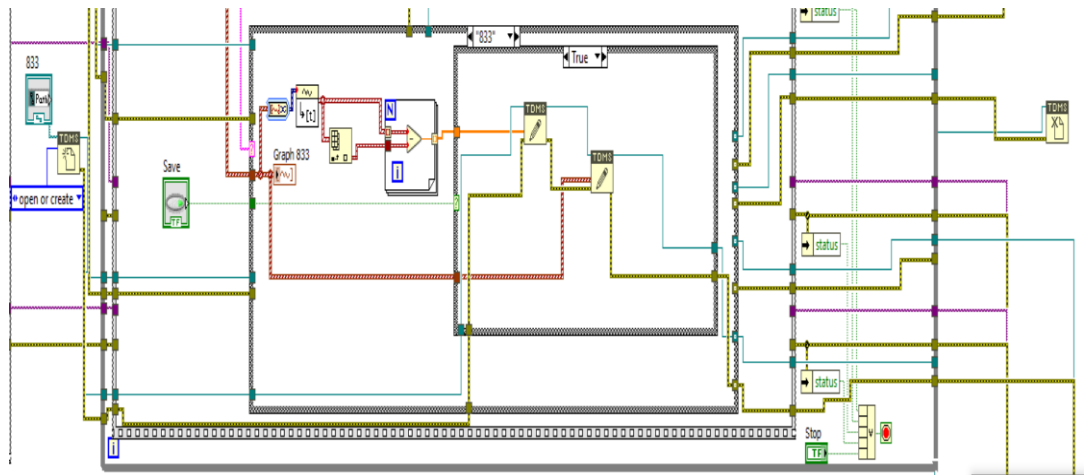


Figure 2.37. TDMS operation

Time	Dev1/ai0	Dev1/ai1	Dev1/ai2	Dev1/ai3	Dev1/ai4
0	-0.009781212	-0.022261946	-0.009840581	-0.098643928	0.016987696
1E-05	-0.008613617	-0.020784312	-0.009543735	-0.101777317	0.039884386
2E-05	-0.008494879	-0.020513852	-0.010117638	-0.104442346	0.06188392
3E-05	-0.006997455	-0.019755244	-0.008804918	-0.106137675	0.085070808
4E-05	-0.005955196	-0.01852828	-0.009200713	-0.107931952	0.106047828
5E-05	-0.005222975	-0.018112695	-0.009411804	-0.109323837	0.127935148
6E-05	-0.004470965	-0.017070435	-0.009029202	-0.109779003	0.149143
7E-05	-0.003521058	-0.016305231	-0.009893354	-0.110616773	0.168371872
8E-05	-0.002953752	-0.015170619	-0.008738952	-0.109759213	0.1895401
9E-05	-0.001344187	-0.013363156	-0.008475089	-0.109191905	0.207746472
1E-04	-0.000717512	-0.013251014	-0.008224419	-0.10859821	0.216249369
0.00011	0.001116336	-0.011456744	-0.007789045	-0.106500488	0.216249369
0.00012	0.001452762	-0.0101902	-0.00762413	-0.10480516	0.216249369
0.00013	0.002244351	-0.008923657	-0.006898507	-0.102522733	0.216249369
0.00014	0.003477911	-0.007103001	-0.006252042	-0.099428925	0.216249369
0.00015	0.004454204	-0.006403763	-0.005942003	-0.097205868	0.216249369
0.00016	0.005008317	-0.004992095	-0.005275748	-0.093254501	0.216249369
⋮			⋮		

Figure 2.38. The recorded data that includes amplitude of all wavelength over time

The interface of the calculation of theoretical intensity and phase difference is given below (Figure 2.39).

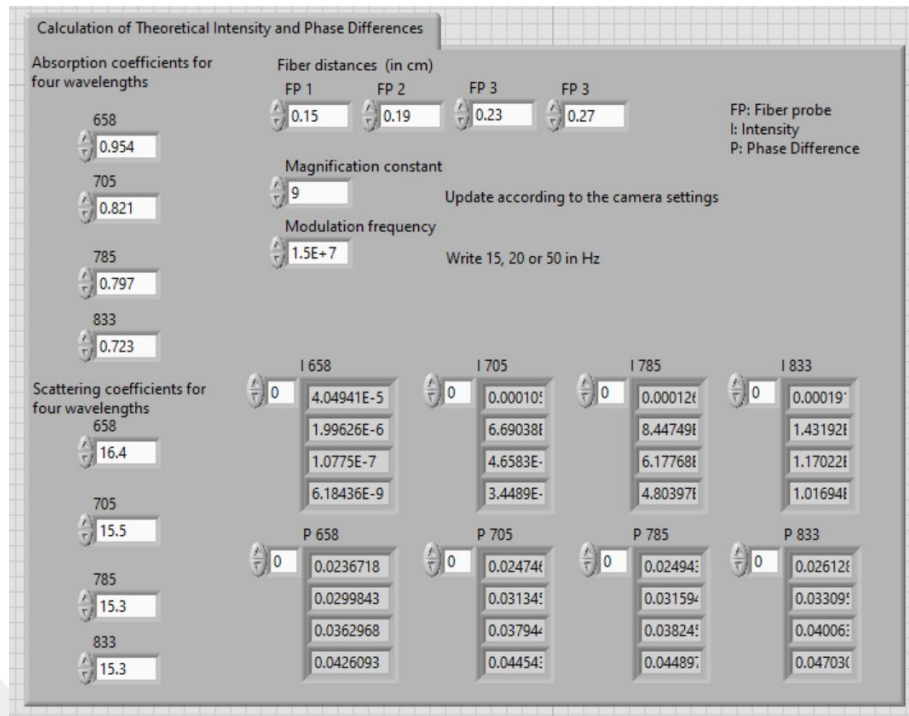


Figure 2.39. Calculation of theoretical intensity and phase difference

The interface of calculation of absorption and reduced scattering coefficients and calibrated values' graphs are given below (Figure 2.40).

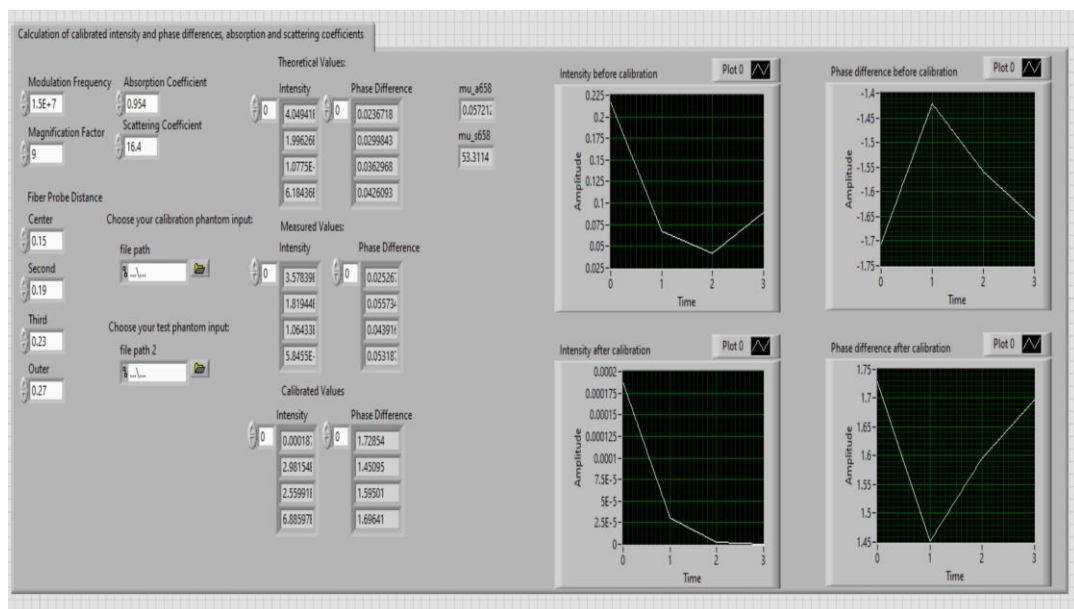


Figure 2.40. Calculation of Absorption and Reduced Scattering coefficients

Input is taken from file and root-mean-square (RMS) calculation is done using below graphical functions (Figure 2.41).

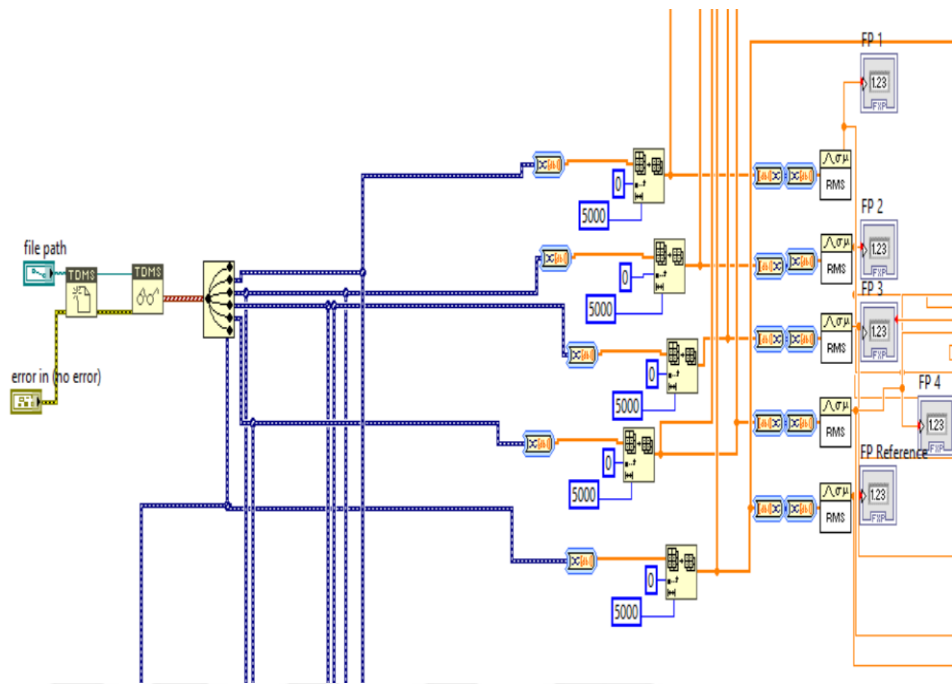


Figure 2.41. RMS calculation

Phase difference calculation is done using below graphical functions (Figure 2.42).

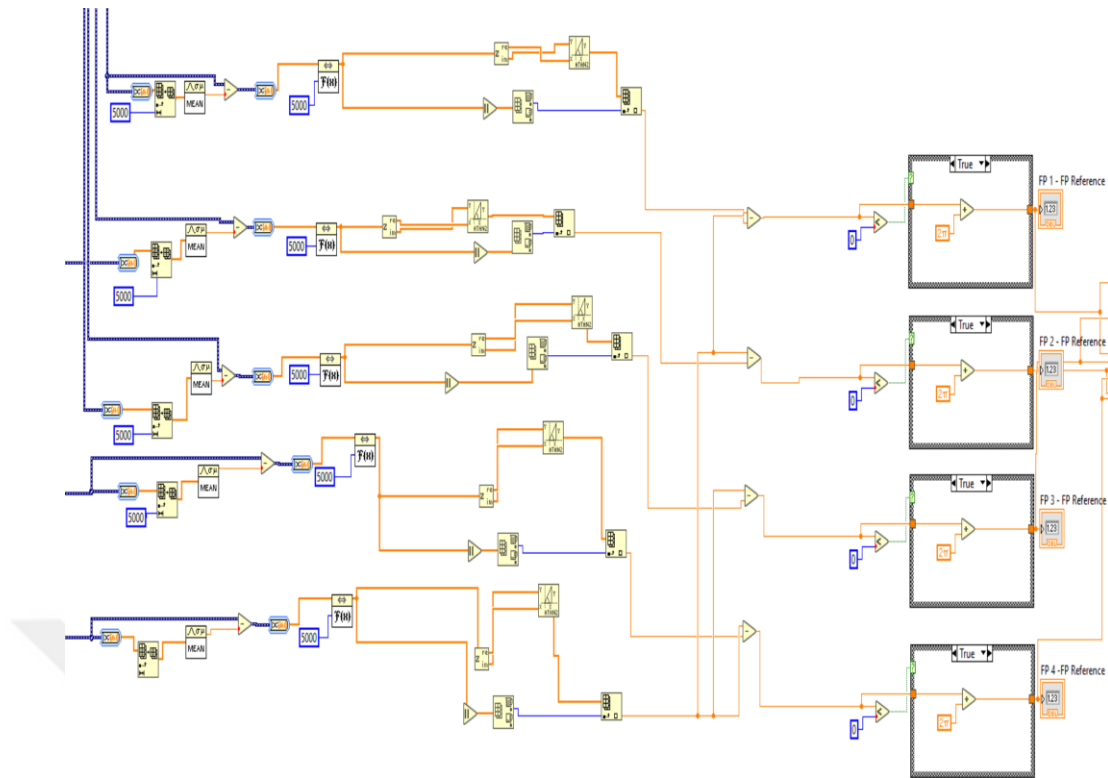


Figure 2.42. Phase difference calculation

Calculation of absorption and reduced scattering coefficients is done using below graphical functions (Figure 2.43).

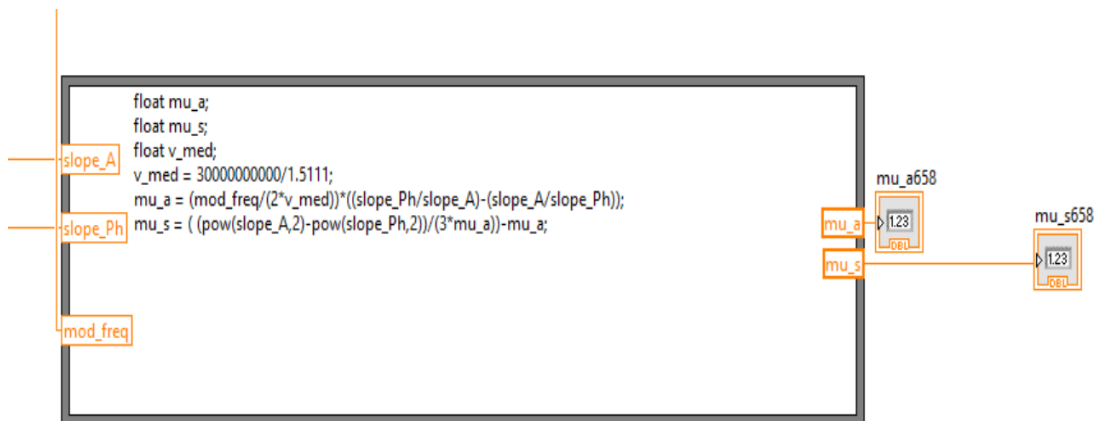


Figure 2.43. The calculation of absorption and reduced scattering coefficients

Feature extraction for regression model is done using the given interface (Figure 2.44).

Feature Extraction

This interface gives results of normalized rms, phase difference, power spectral density and entropy of input signal.

Choose your input file:

file path

C:\User...\test_658.tdms

FP: Fiber probe (FP 1 furthest, FP 4 closest)

PD: Phase difference

PSD: Power spectral density

Run

error in (no error)

status code

0

source

RMS	Normalized RMS	Phase difference	Normalized PD
FP 1	FP 1	FP 1 - FP Reference	FP 1 - FP Reference
0.0167336	0.089455	4.65601	1
FP 2	FP 2	FP 2 - FP Reference	FP 2 -
0.0614493	0.328498	4.62169	0.992625
FP 3	FP 3	FP 3 - FP Reference	FP 3 -
0.111396	0.595506	4.60985	0.990081
FP 4	FP 4	FP 4 - FP Reference	FP 4 - FP Reference
0.184598	0.98683	4.50673	0.96794
FP Reference	FP Reference		
0.187061	1		

Normalized PSD	Normalized Entropy
FP 1	FP 1
0.00809895	0.0198075
FP 2	FP 2
0.110595	0.178865
FP 3	FP 3
0.363981	0.455227
FP 4	FP 4
0.95835	0.977754
FD 5	FP 5
1	1

Figure 2.44. The interface of feature extraction

2.6.4. Optical phantoms

Optical phantoms are the ideal medium for system calibration tests of biomedical optical phantoms. These phantoms are designed to reproduce the optical properties of living biological tissues. There are two kinds of optical phantoms such as liquid and solid. Liquid phantoms are easy and cheap to produce and available for a short duration. Solid phantoms are expensive to produce and durable for long-duration. The absorption and scattering coefficients of liquid phantoms can be measured using an ultraviolet (UV) spectrometer in a glass, plastic, or quartz container. The measurement in these containers affects the reflection angle of light. Therefore, liquid phantoms are not available in our non-contact design. The absorption and scattering coefficients of solid phantoms cannot be measured using Fourier transform infrared spectrophotometer (FTIR) spectrometer. The absorbance can be measured according to wavelengths, but the FTIR spectrometer is not suitable to measure the concentration of a solid

material. A double-integrating sphere is required to measure these coefficients. The production of several optical phantoms is searched to improve the calibration and measurement result in the thesis, but the access of chemicals, measurement devices, and the setup for measurement was out of the boundary of this study.

Two fabricated optical solid phantoms are used in this thesis. Each phantom has its own absorption and scattering coefficients. Titanium oxide is used as a scattering agent and carbon black is used as an absorbing dye on producing solid phantoms. The resulting scattering coefficient varies slightly over the spectrum and the flat absorption coefficient is provided as a function of a wavelength.

Two different optical phantoms are produced by INO Biomimic (Figure 2.45). One of these optical phantoms is analyzed at 650 nm, 700 nm, 750 nm, 800 nm, and 850 nm wavelengths. The thickness of the sample is 2 cm. The refractive index of the sample is 1.5111. The optical properties of the first phantom (OP-HBO-R-650-1-22) and second phantom (OP-HBO-R-850-0.7-15) were given in and , respectively.

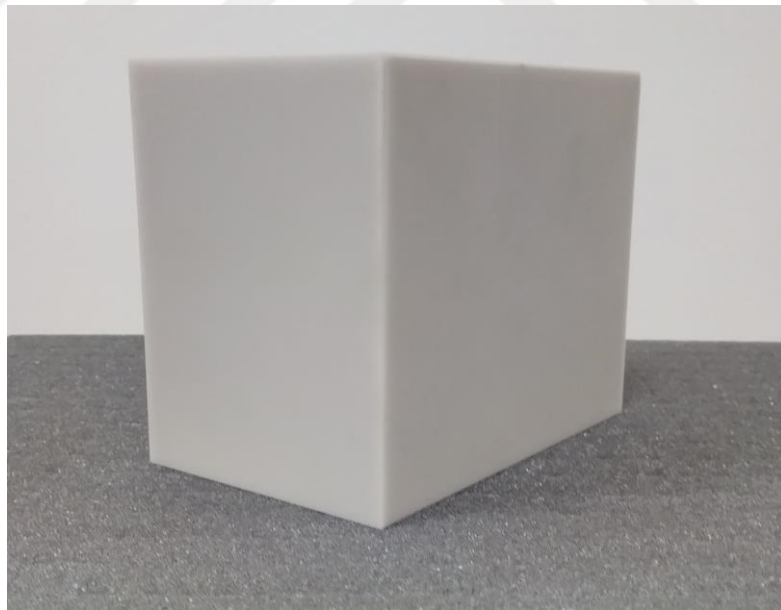


Figure 2.45. Optical phantom sample

Table 2.5. First phantom (OP-HBO-R-650-1-22)

Wavelength (nm)	Target optical properties		Fit results	
	μ_a	μ'_s	μ_a	μ'_s
650	1	22	1.18	22
700	1	22	1.15	22.1
750	1	22	1.11	21.9
800	1	22	1.07	21.9
850	1	22	1.04	22.6

Table 2.6. Second phantom (OP-HBO-R-850-0.7-15)

Wavelength (nm)	Target optical properties		Fit results	
	μ_a	μ'_s	μ_a	μ'_s
650	0.7	15	0.954	16.4
700	0.7	15	0.821	15.5
750	0.7	15	0.797	15.3
800	0.7	15	0.753	15.5
850	0.7	15	0.723	15.3

2.7. Results and Discussion

Custom transimpedance amplifier designs are introduced in this section. The experiments and results are given with tables and figures.

2.7.1. Single stage transimpedance amplifier

In this section, the test procedure of the proposed design with two-layer single-stage TIA, calibration, and the determination of absorption and reduced scattering coefficients are mentioned. First, a two-layer single-stage TIA with OPA657 and RF amplifier circuit is used to determine the absorption and reduced scattering coefficients on optical phantoms with our proposed FDMD based system at a frequency of 15 MHz.

The design was calibrated with reference and test optical phantoms with known optical properties ($\mu_a = 0.7 \text{ cm}^{-1}$ $\mu'_s = 15 \text{ cm}^{-1}$, $\mu_a = 1 \text{ cm}^{-1}$ $\mu'_s = 22 \text{ cm}^{-1}$) [OP-HBO-R-850-0.7-15, OP-HBO-R-650-1-22, INO] similar to Dehaes, M. et al., (2011). Since there were two different phantoms, the calculated theoretical intensity (I_{AC}^{theo}) and phase (ϕ^{theo}) values used the calibration phantom's absorption and reduced scattering coefficients and then the illumination and collection fibers' distances (r), to find calibration coefficients (I_{AC}^{calib} and ϕ^{calib}) by dividing and subtracting the measured intensity (I_{AC}^{slab}) and phase (ϕ^{slab}) values for the four wavelengths respectively (Bal, U. et al., 2020).

$$I_{AC}^{\text{calib}} = \frac{I_{AC}^{\text{theo}}}{I_{AC}^{\text{slab}}} \quad (2.17)$$

$$I_{AC}^{\text{theo}} = \frac{e^{rS_{AC}^{\text{theo}}}}{r^2} \quad (2.18)$$

$$\varphi^{\text{calib}} = \varphi^{\text{theo}} - \varphi^{\text{slab}} \quad (2.19)$$

$$\varphi^{\text{theo}} = r S_{\varphi}^{\text{theo}} \quad (2.20)$$

The slope of AC intensity and phase differences with respect to distances were calculated by using equations (2.12)-(2.15). We used those calibrated intensity and phase values were used to calculate μ_a and μ'_s by using equations (2.21) and (2.22).

$$\mu_a = \frac{\omega}{2v} \left(\frac{S_{\varphi}}{S_{AC}} - \frac{S_{AC}}{S_{\varphi}} \right) \quad (2.21)$$

$$\mu'_s = \left(\frac{S_{AC}^2 - S_{\varphi}^2}{3\mu_a} \right) - \mu_a \quad (2.22)$$

To test the noncontact FDMD device two optical phantoms were used that had known absorption and reduced scattering coefficients at four different wavelengths. The measurement was taken in normal light and a dark room.

Calibration coefficients are determined using a reference optical phantom. The results of the test optical phantom's measurements are calibrated with calibration coefficients.

The calibration phantom's coefficients were $\mu_a = 0.7 \text{ cm}^{-1}$ $\mu'_s = 15 \text{ cm}^{-1}$, and the test phantoms are $\mu_a = 1.0 \text{ cm}^{-1}$ $\mu'_s = 22 \text{ cm}^{-1}$. The intensity before calibration (Figure 2.46) and after calibration (Figure 2.47) were plotted with respect to distance on the tissue for one wavelength of 658 nm. The phase differences before calibration (Figure 2.48) and after calibration (Figure 2.49) were plotted with respect to distance on the optical phantoms for one wavelength of 658 nm. As expected, intensity decreased with distance and phase increased with distance.

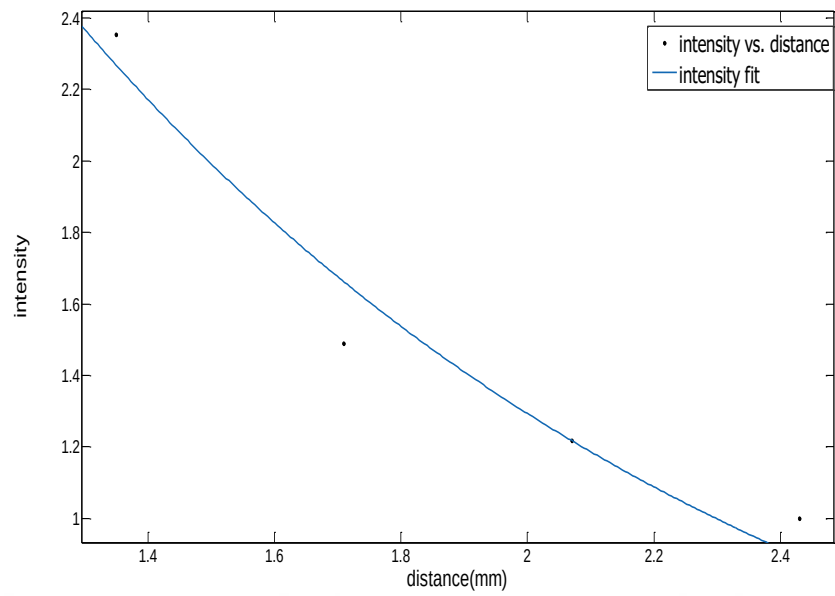


Figure 2.46. Intensity versus fiber distance at 658 nm before calibration

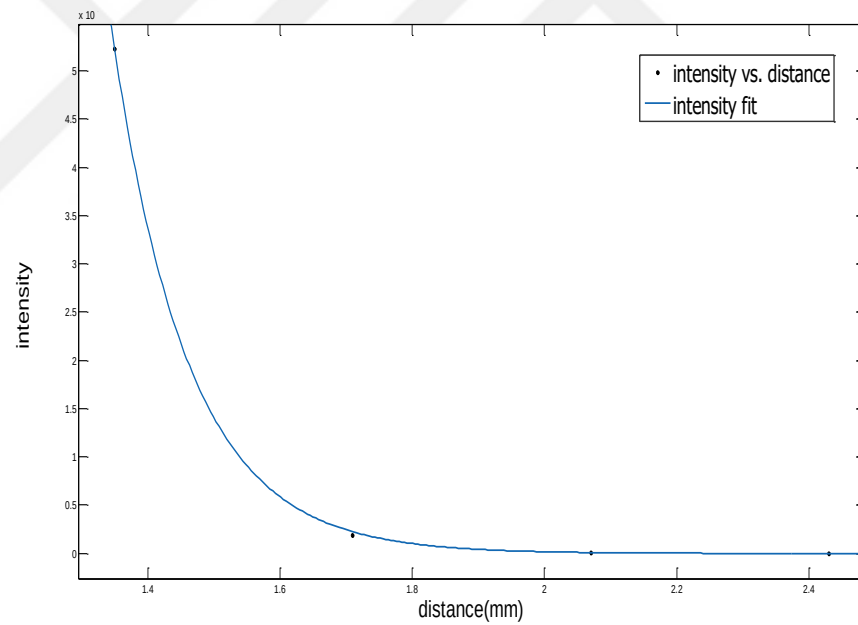


Figure 2.47. Intensity versus fiber distance at 658 nm after calibration

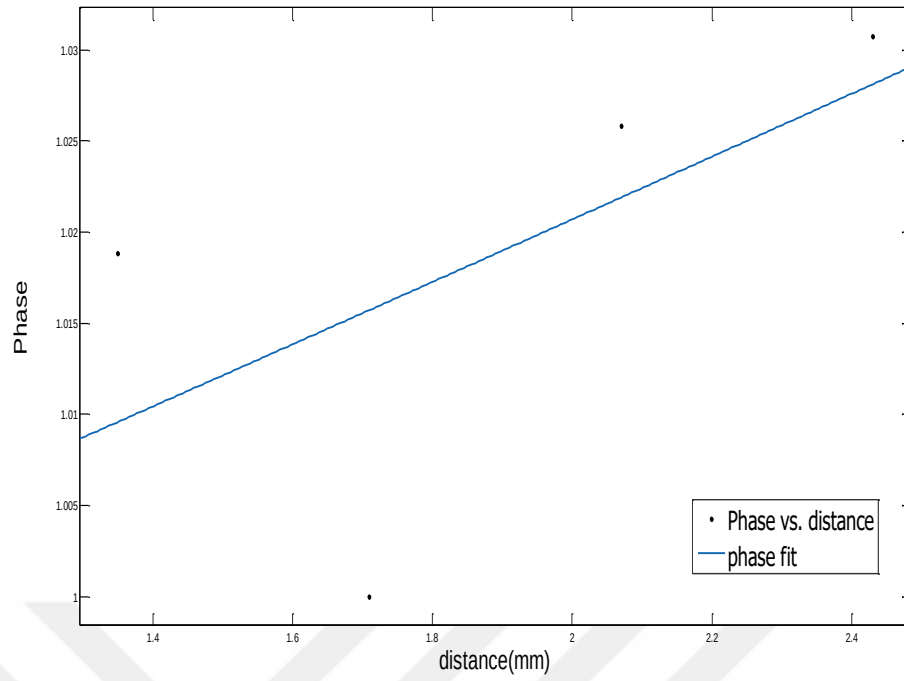


Figure 2.48. Phase difference versus fiber distance at 658 nm before calibration

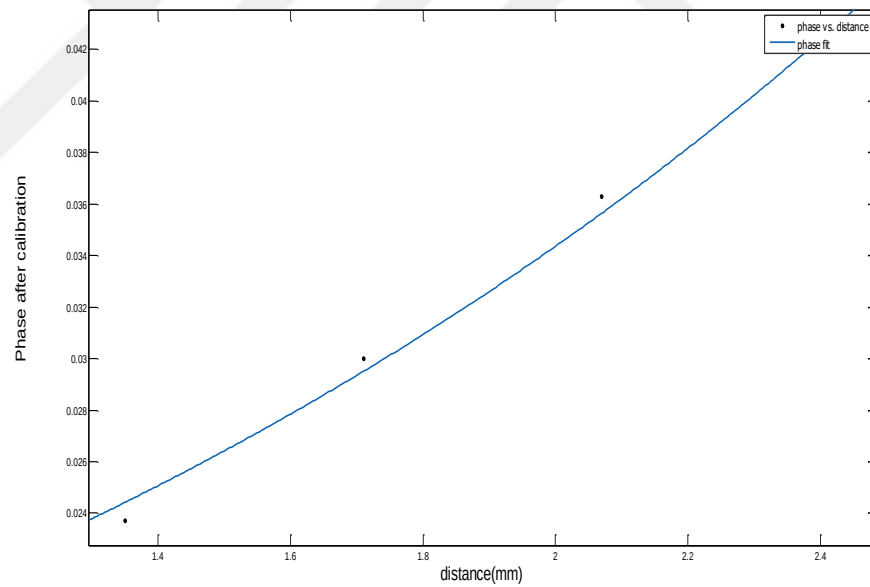


Figure 2.49. Phase difference versus fiber distance at 658 nm after calibration

The average and standard deviation of thirty measurements for absorption and reduced scattering coefficients are given in Table 2.7 and Table 2.8. The error for absorption coefficients is 32-41% and the error for reduced scattering

coefficients is 9.7-21.8% for choosing the first phantom as calibration phantom. The first phantom's measurement is a lower error than the second phantom's measurement. Underestimation of coefficients is likely the result of an insufficient modulation frequency in the custom electronic design. When comparing the measurements at 15 MHz with measurements at 10 MHz it was observed that the phase difference between the four distances increased with increasing frequency which resulted in a more accurate and reproducible estimation of absorption coefficients (Bal, U. et al., 2020).

Only two clinical blood gas measurement is compared with measurement by the device. The total hemoglobin and oxygen saturation can be determined with an error, but the proposed design is not available for clinical uses with accuracy rate and repeatability. It is observed that the limitation of bandwidth of the two-layer single-stage TIA with OPA657 and the absorption and reduced scattering coefficients of the optical phantoms are higher than tissues affect the results.

Table 2.7. Measured absorption and reduced scattering coefficients when the first phantom was test phantom

Wavelength (nm)	Calibration Phantom		Test Phantom		Total 30 Experiments (mean±std)	
	μ_a (cm ⁻¹)	μ'_s (cm ⁻¹)	μ_a (cm ⁻¹)	μ'_s (cm ⁻¹)	μ_a (cm ⁻¹)	μ'_s (cm ⁻¹)
658	0.954	16.4	1.18	22	0.795± 0.158	19.876± 4.273
705	0.821	15.5	1.15	22.1	0.690± 0.119	18.845± 3.494
785	0.797	15.3	1.11	21.9	0.670± 0.099	17.134± 2.577
833	0.723	15.3	1.04	22.6	0.613± 0.103	17.927± 2.893

Table 2.8. Measured absorption and reduced scattering coefficients when the second phantom was test phantom

Wavelength (nm)	Calibration Phantom		Test Phantom		Total 30 Experiments (mean±std)	
	μ_a (cm ⁻¹)	μ'_s (cm ⁻¹)	μ_a (cm ⁻¹)	μ'_s (cm ⁻¹)	μ_a (cm ⁻¹)	μ'_s (cm ⁻¹)
658	1.18	22	0.954	16.4	1.523±0.376	17.798±4.803
705	1.15	22.1	0.821	15.5	1.473±0.418	18.303±5.177
785	1.11	21.9	0.797	15.3	1.303±0.262	19.553±4.230
833	1.04	22.6	0.723	15.3	1.221±0.246	20.250±4.246

The results underestimated the absorption coefficients for the test phantom (real: $\mu_a = 0.7 \text{ cm}^{-1}$, estimated 0.795 ± 0.158 , 0.690 ± 0.119 , 0.670 ± 0.099 , $0.613 \pm 0.103 \text{ cm}^{-1}$ for the wavelengths of 658 nm, 705 nm, 785 nm, and 833 nm, respectively) (Bal, U. et al., 2020). Thirty experiments (are given in Table A.1) were performed using calibration based on a test phantom. When the calibration and test phantom were inverted, similar results were produced with a slightly larger error, but the data was overestimated.

To be able to observe the phase difference in FDMD measurements on tissue with sufficient accuracy, modulation of the light should be at least 50 MHz. But the proposed non-contact system amplified reflected light through the PMTs and TIAs only up to 15 MHz. An improved TIA should allow an increase in bandwidth from 50 to 100 MHz (Bal, U. et al., 2020).

2.7.2. Four-layer multi-stage transimpedance amplifier

Transimpedance amplifiers are critical to amplify the output signal from a PMT. TIAs provide low noise, high bandwidth, and high gain and increases efficiency. The first design for the TIA was two-layer and single-stage with OPA657. Two-layer printed circuit boards (PCBs) are usable in a frequency range up to 25

MHz. Above 10 MHz, multi-layer PCBs are should be used. A four-layer PCB also produces 15 dB less radiation than a two-layer PCB.

A four-layer multi-stage TIA is designed to decrease noise and increase bandwidth. The four-layer multi-stage TIA includes an operational amplifier based current to voltage converter part and MMIC part. The overall design is tried to observe the changes in the amplitude and phase differences of signals. After that, the MMIC section is canceled and a current to voltage converter with RF amplifier is used to determine the coefficients. A commercial TIA60 for PMTs is also used. It has a large operational bandwidth range from DC to 60 MHz (3 dB).

All measurements with these circuits are made on optical phantoms. The design was calibrated with reference and test optical phantoms with known optical properties ($\mu_a = 0.7 \text{ cm}^{-1}$ $\mu'_s = 15 \text{ cm}^{-1}$, $\mu_a = 1 \text{ cm}^{-1}$ $\mu'_s = 22 \text{ cm}^{-1}$) [OP-HBO-R-850-0.7-15, OP-HBO-R-650-1-22, INO] similar to Dehaes, M. et al., (2011).

As a first experiment, the changes of light intensity were observed according to changes in PMT gain with four-layer multi-stage TIA (Figure 2.50). The changes in PMT gain affect the output signal of PMT. For different three PMT gains, signals are recorded at 15, 20, and 50 MHz.



Figure 2.50. The implementation of four-layer multi-stage TIA

When the laser diode is off, there were no changes in the intensity of light with a PMT gain is 0.25V because the reflected signal has a very low amplitude (Figure 2.51). The signals at 15, 20, and 50 MHz are measured. The changes of light

intensity are given here for only 658 wavelengths on and off position of the light source. There were four fiber detectors, only the outer probe's intensity was given. It is observed that when the frequency is increased, the changes in the intensity of light is increased (Figure 2.52). It is expected to the amplitude of light intensity is decreased when the distance is increased to the light source in the FDMD method. But it was not observed when the PMT gain is 0.25V.

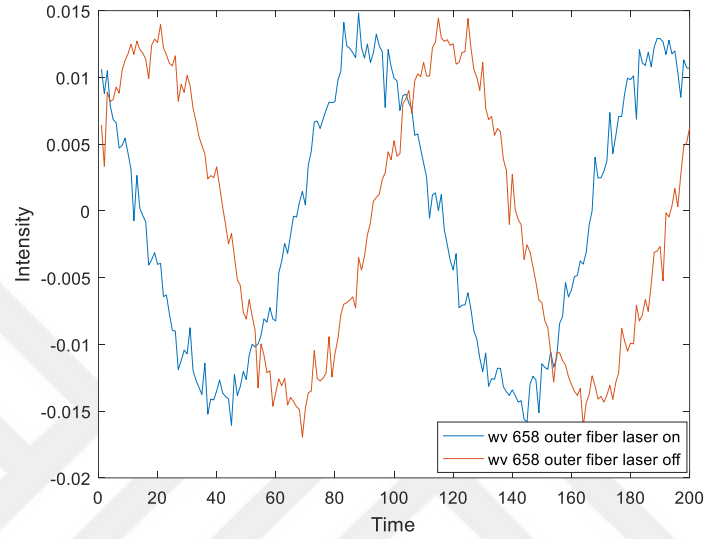


Figure 2.51. Intensity changes at on/off laser diodes at 15 MHz, 0.25V PMT gain, only 658 nm, without calibration

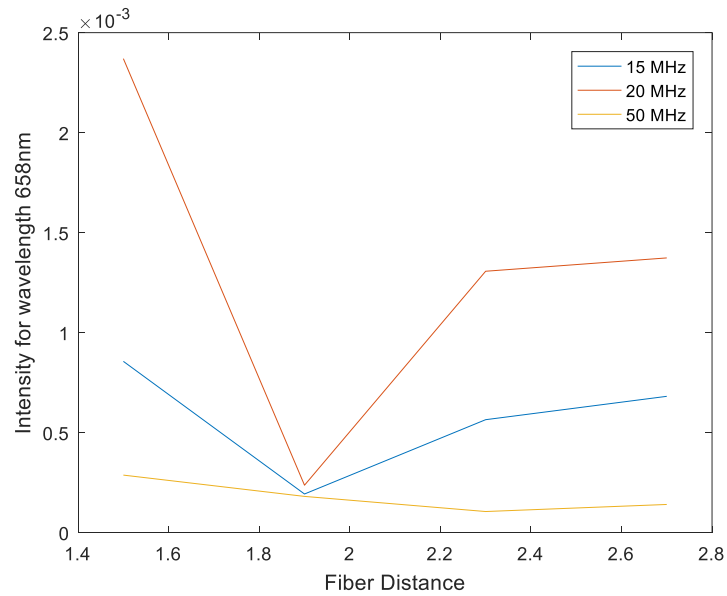


Figure 2.52. Intensity versus fiber distances at 15, 20, and 50 MHz, 0.25V gain, only 658 nm

When the laser diode is off, there were significant changes in the intensity of light with a PMT gain is 0.6V (Figure 2.53). The signals at 15, 20, and 50 MHz are measured. When the frequency is increased, the noise is increased in the signals and the intensity is decreased (Figure 2.54). But the intensity of reflected light of this signal is greater than the intensity of reflected light at 0.25V PMT gain.

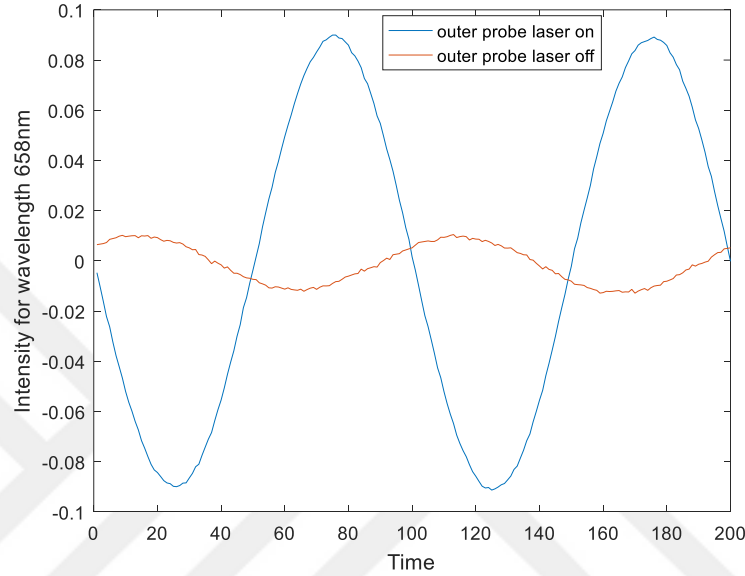


Figure 2.53. Intensity changes at on/off laser diodes at 15 MHz, 0.6V PMT gain, only 658 nm, without calibration

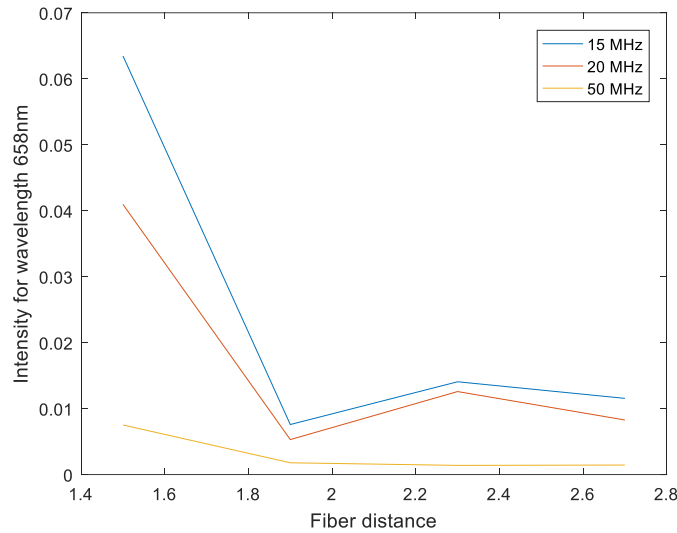


Figure 2.54. Intensity versus fiber distances at 15, 20, and 50 MHz, 0.6V gain, only 658 nm

The absorption and reduced scattering coefficients are determined with changes in the PMT gain as 0.4, 0.5, and 0.6V for 15, 20, and 50 MHz. The errors of the

absorption coefficients are between 40-67%, 41-64%, and 57-74% for four different wavelengths at 0.4V, 0.5V and 0.6V, respectively. The errors of the scattering coefficients are between 0.28-47%, 1.8-25% and 2.8-71% for four different wavelengths at 0.4V, 0.5V, and 0.6V, respectively. The comparison between the real and calculated values for μ_a (Figure 2.55) and μ'_s (Figure 2.56) at 15 MHz is given as below.

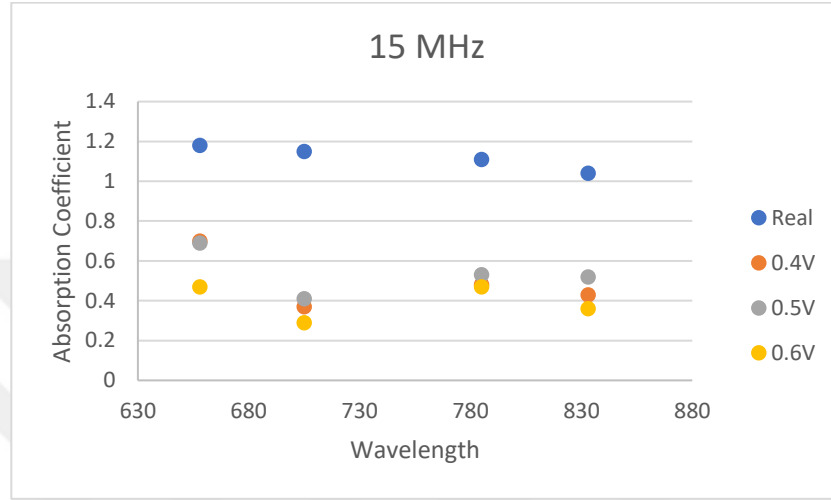


Figure 2.55. Absorption coefficient versus wavelength at 15 MHz with four-layer multi-stage TIA

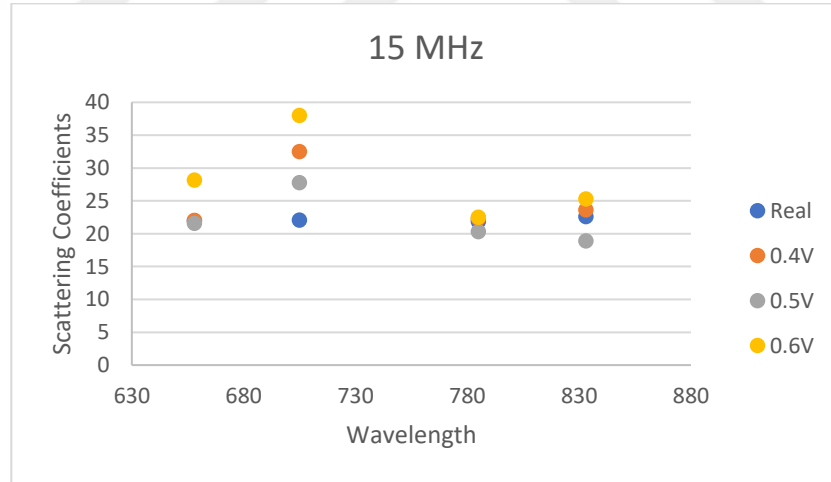


Figure 2.56. Scattering coefficient versus wavelength at 15 MHz with four-layer multi-stage TIA

As a second experiment, the changes of light intensity were observed according to changes in PMT gain with the four-layer current to voltage converter stage and RF amplifier (Figure 2.57). For different three PMT gains, signals are recorded at 15, 20, and 50 MHz. The absorption and reduced scattering coefficients are

determined with changes in the PMT gain as 0.5 and 0.6V for 15, 20, and 50 MHz. The errors of the absorption coefficients are between 1.7-41% and 6.7-16.2% for four different wavelengths at 0.5V and 0.6V, respectively.

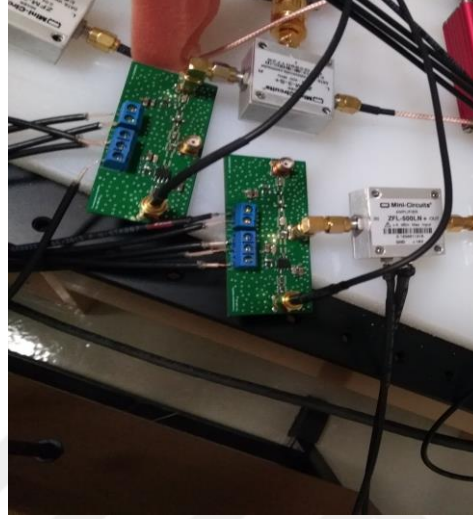


Figure 2.57. The implementation of four-layer first stage with RF amplifier

The errors of the scattering coefficients are between 25.4-50% and 29-41% for four different wavelengths at 0.5V and 0.6V, respectively. The comparison between the real and calculated values for μ_a and μ'_s at 15 MHz is given below (Figure 2.58 and Figure 2.59).

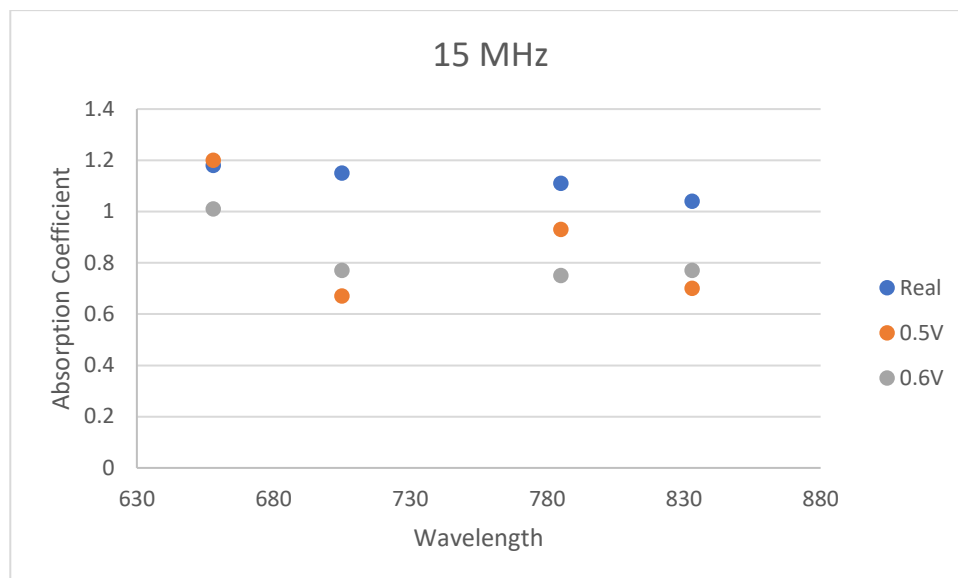


Figure 2.58. Absorption coefficient versus wavelength at 15 MHz with four-layer first stage with RF amplifier

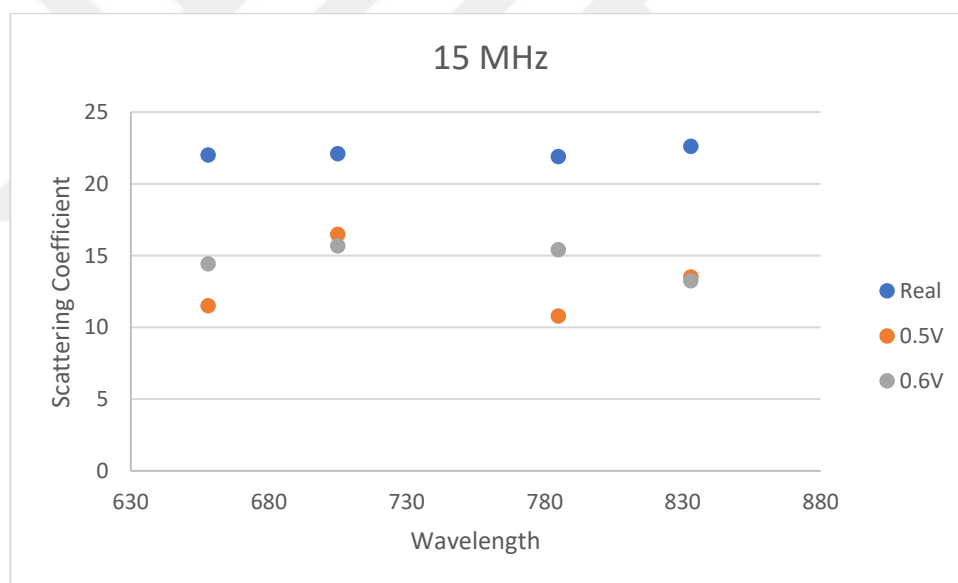


Figure 2.59. Scattering coefficient versus wavelength at 15 MHz with four-layer first stage with RF amplifier

As a third experiment, the changes of light intensity were observed according to changes in PMT gain with TIA60 (Figure 2.60) for only one PMT output.

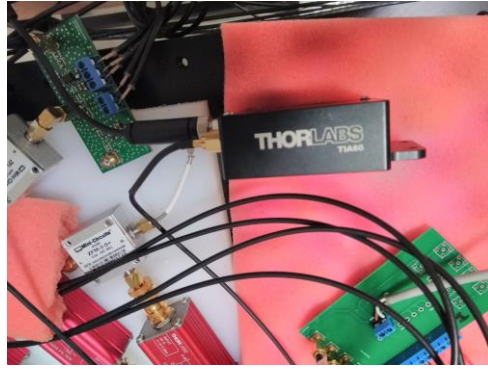


Figure 2.60. Thorlabs TIA60

When the PMT gain was 0.6V, the intensity of light was observed at 15 MHz and 50 MHz (Figure 2.61 and Figure 2.62). As expected, the intensity was much greater than laser diode off mode and the intensity at 50 MHz is greater than intensity at 15 MHz.

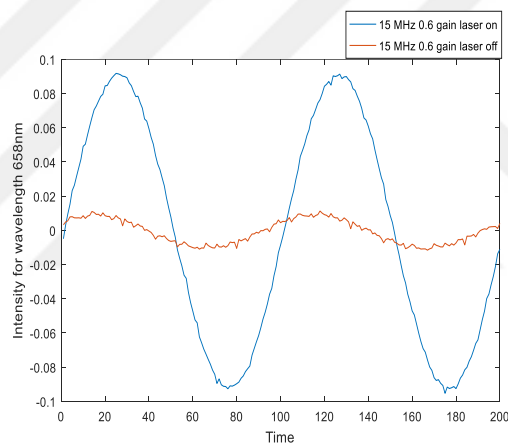


Figure 2.61. Intensity changes at on/off laser diodes at 15 MHz, 0.6V PMT gain, only 658 nm

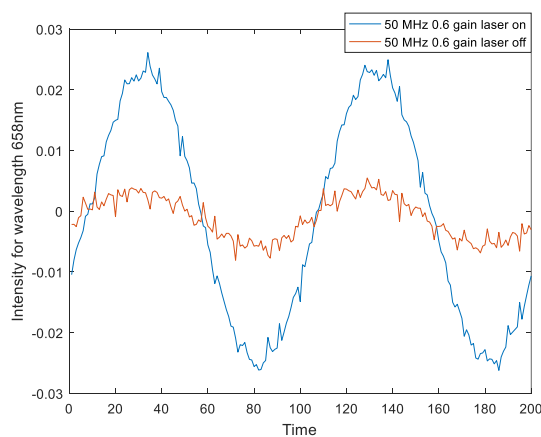


Figure 2.62. Intensity changes at on/off laser diodes at 50 MHz, 0.6V PMT gain, only 658 nm

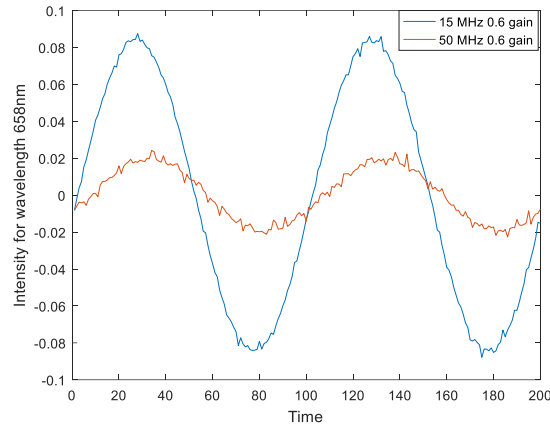


Figure 2.63. The comparison of intensity between 15 MHz and 50 MHz, 0.6V PMT gain, only 658 nm

Four-layer multi-stage amplifier, four-layer current to voltage converter, and RF amplifier and TIA60 was tried to optimize the amplification stage by changing the gain of the PMT. The light intensity is very low at the minimum gain level (0.25V) and this gain is not available for measurement. Results are improved when increasing the gain level to 0.6V. The best intensity and blocking noise were observed at 15 MHz with the different frequencies and PMT gain was 0.6V. The error of absorption and reducing scattering coefficients at 15 MHz and 0.6V is lower than other frequencies when a four-layer current to voltage converter and RF amplifier was used. The error of the absorption coefficient for four wavelengths is between 6.8-16.2% and the error of the scattering coefficient for four wavelengths is between 2.8-71%. TIA60 was used with only one output of PMT and the minimum gain level did not affect the signal.

2.8. Measurements from human

From previous results, the best suitable transimpedance amplifier is a four-layer current to voltage converter and RF amplifier. 24 measurements are taken by our non-contact proposed design from 24 healthy volunteers. Table 2.9 gives the laboratory hemoglobin values that are taken by blood gas analysis from volunteers. The pool of subjects comprised healthy men and women, from 21 to 42 years of age. All clinical data were collected from Muğla Sıtkı Koçman University Training Research Hospital.

Table 2.9. Human data

Gender	Age	Laboratory HGB (g/dL)
Female	21	12.3
Female	21	12.1
Female	22	9.3
Female	22	14.2
Female	23	14.6
Female	23	11.2
Female	23	13.3
Female	23	12.3
Female	26	12.2
Female	26	11.1
Female	26	12.1
Female	26	15.7
Female	26	12.1
Female	26	11.5
Male	19	14.7
Male	21	15.1
Male	22	16.6
Male	22	15.40
Male	22	16.9
Male	22	14.9
Male	23	16.00
Male	23	11.10
Male	25	16.6
Male	26	15.5
Male	26	14.0

Table 2.9. (continue)

Gender	Age	Laboratory HGB (g/dL)
Male	26	15.9
Male	42	16.0
Male	42	16.0

Total hemoglobin and three hemoglobin species are taken by GEM OPL oxygenation portable laboratory. GEM OPL is used to measure the total hemoglobin and the relative concentrations of oxy-, carboxy-, and methemoglobin in rapid and accurate way. Direct values are obtained in 10 seconds. The whole blood sample is injected into a disposable cuvette. Analysis is accomplished by inserting this cuvette into the instrument. This device illuminates the sample with multiple wavelengths, records the optical absorbance of the sample at each wavelength, and displays the results.

Table 2.10. Total hemoglobin and three hemoglobin species' values

Gender	Age	tHb (g/dL)	HbO ₂ (%)	HbCO (%)	HbMet (%)
Male	26	15.9	95.1	5.2	2.6
Female	23	12.3	95.9	4.2	3.5
Male	42	16	94.2	3.6	0.4
Female	26	12.8	97.1	2.3	0.3

3. NON-CONTACT TOTAL HEMOGLOBIN ESTIMATION USING ARTIFICIAL INTELLIGENCE TECHNIQUES

In this section of the thesis, a set of regression models and deep learning architecture models are introduced. The FDMD method is combined with regression models and deep learning methods to estimate total hemoglobin. The signal's features are extracted using RMS, phase difference, power spectral density (PSD), and entropy functions because regression models need to feature for training. Then, one dimensional (1-D) signals are converted to scalograms using continuous wavelet transform and CNN algorithms are applied.

3.1. Data Preprocessing

First, feature extraction and the conversion of the 1-D signal are discussed in this section. K-fold cross-validation is mentioned that applied to both regression and deep learning models.

3.1.1. Feature extraction for regression

Measurements from 24 healthy volunteers are used to extract features. The RMS, phase differences, entropy, and PSD are the chosen features to train the regression models. These features are extracted using LabVIEW and the normalized values are trained using the regression tool of MATLAB. The dataset is split as training including 20 measurements and testing including 4 measurements.

RMS is calculated using equation (3.1)

$$x_{\text{RMS}} = \sqrt{\frac{1}{N} \sum_{n=1}^N |x_n|^2} \quad (3.1)$$

Phase difference means the measurement between two signals via Fourier Fast Transform (FFT). The reference signal and four amplified and filtered PMT signals are used to calculate the phase differences.

Entropy is calculated using LabVIEW Entropy Virtual Instrument (VI) that computes the entropy of a univariate or multivariate time series. Shannon entropy is used in this thesis.

$$E = \sum_{i=1}^n [x_t^2(i) \log(x_t^2(i))] \quad (3.2)$$

When $x_t^2(i)=0$, let $\log(x_t^2(i)=0)$, n is the number of samples of the input time series.

PSD is calculated using LabVIEW Power Spectral Density VI computes the power spectral density of scaled signal [EU] and returns the result in the selected units. Hanning window is used as the time domain window. The results are expressed in EU^2/Hz .

The extracted features are recorded in an excel file for each person (Figure 3.1).

	20MHz	p1	p21	p22	p23	p24	p25	p26	p27	p28	p29
	tHb	12.2	16	12.1	9.3	15.4	14.6	16	14.2	15.7	11.1
norm rms	658	0.239979	0.287717	0.356295	0.295263	0.302413	0.292704	0.291263	0.232372	0.281988	0.261973
		0.260629	0.261861	0.453311	0.436062	0.42025	0.47137	0.40636	0.393465	0.404846	0.405576
		0.440133	0.346817	0.449036	0.390906	0.353718	0.4905	0.331115	0.285624	0.320689	0.354164
		0.922669	0.841761	0.919327	0.872798	0.785639	0.93674	0.758124	0.640264	0.814864	0.90094
norm ph		0.543815	0.492505	0.926454	0.433383	0.456319	0.42213	0.434799	0.787296	0.782788	0.797031
		0.756145	0.709729	0.654865	0.583393	0.558786	0.649849	0.53244	0.538915	0.532632	0.52411
		0.863164	0.826666	0.801045	0.766461	0.751268	0.829489	0.732464	0.7168	0.727767	0.753826
		1	1	1	1	1	1	1	1	1	1
norm psd		0.05959	0.084854	0.13315	0.089518	0.095744	0.088033	0.08839	0.055475	0.082838	0.071644
		0.070902	0.072507	0.215398	0.196228	0.186493	0.222742	0.172121	0.158642	0.169596	0.169848
		0.202479	0.128165	0.211332	0.158592	0.130166	0.238107	0.115356	0.083437	0.106751	0.129188
		0.874714	0.767916	0.8808	0.798287	0.631858	0.846848	0.610837	0.423247	0.692236	0.851344
		1	1	1	1	1	1	1	1	1	1
norm ent		0.106889	0.144146	0.204031	0.150511	0.156478	0.148338	0.147157	0.101307	0.139508	0.123606
		0.122574	0.123455	0.29918	0.281623	0.265761	0.318124	0.251829	0.23931	0.250275	0.251072
		0.285779	0.195345	0.294823	0.236724	0.201879	0.33843	0.181286	0.142526	0.172135	0.202172
		0.874905	0.757575	0.870197	0.800338	0.686591	0.896589	0.651578	0.508549	0.723267	0.842306
		1	1	1	1	1	1	1	1	1	1
norm rms	705	0.177184	0.216851	0.614452	0.222073	0.253154	0.220628	0.221422	0.600597	0.553251	0.5163
		0.230458	0.230737	0.449747	0.417782	0.371013	0.522877	0.344663	0.376489	0.354541	0.360118

Figure 3.1. Extracted features for each person

3.1.2. Scalogram images for deep learning

The measured data is collected using the DAQ board and LabVIEW interface from 24 healthy volunteers. The data of clinical blood Hb levels of people are measured by blood gas analysis. All clinical data were collected from Muğla Sıtkı Koçman University Training Research Hospital. This 1-D signal for each wavelength is concatenated as one column vector. The 1-D signal is converted to a two-dimensional (2-D) signal. 2-D conversion signal can be represented by Continuous Wavelet Transform (CWT) that contains much information in terms of frequency-time transformations (Moral, Ö.T., and Bal, U. 2020). The absolute value of the CWT plotted as a function of time and frequency is called the scalogram. The scalogram is used as an input image to the system (Figure 3.2).

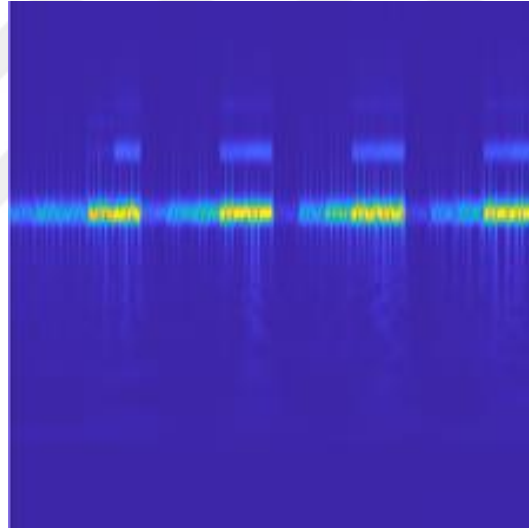


Figure 3.2. A scalogram sample from dataset

The CWT is obtained using the analytic Morse wavelet. A wavelet is defined as a function with the following equation,

$$\int_{\mathbb{R}} \psi(x) dx = 0 \quad (3.3)$$

For every f , ψ defines the CWT (Johansson, E. 2005)

$$W_{\psi}f(a,b)=\int_{\mathbb{R}} f(x)\frac{1}{\sqrt{a}}\psi\left(\frac{x-b}{a}\right)dx \quad (3.4)$$

for all $a, b \in \mathbb{R}_+ \times \mathbb{R}$, where $\psi_{a,b} = \frac{1}{\sqrt{a}}\psi\left(\frac{x-b}{a}\right)$.

The dataset is augmented by flipping and rotating for avoiding overfitting. For every 24 images, new sample images are produced using a combination of 90, 180, 270 of rotation and flipping transformations (Moral, Ö.T., and Bal, U. 2020). (Figure 3.3). The new dataset contains six times more images than the original dataset has. The dataset contains 144 scalogram images. Each measured data is represented by 144 images of 535x677 pixels size and 24-bit depth.

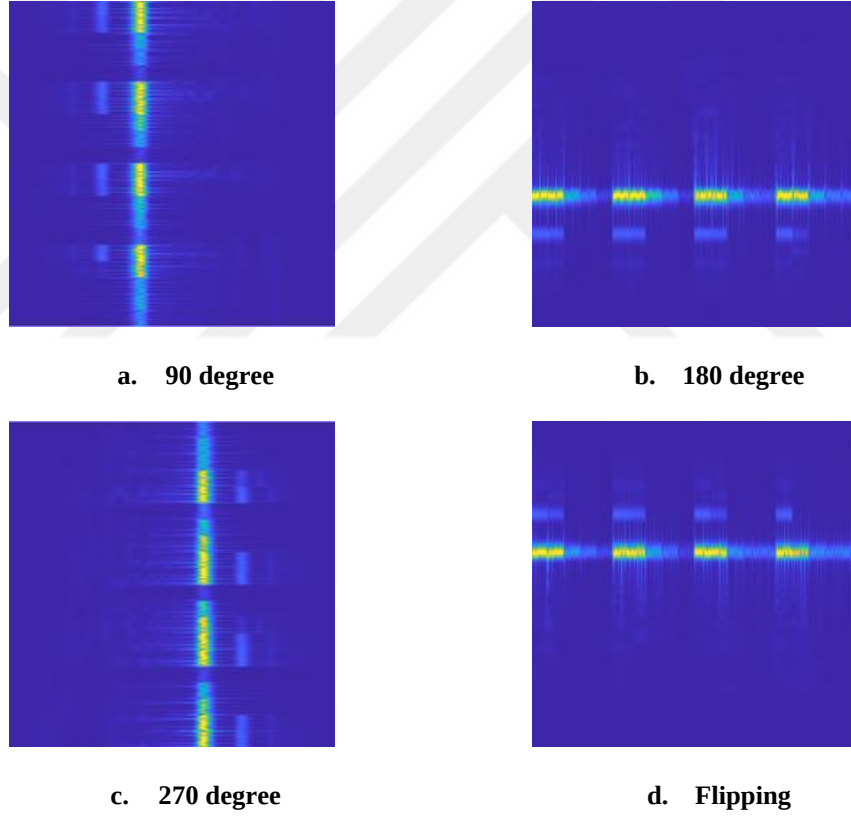


Figure 3.3. Samples from augmented dataset

The 144 data have been split into two sets where the first 120 data for training purposes, the remaining 24 data have been considered for testing. The training

data is divided into 96 training, 24 test data in the first experiment (80:20) (Moral, Ö.T., and Bal, U. 2020).

The 144 data have been split into two sets where the first 120 data for training purposes, the remaining 24 data have been considered for testing. The training data is 5-folded with 96 training, 24 test data in the second experiment.

3.1.3. K-fold cross validation

The model learned the dataset correctly when k-fold cross-validation is used. The whole dataset D is split into k disjoint subsets $D_1, D_2, D_3, \dots, D_k$. $\{k-1\}$ subsets are added to the training set and the remaining is used for testing (Zhang, B. et al., 2019). The choice of k is a trade-off between the efficiency and the accuracy of the model.

For example, by applying $k = 5$; the dataset images are partitioned into five equal groups (Figure 3.4). Four of these groups are counted to be the training dataset, while the one partition left was used for test data. The training was iterated five times, every time using a diverse partition as a test group and the leftover four partitions like a training dataset. The mean result is considered as the result of the model (Samir, S. et al., 2020).

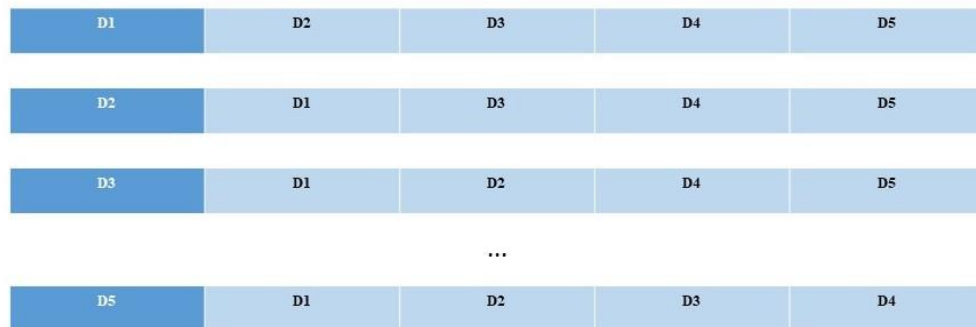


Figure 3.4. 5-fold cross validation on D

3.2. Methods

3.2.1. Regression

Regression describes the relationship between an output variable and one or more input variables. Linear regression models have predictors that are linear in the model parameters. There are five types of regression, such as linear, interactions linear, robust linear, and stepwise linear regression. In the regression trees, they follow the tree from the root (beginning) node down to a leaf node. The leaf nodes contain the values of the response. Three types of regression trees are used in the regressionLearner app, such as a fine tree, medium tree, and coarse tree (www.mathworks.com). In a support vector machine (SVM), a support vector refers to a small subset of the training observations. These vectors are used to support the optimal location of a decision surface. SVM creates the decision surface such that the margin of separation between the two classes in the data is maximized. The decision surface construction requires only the support vectors chosen from the training data. The rest of the training data are irrelevant, once trained. There are several types of SVM, such as linear, quadratic, cubic, fine gaussian, medium gaussian, and coarse gaussian (www.mathworks.com). In gaussian process regression (GPR), the response is modeled using a probability distribution over a space of functions. Rational quadratic, squared exponential, matern 5/2, and exponential GPR are types of this regression model (www.mathworks.com). A regression tree ensemble is composed of a weighted combination of multiple regression trees. This model combines results from many weak learners into one high-quality ensemble model. Boosted trees use least-squares boosting with regression tree learners. Bagged trees use bootstrap aggregating or bagging with regression tree learners (www.mathworks.com).

Regression models use the root-mean-square error (RMSE), R-squared, mean squared error (MSE), and mean absolute error (MAE) parameters to evaluate performance. RMSE is always positive. The smaller values of RMSE, the better performance is. R-squared is the coefficient of determination. This parameter compares the trained model with the model where the response is constant and

equals the mean of the training response (www.mathworks.com). If R-squared is negative, it means your model is worse than this constant model. R-squared should close to 1. MSE is the square of the RMSE. The smaller values of MSE, the better performance is. The MAE is always positive and like the RMSE, but less sensitive to outliers. It is always smaller than 1 and usually larger than 0. The predicted vs. actual plot is used to check model performance.

The measurement data from healthy volunteers are processed using LabVIEW. 18 features for each wavelength are extracted to train regression models. There are five channels that are connected to DAQ. The first one is the further fiber probe's output, the fourth one is the closest fiber probe's output and the last one is the reference output. The data subset is created using the array subset function. The array length is 5000. The root mean square of the five-input data is computed using RMS VI. These values are normalized by dividing the maximum. RMS value. The phase difference is computed and firstly, 2π is added to the phase difference if it is less than zero. Then it is normalized by dividing max. phase difference value. The entropy (Shannon) is computed using TSA ENTROPY VI, then it is normalized by dividing max. entropy value. The power spectral density is computed using SVFA Power Spectral Density.vi, the maximum values of results are taken and then it is normalized according to maximum value.

MATLAB regressionLearner app is used to train and validate the given values. This application chooses among various algorithms to train and validate regression models and assess the regression model performance. To protect against overfitting by applying cross-validation. The number of folds (or divisions) is selected to partition the data set. The application partitions the data into k disjoint folds. For each fold, a model is trained using the out-of-fold observation. The model performance using in-fold data is assessed and the average test error overall folds. The cross-validation method gives a good estimate of the predictive accuracy of the final model trained using the full data set.

Principal component analysis (PCA) is also applied to reduce the dimensionality of the predictor space with these models (www.mathworks.com). Reducing dimensionality can prevent overfitting. PCA linearly transforms and generates a

new set of variables called principal components. Each principal component is a linear combination of the original variables and all the principal components are orthogonal to each other.

3.2.2. Deep learning: convolutional neural networks

Deep learning networks are powerful tools for images and signal data and can work without extracting signal features. Deep learning networks such as convolutional neural networks (CNNs) can process data if the input data is a one-dimensional signal, time-series data, or even text.

Convolutional neural networks are one type of deep, feedforward networks that process data in the form of multiple arrays (LeCun, Y., Bengio, Y., and Hinton, G., 2015). These networks have three types of layers: convolutional, pooling, and fully connected layers (Figure 3.5). The convolutional layer includes feature maps and this layer detects local conjunctions of features from the previous layer whereas the pooling layer merges semantically similar features into one (LeCun, Y., Bengio, Y., and Hinton, G., 2015).

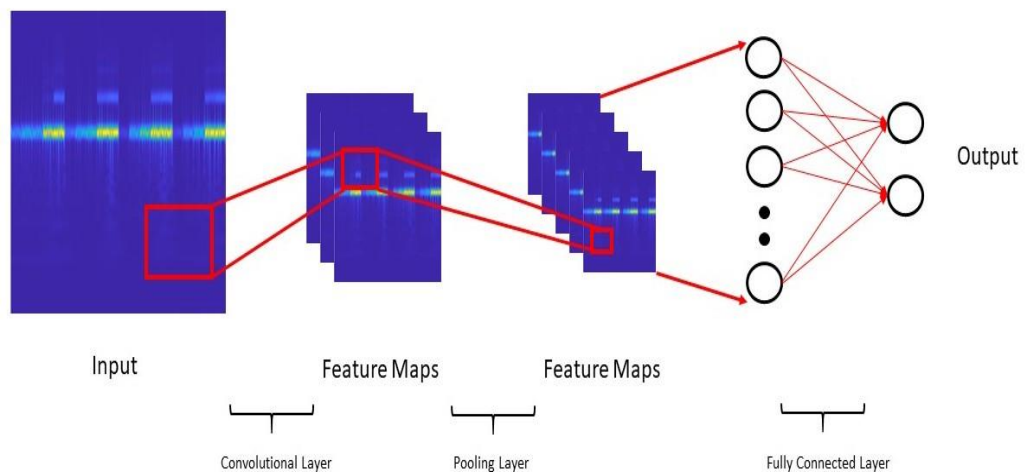


Figure 3.5. Convolutional neural networks

Deep CNN learns features from raw sensor data. Many CNN architectures have been developed namely AlexNet, VGG16, and GoogleNet in recent years. Transfer learning is mostly used in deep learning applications especially in a

smaller number of training images. A pre-trained network can be used as a starting point to learn a new task with randomly initialized weights from scratch. The last few layers of the model are changed when this approach is used.

The six pre-trained CNN architecture is used to training such as VGG16, VGG19, GoogleNet, AlexNet, ResNet50, and Inception-v3. These models are trained on the 2012 ImageNet image dataset, which contains 1000 classes. In addition to pre-trained networks, the networks without transferring weights are also trained. The depth is described as the largest number of fully connected layers in the architecture. The input images are in RGB format. Table 3.1. lists model specifications.

Table 3.1. The specifications of CNN models

CNN architectures	Image Input Size	Depth
AlexNet	227x227	8
VGG16	224x224	16
VGG19	224x224	19
GoogleNet	224x224	22
Inception v3	299x299	48
ResNet50	224x224	50

In experiments, we proposed to investigate the use of a CNN model in total hemoglobin estimation problems using an 80:20 divided dataset. First, the AlexNet model is trained using the scalograms. The workflow is given below (Figure 3.6).

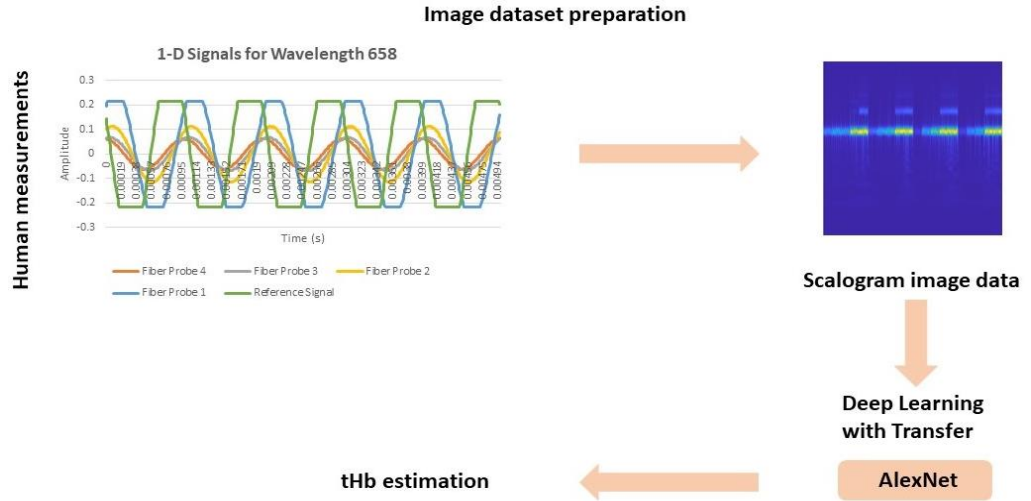


Figure 3.6. The workflow of the first experiment

The signals from volunteers are recorded at five different fiber probe distances for every four wavelengths (658 nm, 705 nm, 785 nm, and 833 nm) from 24 healthy volunteers. These signals are combined as one column vector for the scalogram process. This column vector is converted to scalograms using MATLAB for 20 and 50 MHz, respectively. The 1-D signals of measurement become 2-D scalograms using CWT. By transforming these signals from the time domain to the frequency domain, they can be trained with deep learning models. The parameters of CNN training such as the initial learning rates, minibatch size, and training learning methods (adaptive moment optimization (adam), stochastic gradient descent with momentum (sgdm), and root mean square propagation (rmsprop) are changed to make optimization with fixed gradient threshold, epoch and validation frequency.

After this optimization, the 5-fold cross-validation is applied to the dataset. Six different pre-trained CNN models are trained on this dataset. Also, these models are trained without weights from the ImageNet dataset. The whole dataset was divided into 5 parts. The training and validation processes were realized in totally five rounds. In each model, the specified one part of the dataset was used for testing and the rest of the four parts were used for the training. The workflow is given below (Figure 3.7).

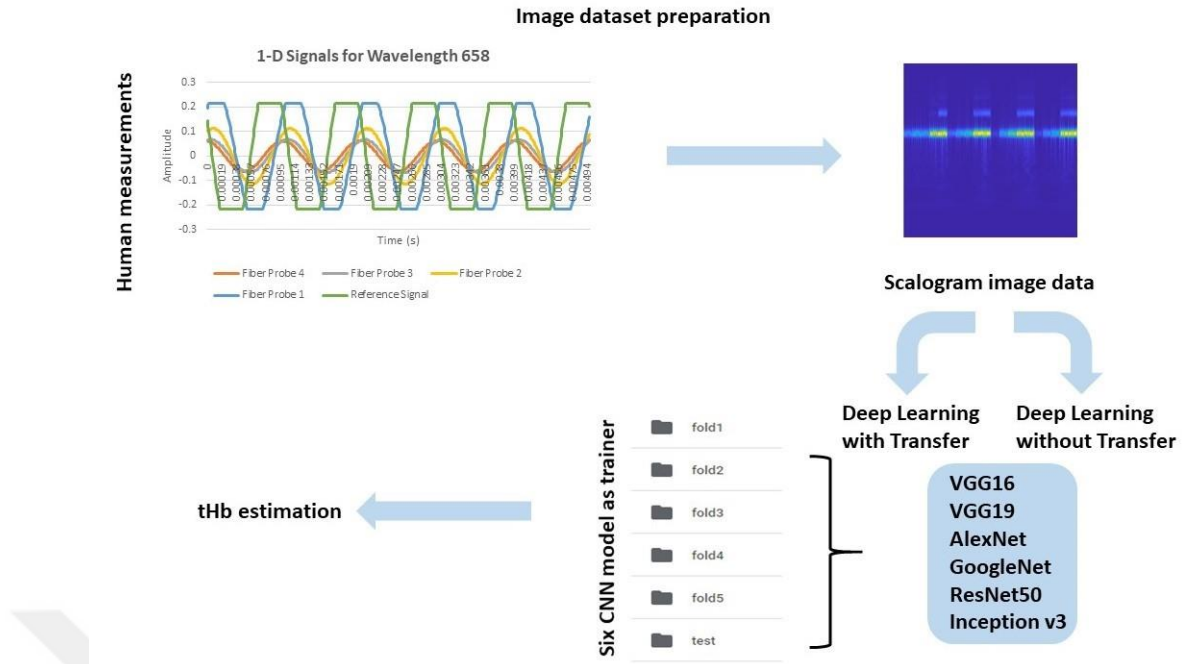


Figure 3.7. The workflow of the second experiment

3.3. Results & Discussion

3.3.1. Regression

Four features as RMS, phase difference, entropy, and PSD are trained in regressionLearner for 15, 20, and 50 MHz with 10-fold and 20-fold cross-validation. PCA is applied.

The dataset includes 20 training and 4 test data for 15 MHz. All regression models are trained with 10-fold cross-validation. The dataset includes 20 training and 4 test data for 15 MHz. The best RMSE result is 1.9872 with Medium Tree in all 19 models. The best RMSE result is 1.7722 with Fine Gaussian SWM in all 19 models when PCA is applied (Figure 3.8).

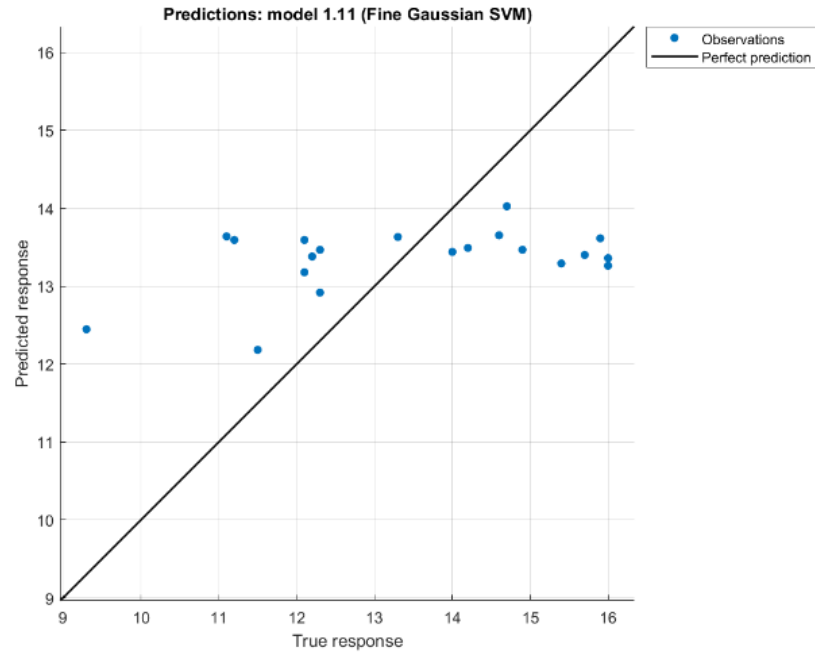


Figure 3.8. Predicted versus true response at 15 MHz, with 10-fold cross validation

The dataset includes 20 training and 4 test data for 20 MHz. The best RMSE result is 2.0703 with Medium Tree in all 19 models. The best RMSE result is 1.9707 with Ensemble Bagged Trees in all 19 models when PCA is applied (Figure 3.9).

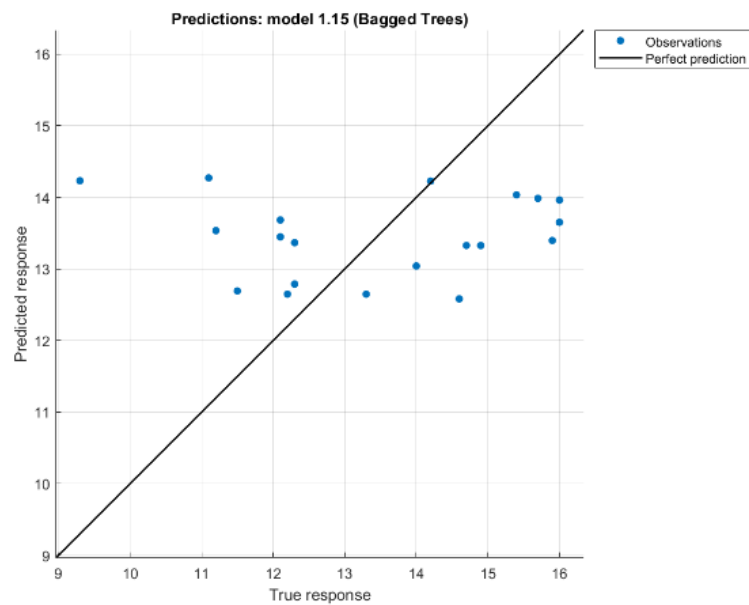


Figure 3.9. Predicted versus true response at 20 MHz, with 10-fold cross validation

The dataset includes 20 training and 7 test data for 50 MHz. The best RMSE result is 2.0246 with Medium Tree in all 19 models. The best RMSE result is 2.0048 with Gaussian Rational Quadratic in all 19 models when PCA is applied (Figure 3.10).

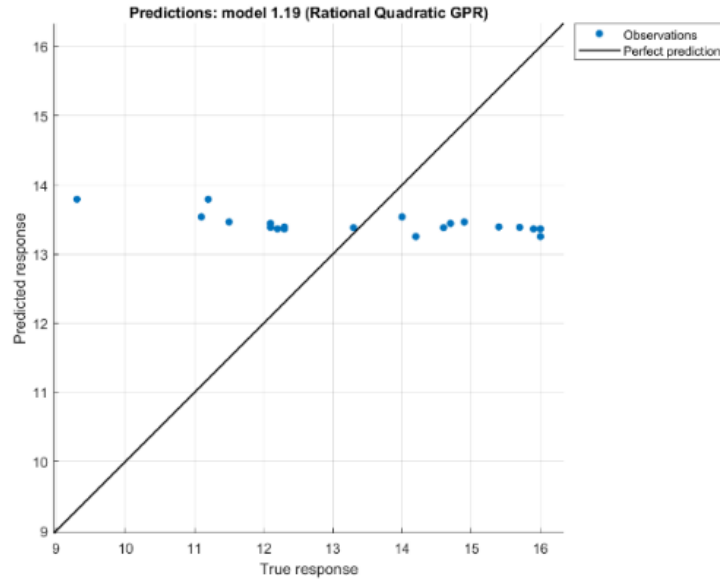


Figure 3.10. Predicted versus true response at 50 MHz, with 10-fold cross validation

All regression models are trained with 20-fold cross-validation. For 15 MHz, the best RMSE result is 2.0139 with Medium Tree in all 19 models and the best RMSE result is 1.6597 with Gaussian Process Regression Matern 5/2 GPR in all 19 models when PCA is applied. For 20 MHz, the best RMSE result is 2.0139 with Gaussian Process Regression Matern 5/2 GPR in all 19 models and the best RMSE result is 1.9575 with Ensemble Bagged Trees in all 19 models when PCA is applied. For 50 MHz, the best RMSE result is 1.8151 with Fine Tree in all 19 models and the best RMSE result is 2.0139 with Medium Tree in all 19 models when PCA is applied. The errors for coefficients for 10-fold cross-validation and predicted values for coefficients at four wavelengths are given in Table A.2-Table A.4.

Using the best models, the total hemoglobin is predicted. The minimum error rate is 7.4%, 10.75%, and 10.99% at 15, 20, and 50 MHz, respectively. The coefficient of cross-validation is up to 20, and experiments reran. The minimum

error rate is 5.13%, 9.83%, and 10.99% at 15, 20, and 50 MHz. The predicted hemoglobin values are given in Table 3.2 and comparisons for 15 and 20 MHz are shown in Figure 3.11 and Figure 3.12, respectively. The model statistics and prediction results for 10-fold cross-validation are given in Table A.6 and Table A.7, respectively.

Table 3.2. Predicted tHb values from regression models

Measured tHb	Predicted tHb 10-fold cross validation			Predicted tHb 20-fold cross validation		
	15 MHz PCA	20 MHz PCA	50 MHz PCA	15 MHz PCA	20 MHz PCA	50 MHz PCA
16.9	13.5	12.5	13.4	13.4	12.5	13.8
12.1	13	13.5	13.4	12.7	13.3	13.8
15.5	13.7	12.5	13.4	13.7	12.8	13.8
15.1	13	13.8	13.4	12.9	13.9	11.3

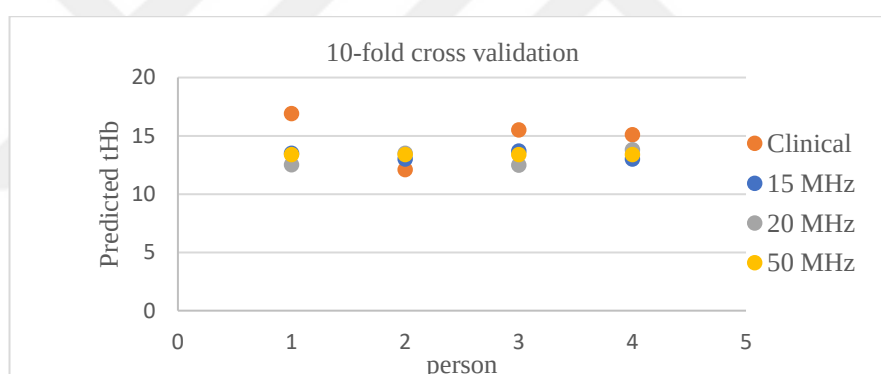


Figure 3.11. Comparison for clinical tHb and predicted tHb at 15, 20, and 50 MHz



Figure 3.12. Comparison for clinical tHb and predicted tHb at 15, 20, and 50 MHz

There are only four clinical measurements for HbO₂, HbCO, and HbMet species. The regression models have applied this measurement. Dataset is split as training includes three measurements and test includes one measurement. The best RMSE is 0.7966 with Linear Regression for HbO₂ (Figure 3.13), 0.96 with Ensemble Bagged Trees for HbCO (Figure 3.14), 0.6863 with Linear SVM for HbMet at 20 MHz (Figure 3.15). The best RMSE is 0.949 with Linear SVM for HbO₂, 0.98 with Linear Regression for HbCO, 1.0632 with Cubic SVM for HbMet when PCA is applied at 20 MHz.

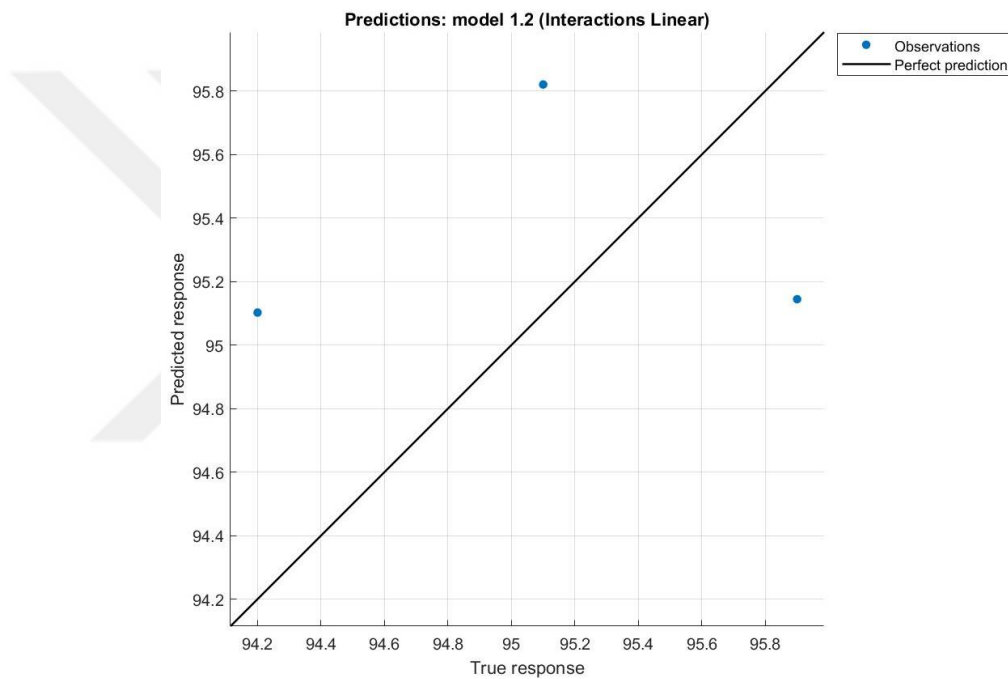


Figure 3.13. Predicted versus true response for HbO₂ at 20 MHz

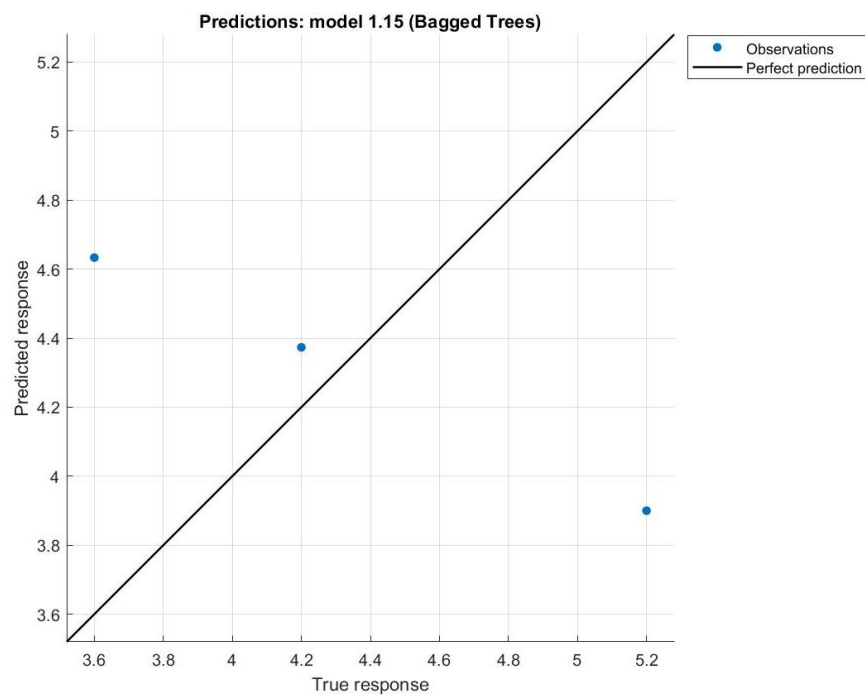


Figure 3.14. Predicted versus true response for HbCO at 20 MHz

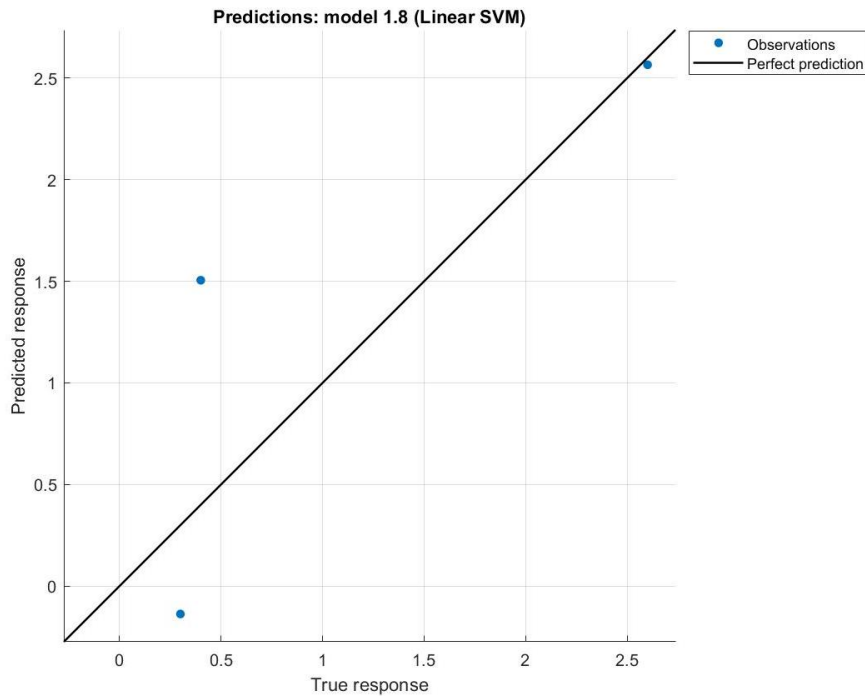


Figure 3.15. Predicted versus true response for HbMet at 20 MHz

The best RMSE is 0.3609 with Linear Regression for HbO₂ (Figure 3.16), 0.6538 with Linear Regression Interactions for HbCO (Figure 3.17), 1.2247 with Linear Regression for HbMet at 50 MHz (Figure 3.18).

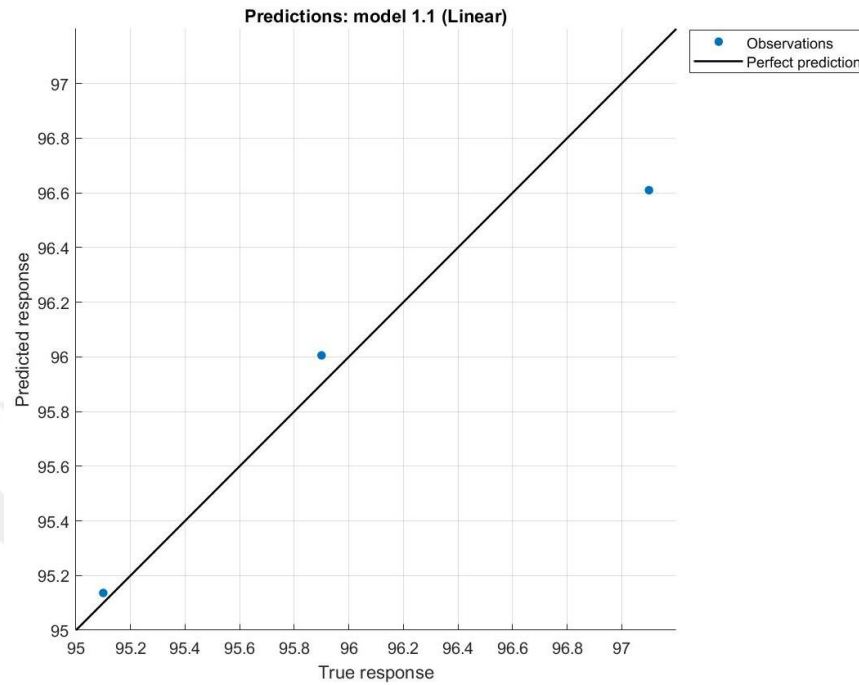


Figure 3.16. Predicted versus true response for HbO₂ at 50 MHz

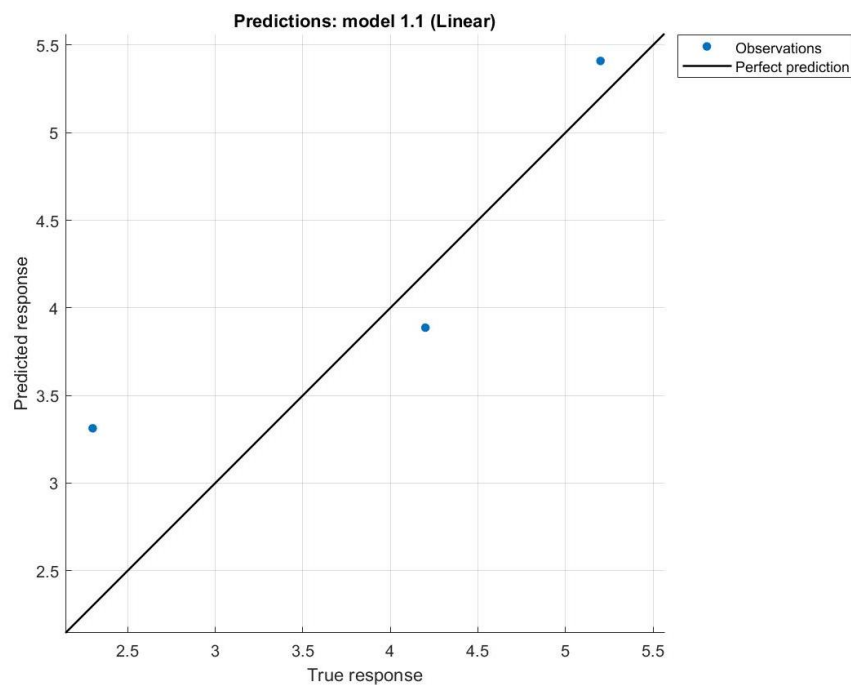


Figure 3.17. Predicted versus true response for HbCO at 50 MHz

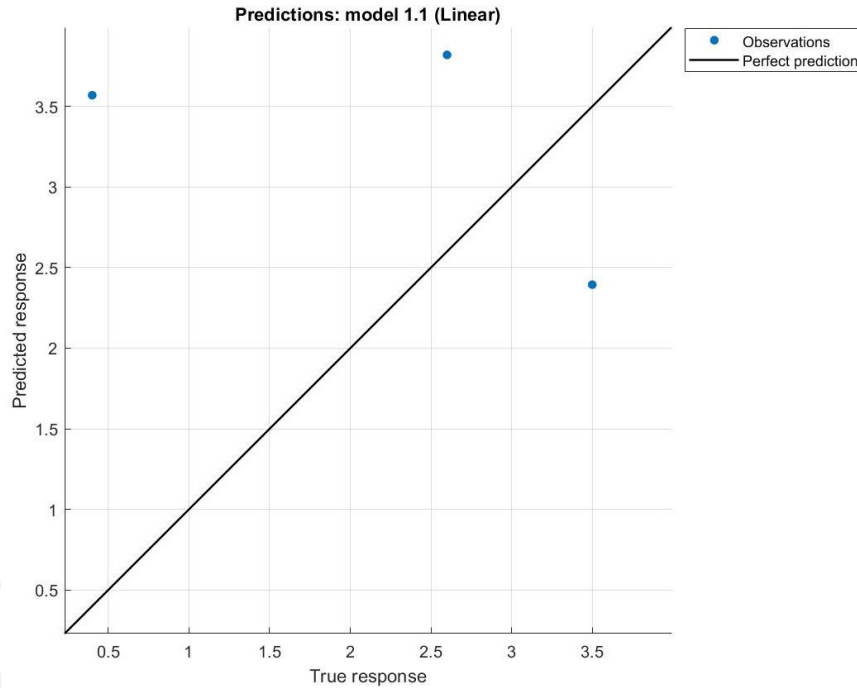


Figure 3.18. Predicted versus true response for HbMet at 50 MHz

The best RMSE is 0.2902 with Linear Regression for HbO₂, 0.6238 with Linear Regression for HbCO, 1.5466 with Cubic SVM for HbMet when PCA is applied at 50 MHz.

Using the best models, the three hemoglobin species are predicted. In the experiments, four trial is tried with changing the dataset (Table 3.3). The minimum error rate is at 20 MHz 0.30%, 3.74%, and 0.80% for HbO₂, HbCO and HbMet, respectively. The minimum error rate is at 50 MHz 0.06%, 6.70%, and 48.43% for HbO₂, HbCO and HbMet, respectively (Table 3.4, Table 3.5 and Table 3.6).

Table 3.3. Experiments

Experiment	Training	Test
Trial 1	Person 1, 2, 3	Person 4
Trial 2	Person 2, 3, 4	Person 1
Trial 3	Person 1, 2, 4	Person 3
Trial 4	Person 1, 3, 4	Person 2

Table 3.4. Predicted HbO₂ values from regression models

Experiments	Clinical HbO ₂	Predicted HbO ₂			
		20 MHz	20 MHz + PCA	50 MHz	50 MHz + PCA
Trial 1	97.1	94.737	94.467	94.8086	95.00667
Trial2	95.1	95.812	95.733	96.1141	95.733
Trial3	94.2	96.069	96.0922	94.6725	96.7369
Trial4	95.9	95.588	95.607	95.8446	95.4667

Table 3.5. Predicted HbCO values from regression models

Experiments	Clinical HbCO	Predicted HbCO			
		20 MHz	20 MHz + PCA	50 MHz	50 MHz + PCA
Tria1	2.3	4.2978	4.3822	3.3564	3.2893
Trial2	5.2	3.2683	3.4372	3.2239	5.5488
Trial3	3.6	3.7347	4.02	2.2694	2.8762
Trial4	4.2	6.484	7.4332	3.6878	3.5432

Table 3.6. Predicted HbMet values from regression models

Experiments	Clinical HbMet	Predicted HbMet			
		20 MHz	20 MHz + PCA	50 MHz	50 MHz + PCA
Tria1	0.3	0.7882	0.1234	3.3927	2.1667
Trial2	2.6	1.3716	0.7786	1.3011	1.3407
Trial3	0.4	0.4129	0.635	2.0429	2.22
Trial4	3.5	1.4873	3.4719	0.594	1.4714

3.3.2. Deep Learning

1-D signals become 2-D scalograms using CWT. These scalogram images are classified at four classes named as 9-10, 11-12, 13-14, and 15-16. The classes for training are identified as total hemoglobin values between 9-16 g/dL. These numbers identify tHb concentration (tHb is 12-16 g/dL for females and 13-18 g/dL for males).

In the first experiment, a pre-trained deep architecture, AlexNet is used to training the dataset with different training options. The initial learning rates (10^{-3} , 10^{-4} , 10^{-5} , 10^{-6} , and 10^{-7}), minibatch sizes (8, 16, 32, 64, and 128), and training learning methods (adam, sgdm, and rmsprop) are changed to make optimization. AlexNet model is trained using three learning methods adam, sgdm, and rmsprop with 500 epochs. The gradient threshold is 10 and the validation frequency is 100.

We observed that the optimum results are taken with initial learning rates between 10^{-3} and 10^{-5} . Figure 3.19, Figure 3.20 and Figure 3.21 show the validation and test accuracies with different learning methods with 8 minibatch sizes at 20 MHz.

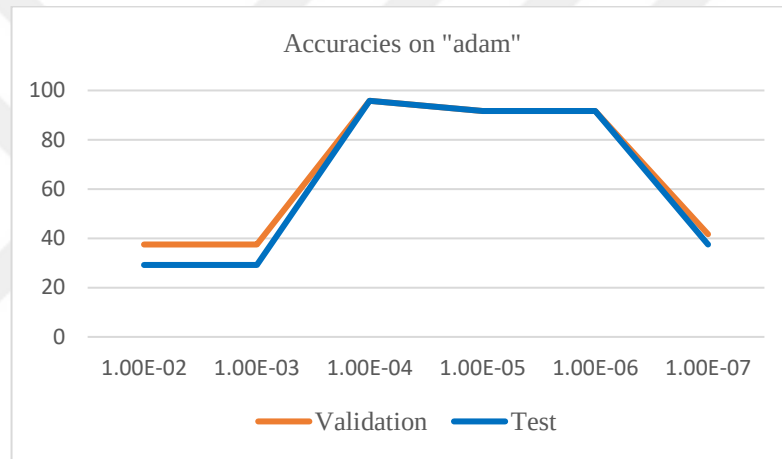


Figure 3.19. Accuracies with “adam” and 8 minibatch size

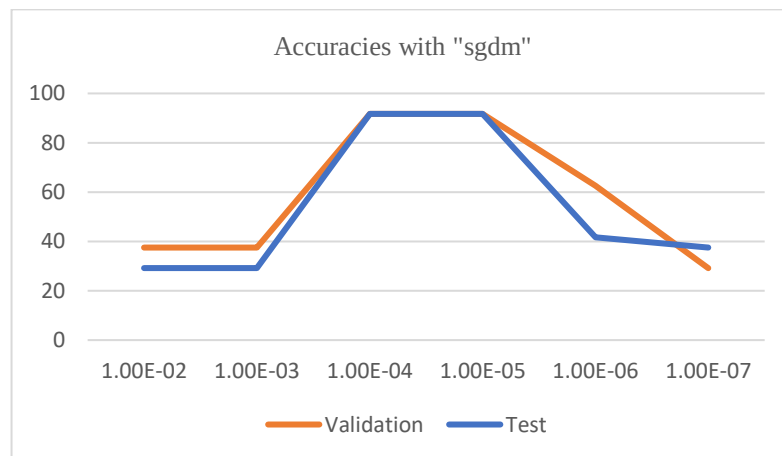


Figure 3.20. Accuracies with “sgdm” and 8 minibatch size

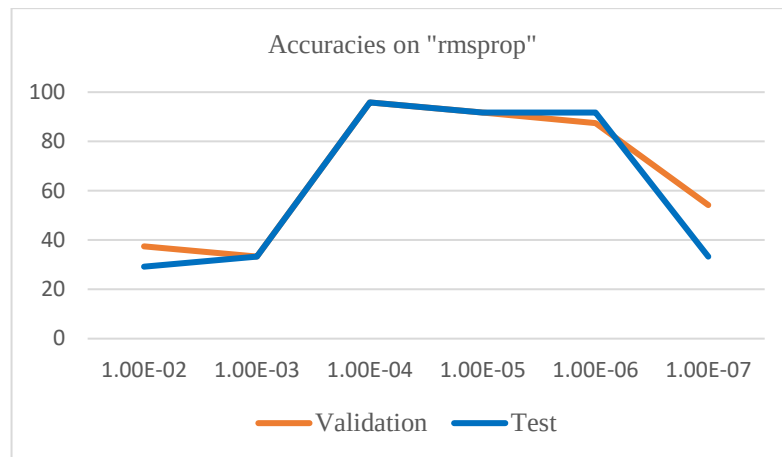


Figure 3.21. Accuracies with “rmsprop” and 8 minibatch size

Figure 3.22, Figure 3.23, and Figure 3.24 show the validation and test accuracies with different learning methods with 16 minibatch size at 20 MHz.

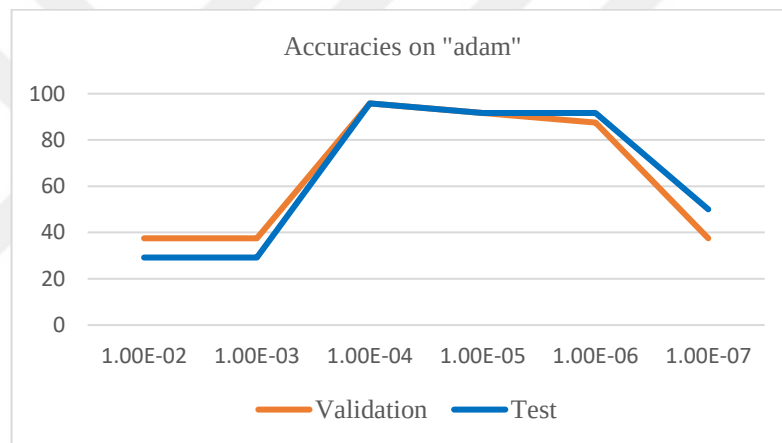


Figure 3.22. Accuracies with “adam” and 16 minibatch size

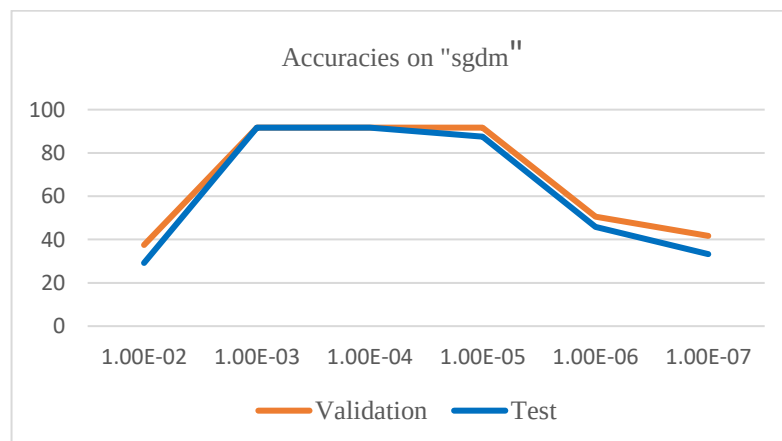


Figure 3.23. Accuracies with “sgdm” and 16 minibatch size

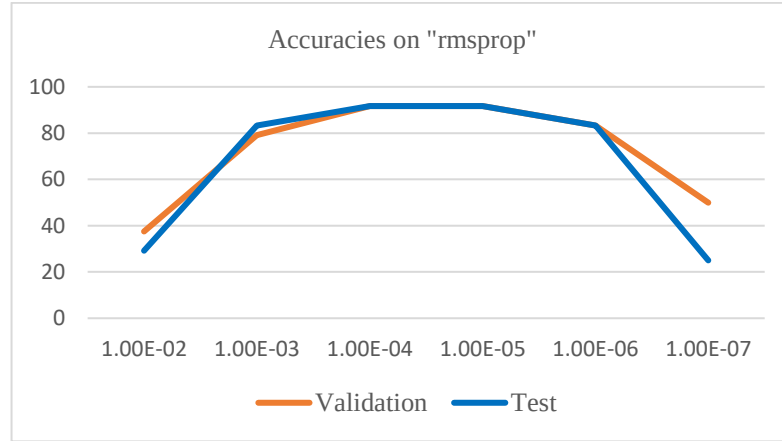


Figure 3.24. Accuracies with “rmsprop” and 16 minibatch size

Table 3.7 gives the results of validation and test accuracies at 20 MHz according to the different parameters.

Table 3.7. Validation and test accuracies at 20 MHz

Training method	MiniBatch Size	Initial Learning Rate	Validation Accuracy (%)	Test Accuracy (%)
sgdm	8	1e-5	91.7	91.7
sgdm	16	1e-5	91.7	87.5
sgdm	32	1e-3	91.7	91.7
sgdm	64	1e-3	91.7	95.8
sgdm	128	1e-4	91.7	91.7
adam	8	1e-4	95.8	95.8
adam	16	1e-6	87.5	91.7
adam	32	1e-5	91.7	91.7
adam	64	1e-5	91.7	91.7
adam	128	1e-5	91.7	91.7
rmsprop	8	1e-4	95.8	95.8
rmsprop	16	1e-4	91.7	91.7
rmsprop	32	1e-4	95.83	91.7

Table 3.7. (continue)

Training method	MiniBatch Size	Initial Learning Rate	Validation Accuracy (%)	Test Accuracy (%)
rmsprop	64	1e-5	91.7	91.7
rmsprop	128	1e-4	91.7	91.7

Table 3.8 gives the results of validation and test accuracies at 50 MHz for the best parameters that are chosen according to the results of experiments at 20 MHz.

Table 3.8. Validation and test accuracies at 50 MHz

Training method	MiniBatch Size	Initial Learning Rate	Validation Accuracy (%)	Test Accuracy (%)
sgdm	8	1e-5	91.7	91.7
sgdm	16	1e-5	91.7	87.5
adam	8	1e-6	91.7	91.7
adam	16	1e-6	87.5	91.7
rmsprop	64	1e-3	91.7	91.7

The accuracy graph of training with 10^{-5} initial learning rate, 16 minibatch sizes, and sgdm learning method at 20 MHz is given in Figure 3.25. This is the optimum result among other results.

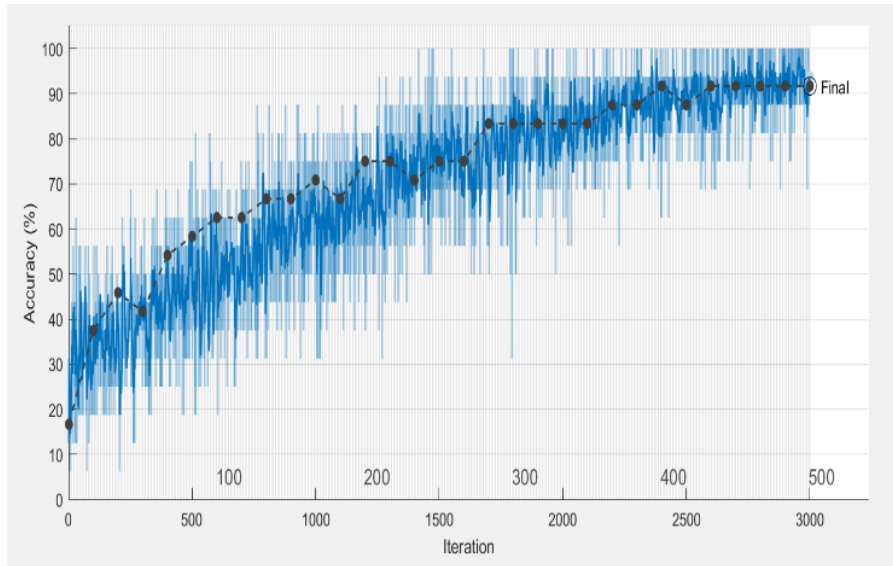


Figure 3.25. The accuracy plot

The loss graph of training with 10^{-5} initial learning rate, 16 minibatch sizes, and sgd learning method at 20 MHz is given in Figure 3.26.

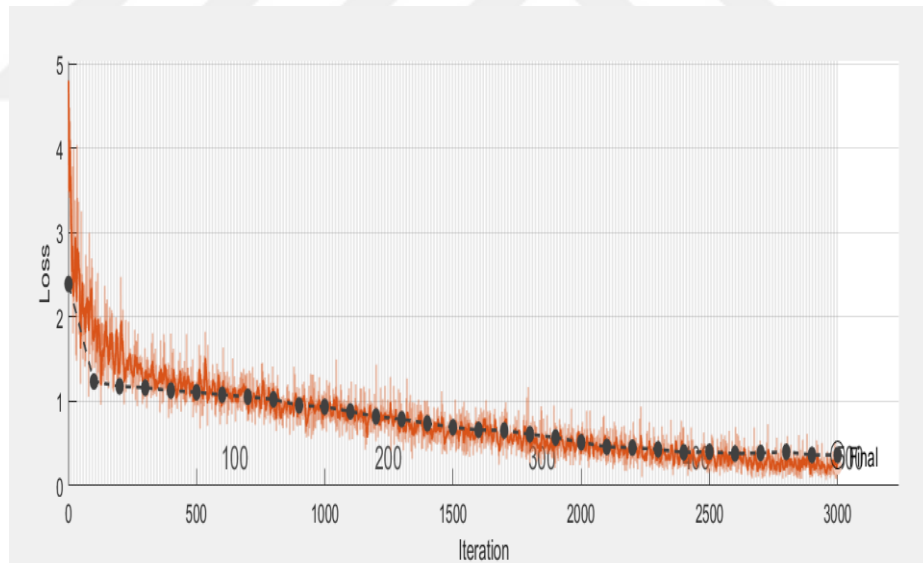


Figure 3.26. The loss plot

The confusion matrix of these graphs is given in Figure 3.27.

Confusion Matrix						
Output Class	11-12	13-14	15-16	9-10		
	7 29.2%	1 4.2%	1 4.2%	0 0.0%	77.8% 22.2%	
	0 0.0%	6 25.0%	0 0.0%	0 0.0%	100% 0.0%	
	0 0.0%	1 4.2%	7 29.2%	0 0.0%	87.5% 12.5%	
	0 0.0%	0 0.0%	0 0.0%	1 4.2%	100% 0.0%	
		11-12	13-14	15-16	9-10	
		100% 0.0%	75.0% 25.0%	87.5% 12.5%	100% 0.0%	87.5% 12.5%
		Target Class				

Figure 3.27. The confusion matrix

A sample for accuracies and classes is given in Figure 3.28.

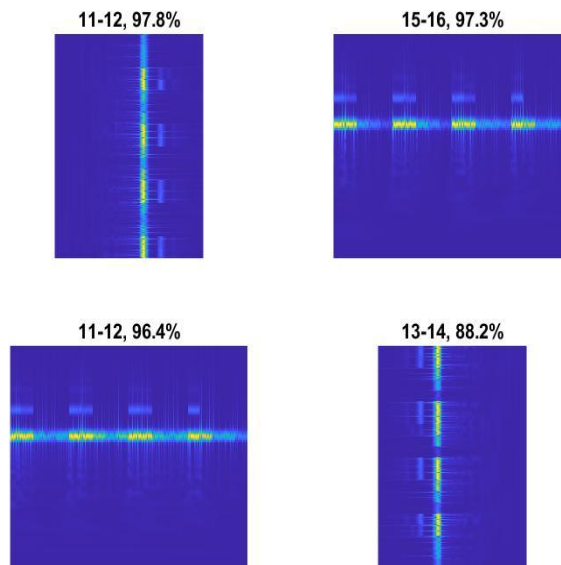


Figure 3.28. tHb classes and their accuracies

In the last experimental setup, we applied the 5-fold cross-validation method to the dataset. The whole dataset was divided into 5 parts. The training and

validation processes were realized in totally five rounds. In each model, the specified one part of the dataset was used for testing and the rest of the four parts were used for the training. The six different pre-trained deep learning architectures are trained such as VGG16, VGG19, AlexNet, ResNet50, Inception-v3. These architectures are trained without weights. It means that these architectures are trained with our dataset and extracted weights. Table 3.9 and Table 3.10 shows the average accuracies for deep learning with transfer and deep learning without transfer for both 20 and 50 MHz. We trained models using sgdm as learning methods with 500 epochs. The minimum batch size is 5, the gradient threshold is 10, the initial learning rate is 0.0001, and the validation frequency is 4.

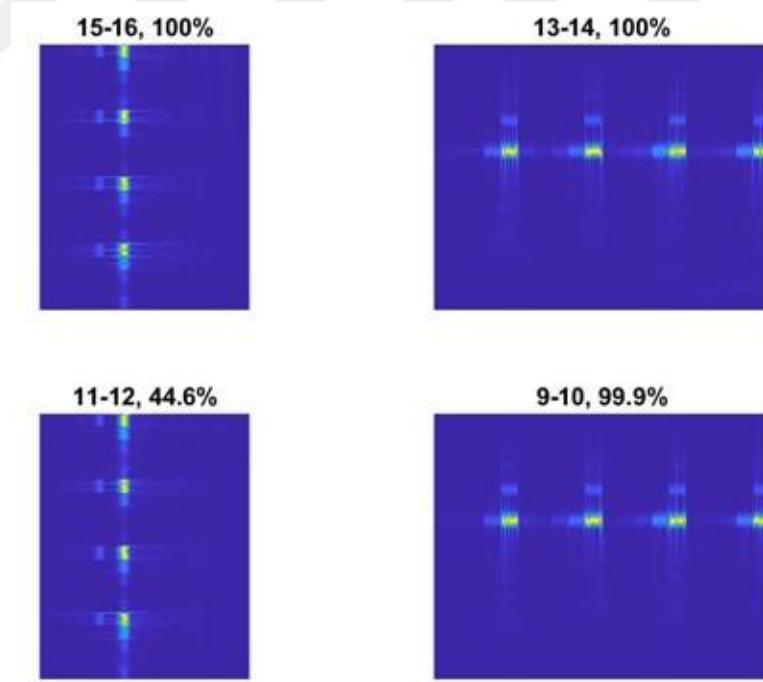
A sample for accuracies and classes is given in Table 3.9. The best accuracy and loss plots of transfer learning are given in Figure A.1-Figure A.4.

Table 3.9. 5-fold cross validated 20 MHz total hemoglobin estimation accuracies

20 MHz	Transfer Learning		Deep Learning without Transfer	
	Validation Accuracy (%) (mean±std)	Test Accuracy (%) (mean±std)	Validation Accuracy (%) (mean±std)	Test Accuracy (%) (mean±std)
Inception v3	94.17±6.27	95.85±3.71	94.17±6.24	83.34±27.24
AlexNet	94.17±4.99	97.49±3.34	90.83±5.53	94.16±3.31
VGG16	95.00±4.08	95.83±3.72	91.67±5.27	86.66±6.12
ResNet50	95.00±4.86	95.83±3.72	90.84±6.67	95.00±3.11
VGG19	95.83±3.73	95.83±3.72	81.67±11.36	78.29±8.15
GoogleNet	95.00±4.08	95.83±3.72	92.51±4.08	96.66±3.11

Table 3.10. 5-fold cross validated 50 MHz total hemoglobin estimation accuracies

	Transfer Learning		Deep Learning without Transfer	
50 MHz	Validation Accuracy (%) (mean±std)	Test Accuracy (%) (mean±std)	Validation Accuracy (%) (mean±std)	Test Accuracy (%) (mean±std)
Inception v3	94.17±8.16	97.50±3.32	92.5±7.17	96.66±3.12
AlexNet	95.83±3.72	95.84±3.71	93.33±7.73	96.66±3.11
VGG16	93.33±7.73	97.50±3.33	90.83±10.67	95.01±4.07
ResNet50	96.67±3.12	96.66±3.11	95.83±5.26	95±4.85
VGG19	95.00±4.86	97.51±3.32	75.83±12.74	85.84±11.94
GoogleNet	95.83±3.72	95.84±3.71	94.16±8.17	97.49±3.35

**Figure 3.29. Samples from dataset with their accuracies**

4. CONCLUSIONS AND FUTURE WORKS

Using a non-contact measurement device with two-layer single-stage TIA, estimated values for $\mu_a=1 \text{ cm}^{-1}$ were 0.795 ± 0.158 , 0.690 ± 0.119 , 0.670 ± 0.099 , and $0.613\pm0.103 \text{ cm}^{-1}$ for wavelengths of 658 nm, 705 nm, 785 nm, and 833 nm respectively and for $\mu'_s=22 \text{ cm}^{-1}$ estimated values are 19.876 ± 4.273 , 18.845 ± 3.494 , 17.134 ± 2.577 and $17.927\pm2.893 \text{ cm}^{-1}$ (Bal, U. et al., 2020). Current methods with contact manner reached up to 20% error. It was expected that the non-contact design would give results in low light levels comparable to contact measurements. However, it was still possible to reasonably predict μ_a and μ'_s in phantoms with a modulated frequency of 15 MHz using a custom-designed two-layer single-stage amplifier.

The improvement is observed when the custom designed four-layer multi-stage amplifier with an RF amplifier is used in this design. Four-layer multi-stage TIA's gain is greater than of two-layer single-stage between 0-100 MHz. There was 2 dB gain difference among them. The output signal is higher with the PCB which includes the MMIC part. The gain is 20 dB between 0-400 MHz. But the error rate is minimized using four-layer multi-stage OPA657 part with an RF amplifier.

Using a non-contact measurement device, deep learning architectures are trained for total hemoglobin estimation (Moral, Ö.T., and Bal, U. 2020). First, only one model, AlexNet is used to train the dataset. The experimental results achieved up to 87.5% of test accuracy with transfer learning using AlexNet for 20 MHz and 50 MHz in approximately 0.25 seconds. Second, six different deep learning architectures (VGG16, VGG19, AlexNet, ResNet50, GoogleNet, and Inception-v3) are trained to estimate tHb. The experimental results achieved up to $97.49\pm3.34\%$ of test accuracy with transfer learning using AlexNet and $96.66\pm3.11\%$ of test accuracy with deep learning using GoogleNet for 20 MHz, whereas $97.51\pm3.32\%$ of test accuracy with transfer learning using VGG19 and $97.49\pm3.35\%$ of test accuracy with deep learning using GoogleNet for 50 MHz in

approximately 0.25 seconds. It was expected that when the modulation frequency is increasing, the accuracy of estimation will increase. It can be concluded that the non-contact estimation of total hemoglobin can be performed with the proposed design and deep learning methods.

The low-level signals are obtained with the proposed design. To able to observe the phase difference in FDMD measurements on tissue with sufficient accuracy, modulation of the light should be at least 50 MHz. The proposed non-contact system amplified reflected light through the PMTs and TIAs up to 15 MHz without oscillation. But the signal at 20 or 50 MHz is a low level and oscillation was observed at these levels. An improved multi-layer TIA should allow an increase in bandwidth from 50 to 100 MHz. Besides, the response time of PMT or photodiode restricts the bandwidth. PMT or photodiode with fast response time should be chosen for increasing the frequency.

The back reflections of camera lens from the center of the fiber probe, caused an unexpected light distribution. The collection and illumination paths are separated with a second fiber probe and two separate camera lenses are used in this thesis study. To reduce the effects of back reflections, the improved fiber probe can be designed, and the distance of the camera lens can be adjusted accurately.

In addition, using an optical phantom closer to skin μ_a and μ'_s while performing calibration will enable us to reach better calibration coefficients. Therefore, error rates can be reduced in tissue measurements.

Deep learning models requires large datasets. Raw signal measurement from healthy volunteers helps to improve the accuracy of CNN models.

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APPENDIX

Thirty measurements on optical phantoms (Table A.1) at 15 MHz are given below. Test phantom is $\mu_a=1.0 \text{ cm}^{-1}$ $\mu'_s=22 \text{ cm}^{-1}$. Calibration phantom is $\mu_a=0.7 \text{ cm}^{-1}$ $\mu'_s=15 \text{ cm}^{-1}$.

Table A.1. Thirty measurements on optical phantoms

Wavelength (nm)							
658		705		785		833	
μ_a	μ'_s	μ_a	μ'_s	μ_a	μ'_s	μ_a	μ'_s
0.7337	13.4309	0.6437	16.0148	0.7133	13.9977	0.4787	21.1680
1.0139	14.5900	0.7526	16.6595	0.7688	14.4663	0.4939	21.6546
0.4876	32.5385	0.5169	24.9880	0.6479	18.1198	0.5425	19.8802
0.5918	25.5880	0.6244	19.9162	0.6413	17.8934	0.5504	18.6767
0.9509	16.4935	0.6853	18.6220	0.5500	21.2918	0.5376	20.4464
0.7243	21.7977	0.6620	19.3486	0.5885	19.8211	0.5694	19.3198
0.8508	18.4043	0.6619	19.5221	0.6772	17.1484	0.5742	19.2766
1.2868	12.1664	0.8428	15.4982	0.7509	15.6537	0.6163	18.6903
0.6759	22.7770	0.6732	18.3843	0.5928	19.2450	0.5537	19.5369
0.8248	18.5166	0.6458	19.2204	0.5464	20.9233	0.6026	17.9772
0.6944	22.4520	0.5038	25.1822	0.5474	20.8024	0.5265	20.5631
0.5858	26.6758	0.5202	24.3536	0.5940	19.1269	0.4885	22.0970
0.7399	20.8422	0.6426	19.4414	0.7015	15.9346	0.5489	19.6580
0.9211	16.5277	0.6177	20.2775	0.6374	17.6281	0.5970	18.1019

Table A.1. (continue)

Wavelength (nm)							
658		705		785		833	
μ_a	μ'_s	μ_a	μ'_s	μ_a	μ'_s	μ_a	μ'_s
0.7610	20.2025	0.5974	20.2025	0.5358	21.4170	0.6126	17.7092
0.6323	24.4375	0.6208	20.0455	0.5802	19.7391	0.5622	19.2732
0.7051	21.7609	0.5071	24.8975	0.7055	15.8764	0.5161	20.8991
0.8688	17.4838	0.4914	5.7235	0.6407	17.5725	0.5586	19.3554
0.9482	15.8758	0.6657	18.7684	0.6036	18.7334	0.5512	19.5502
0.7568	20.1867	0.6948	17.9272	0.6607	17.0461	0.5096	21.0890
0.8388	18.3796	0.7093	17.4750	0.7336	15.0972	0.6991	15.0718
0.8272	18.5432	0.9109	13.1878	0.7109	15.5471	0.6771	15.5753
0.6856	22.6842	0.8658	13.8858	0.6770	16.3946	0.7115	14.7547
0.6939	22.5358	0.6813	18.1462	0.6976	15.9487	0.7358	14.2482
0.7137	21.7227	0.6439	19.3980	0.6813	16.4065	0.8502	12.1653
0.7050	21.8730	0.8055	15.1456	0.6616	16.8510	0.8181	12.6823
0.9815	15.4429	0.6947	17.8702	0.6912	16.2024	0.6838	15.4751
0.9662	15.6186	0.8870	13.5915	0.6710	16.6487	0.6628	15.9778
0.8348	18.4485	0.8866	13.6773	0.9336	11.4761	0.7645	13.7165
0.8466	18.2838	0.6949	17.9667	0.9724	11.0003	0.7924	13.2039

All results are given for regression models. The errors of coefficients for four-layer multi-stage amplifier and real/predicted coefficients at 15 MHz are given in Table A.2 and Table A.3, respectively.

Table A.2. Errors of coefficients for four-layer multi-stage amplifier

Error of Absorption Coefficient (%)				Error of Scattering Coefficient (%)		
	0.4V	0.5V	0.6V	0.4V	0.5V	0.6V
658	40.677966	41.525424	60.169492	0.2727273	1.7727273	28.181818
705	67.826087	64.347826	74.782609	47.058824	25.656109	71.945701

Table A.2. (continue)

	Error of Absorption Coefficient (%)			Error of Scattering Coefficient (%)		
	0.4V	0.5V	0.6V	0.4V	0.5V	0.6V
785	56.756757	52.252252	57.657658	1.8721461	7.260274	2.7853881
833	58.653846	50	65.384615	4.5575221	16.371681	11.946903

Table A.3. Real and predicted coefficients at 15 MHz for four-layer multi-stage amplifier

	Absorption Coefficient				Scattering Coefficient			
	Real	0.4V	0.5V	0.6V	Real	0.4V	0.5V	0.6V
658	1.18	0.7	0.69	0.47	22	22.06	21.61	28.2
705	1.15	0.37	0.41	0.29	22.1	32.5	27.77	38
785	1.11	0.48	0.53	0.47	21.9	22.31	20.31	22.51
833	1.04	0.43	0.52	0.36	22.6	23.63	18.9	25.3

The errors of coefficients for OPA657+RF amplifier and real/predicted coefficients at 15 MHz are given in Table A.4 and Table A.5, respectively.

Table A.4. Errors of coefficients for four-layer multi-stage amplifier OPA657+RF amplifier

	Error of Absorption Coefficient		Error of Scattering Coefficient	
	0.5V	0.6V	0.5V	0.6V
658	1.6949153	16.101695	47.727273	34.5
705	41.73913	8.6956522	25.429864	29.095023
785	16.216216	16.216216	50.776256	29.680365
833	32.692308	6.7307692	40.221239	41.460177

Table A.5. Real and predicted coefficients at 15 MHz for four-layer multi-stage amplifier

	Absorption Coefficient			Scattering Coefficient		
	Real	0.5V	0.6V	Real	0.5V	0.6V
658	1.18	1.2	1.01	22	11.5	14.41
705	1.15	0.67	0.77	22.1	16.48	15.67
785	1.11	0.93	0.75	21.9	10.78	15.4
833	1.04	0.7	0.77	22.6	13.51	13.23

The model statistics and clinical/predicted tHb values at 15, 20 and 50 MHz with/without PCA are given in Table A.6 and Table A.7, respectively.

Table A.6. Model statistics at 15, 20 and 50 MHz with / without PCA

Parameters	15 MHz	15 MHz + PCA	20 MHz	20 MHz + PCA	50 MHz	50 MHz + PCA
RMSE	1.9872	1.7722	2.0703	1.9707	2.0246	2.0048
R-squared	0.0	0.21	0.0	0.03	0.0	0.00
MSE	3.9489	3.1407	4.286	3.8838	4.099	4.0191
MAE	1.7739	1.5511	1.855	1.6569	1.8133	1.7539

Table A.7. Clinical and predicted tHb at 15, 20 and 50 MHz with / without PCA

15 MHz		15 MHz + PCA		20 MHz	20 MHz + PCA	50 MHz	50 MHz + PCA
Test	tHb	Predicted tHb	Predicted tHb	Predicted tHb	Predicted tHb	Predicted tHb	Predicted tHb
P31	16.9	13.44	13.4953	13.4400	12.5039	13.4400	13.4400
P32	12.1	13.44	13.0055	13.4400	13.4766	13.4400	13.4400
P33	15.5	13.44	13.7252	13.4400	12.5039	13.4400	13.4400
P34	15.1	13.44	13.0014	13.4400	13.4766	13.4400	13.4400
P2	16.6	x	x	x	x	13.4400	13.4400
P3	16.6	x	x	x	x	13.4400	13.4400

Table A.7. (continue)

	15 MHz		15 MHz + PCA	20 MHz	20 MHz + PCA	50 MHz	50 MHz + PCA
Test	tHb	Predicted tHb	Predicted tHb	Predicted tHb	Predicted tHb	Predicted tHb	Predicted tHb
P10	11.1	x	x	x	x	13.4400	13.4400

Accuracy/loss plots and confusion matrix for AlexNet at 20 MHz are given Figure A.1 and Figure A.2, respectively.

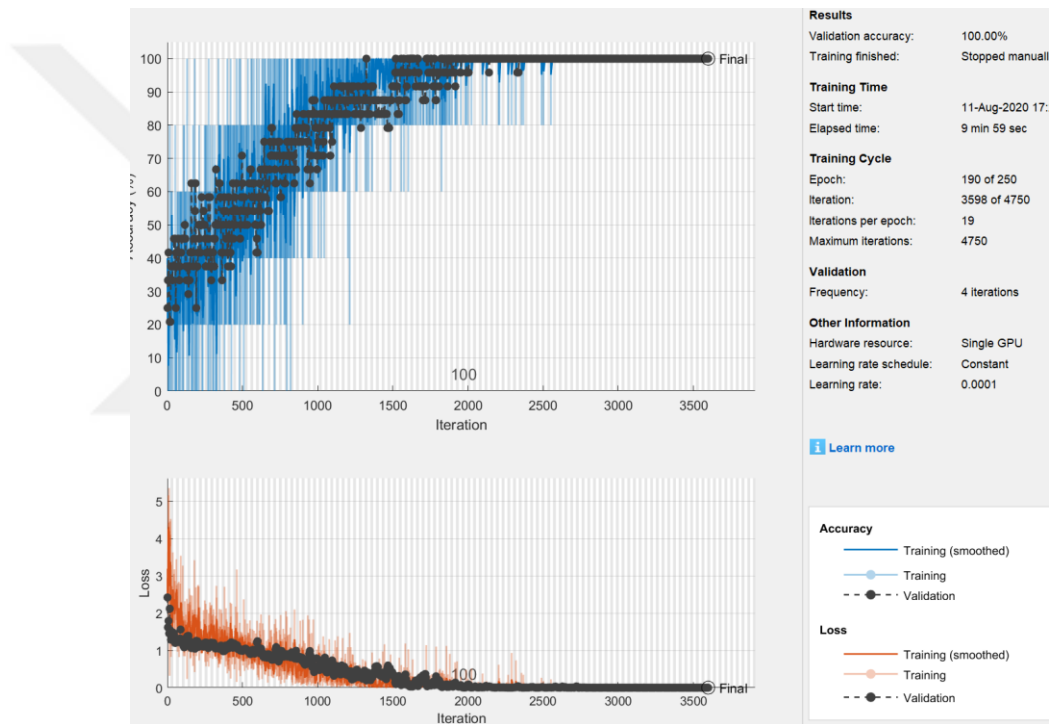


Figure A.1. Accuracy and loss plots for AlexNet (fold3), at 20 MHz, transfer learning

Confusion Matrix					
Output Class	11-12	13-14	15-16	9-10	
	7 29.2%	0 0.0%	0 0.0%	0 0.0%	100% 0.0%
	0 0.0%	8 33.3%	0 0.0%	0 0.0%	100% 0.0%
	0 0.0%	0 0.0%	8 33.3%	0 0.0%	100% 0.0%
	0 0.0%	0 0.0%	0 0.0%	1 4.2%	100% 0.0%
	11-12	13-14	15-16	9-10	
	100% 0.0%	100% 0.0%	100% 0.0%	100% 0.0%	100% 0.0%

Figure A.4. The confusion matrix for AlexNet (fold3), at 50 MHz, transfer learning

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2. “Multiwavelength Oximeter Design”
Funded by: Scientific Research Projects Coordination of Muğla Sıtkı Koçman University, Turkey by grant number 19/079/08/2/1.

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Funded by: TUBITAK by grant number 115E245.
2. 12 months with “TUBITAK - 2210-C Yurt İçi Öncelikli Alanlar Yüksek Lisans Burs Programı” by grant 1649B021803281.

List of Publications:

1. U. Bal, U. Utzinger, A. Bal, **O. T. Moral**, “Non-contact measurement of hemoglobin using FDMD method,” International Eurasian Conference on Science, Engineering and Technology, Ankara, Turkey, 22-23 November 2018
2. U. Bal, U. Utzinger, A. Bal, **O. T. Moral**, "The Determination of Absorption and Reduced Scattering Coefficients of Optical Phantoms Using a Frequency-Domain Multi-Distance Method in a Non-contact Manner," Advances in Electrical and Computer Engineering, vol.20, no.2, pp.3-10, 2020, doi:10.4316/AECE.2020.02001
3. **Ö. T. Moral** and U. Bal, "Non-Contact Total Hemoglobin Estimation Using a Deep Learning Model," 2020 4th International Symposium on Multidisciplinary Studies and Innovative Technologies (ISMSIT), Istanbul, Turkey, 2020, pp. 1-6, doi: 10.1109/ISMSIT50672.2020.9254443.