Towards Translation of Portable, Non-invasive, Near-infrared Imaging Systems

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ABSTRACT

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Dr. Qianqian Fang, Adviser

To...

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Here I wish to thank those who have supported me during the process of the thesis work...

PREFACE

Here I'll write a dope section. More personal. Something that states why I started this research.

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LIST OF ACRONYMS

AC alternating current.

DC direct current.

DOT diffuse optical tomography.

fNIRS functional near-infrared spectroscopy.

IR infrared.

LASER Light Amplification by Stimulated Emission of Radiation.

LED light emitting diodes.

LMIC low- and middle-income countries.

MOBI Modular Optical Brain Imaging.

MOXI Mobile-phone-based Oximeter.

NIR near infrared.

OMCI Optical Mammography Co-Imager.

PPG photoplethysmogram.

ROI region-of-interest.

RR ratio-of-ratios.

SLI structured light illumination.

CHAPTER 1

INTRODUCTION

Modern civilization has leveraged medical imaging as a fundamental clincal and research tool for years. Although for the first 80 years or so were heavily focused ont he use of x-rays, the field is growing at a rapid pace due in part to the increasing availabilty of relatively inexpensive computational resources. In recent decades, we have seen an emergence of new imaging technologies that improve on traditional methods being developed and commercialized, including MRI, nuclear imaging (PET, SPECT, etc.), and ultrasound. These contemporary imaging modalities have improved on the ionizing approach of x-ray, and thus, more and more frequently have taken center of routine clinical use.

Although their diagnostic capability advancements are not in question, these "contemporary medicine relies heavily on radiological and mediconuclear investigations and procedures. "Use of radiation for medical examinations and tests is the largest manmade source of radiation exposure." Nuclear imaging relies on the imaging of injected/ingested radioactive isotopes that attach to biochemicaaly active substances in the body. Improving on these methods, ultrasound uses high frequency sound waves to interrogate the interior of the body. Although particularly useful for imaging structures in motion, it finds a limit in dense structures like the skull and requires the application of agents on the surface. MRI is also non-ionizing, using high energy magnets to obtain structural and functional information. It is the typically the most exciting of contemporary modalities since can achive high resolution of the entire body. The drawback is that these machines are immense, extremely expensive, and require the use to be immobile during use, limiting its impact to investigations of immobile functions and to populations with the economic resources to access them. We are in need of an imaging technique is non-invasive, non-ionizing, can be used to diagnose various areas of the body, and is portable and low-cost for use by many.

”Optical imaging is a non-invasive and non-ionising technology, which uses light to probe cellular and molecular function in living subjects. Visible light is a form of electromagnetic radiation, which has properties of both particles and waves. As light travels through tissue, photons can be absorbed, reflected or scattered depending on the tissue composition. ” Though optical imaging can use agents (fluorescence and phosphorescence imaging), in this dissertation we focus on non-invasive (no agent) methods of optical imaging. Optical imaging works because ... ”In addition, in the near-infrared (NIR) part of the electromagnetic spectrum, soft tissues show less scattering and absorption than in the visible band and, therefore, using NIR optical imaging enables the probing depth to be increased to a few centimetres.” The computational headwalls of the past can now be addressed.

My overarching goal is to demonstrate how optical imaging is a conduit for medical imaging innovations for the rest of the 21st century. To do that, we must be bold—we will address modern national and global challenges to show the potential breadth of application of optical imaging. The first challenge is posed by the US Agency of International Development (USAID) through their Saving Lives at Birth Initiative. The goal is to address the heightened high-risk period for babies from onset of labor through 48 hours after birth in LMICs. This period accounds for 48 percent of maternal deaths and 54 percent of neonatal deaths annually. For the second challenge, we turn towards the brain. The Brain Research Through Advancing Innovative Neurotechnologies (BRAIN) Initiative is focused on the development and pplication of new technologies to image the brain for the treatment, cure, and prevention of brain disorders. Through the National Institute of Health (NIH) National Institute of Biomedical Imaging and Bioengineering (NIBIB), we will develop a portable neuroimaging system with features tailored towards use in natural environments. And finally, we will address the challenge of improving breast cancer diagnosis and prevention of unnecessary biopsies through a grant from the National Institute of Health (NIH) National Cancer Institute (NCI) for the development of an optical mammagraphy imager that augments existing x-ray mammography systems and scans. Although the field of medical imaging is continually advancing, at the time of writing, no contemporary imaging technique is suited to address all three aformentioned challenges.

This dissertation will show the potential of optical imaging to address a variety of current application-, user-, and setting-specific needs through the development of multiple near infrared (NIR) systems. Although each of the imaging systems described in this thesis will vary in attributes (such as complexity, cost, and scalability), as the title of this thesis suggests, we will focus on the following requirements:

1. Each NIR system must address portable, either through a stand-alone system or through simple integration into an existing imaging modality system.

2. Each NIR system must be non-invasive (use no reactive agents) and non-ionizing.

3. Each NIR system must utilize only the visible and/or near-infrared spectral window.

To address these challenges while meeting these requirements, at times we will leverage computational improvements of light propagation models. Other times we will integrate technological advancements in sensors to improve existing techniques. We will also take a product-focused lens to ensure what we are building is addressing the needs of users (and prevent us falling into the academic pitfall of building for the sake of building). By demonstrating use cases and designs across a variety of medical imaging attributes, we hope to show the medical community at large the benefits of non-invasive methodologies and ways to translate these technologies outside of the research setting.

This thesis is separated into five aims. The first three aims refer to the development of three individual portable and/or wearable near-infrared imaging systems. We will present the design, fabrication, and characterization of these systems as well as measurements on human test subjects. The fourth aim refers to the validation of new optical systems through characterization with optical phantoms of known optical properties. Finally, the fifth aim condenses the work into a Pugh chart by comparing all three developed NIR systems to an elementary optical imaging system, a finger-clip-based pulse oximeter.

While this introductory chapter sets the challenge and scope of the research for this dissertation, Chapter 2 gives necessary background into the basics of optical imaging, details on the optical imaging techniques used in this work, and defines the "ilities" (attributes) that will be compared between all three systems. Chapter 3 shows how we address the first challenge through the development of a mobile-phone-based pulse oximeter that leverages the sensors inside already ubiquitous mobile phones in LMICs. Chapter 4 addresses the second challenge of advancing neuroimaging through the development of a wearable functional brain imaging system with feature tailored towards its use in natural, unrestricted environments. The third challenge is addressed in Chapter 5. By combining the physiological measurements from optical imaging with the structural imaging from x-ray, we not only improve stand-alone optical imaging reconstructions, but also improve existing x-ray mammography, all without exposing a patient to more ionizing radiation. Chapter 6 discusses the use of additive manufacturing in the development of optical phantoms utilized by all

three systems in the first three aims. Finally, in the conclusion in Chapter **??**, we compare the three systems across their "-ilities."

CHAPTER 2

BACKGROUND

2.1 Basics of Optical Imaging

2.1.1 Light-Tissue Interactions

Biological optical imaging has the capability to detect biological structure, function, and molecular characteristics based on photon interactions with tissue [41]. The interaction of light with tissue is governed primarily by three processes: reflection, scattering, and absorption [43].

The index of refraction, n, is a unitless number that describes how fast light travels through material [41]. It is used to determine how much the path of light is bent upon transitioning from one material to the next. This is governed by Snell's Law of Refraction [41], $n_1 \times sin\theta_1 = n_2 \times sin\theta_2$, which define the angle of incidence, θ_1, and angle of refraction, θ_2, based on two media with indices of refraction n_1 and n_2. Thus, from Snell's Law, we can also determine the amount of light that is reflected when reaching an interface (Figure 2.1).

Once photons enter a turbid media, they move in all directions and may be scattered or absorbed (Figure 2.1). Absorption depends on the component concentrations of tissue [30]. In the visible to near-infrared wavelength range, the primary absorption components include water, hemoglobin, pigment, and lipid [17, 35]. The absorption coefficient, μ_a [cm^{-1}], is defined such that, when a photon propagates over an infinitesimal distance ds, the probability of absorption is $\mu_a \times ds$ [43]. The absorption coefficient depends on the molar extinction coefficient of a given chromophore ϵ [$cm^{-1} \times M^{-1}$], and its Molar concentration, c. Thus, the absorption coefficient per wavelength is

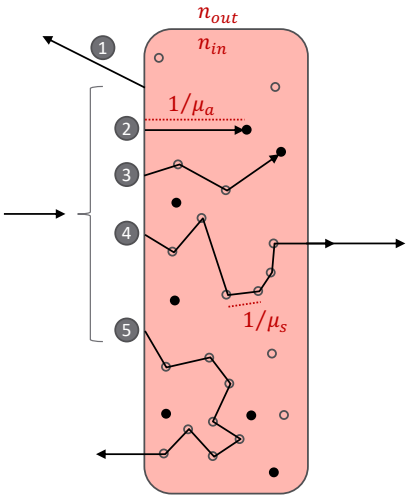

Figure 2.1: Possible interactions when light interfaces with tissue. The pink rectangle represents tissue. White circles are scatterers. Black dots are absorbers. (1) Light reflects without entering the tissue. (2) Light immediately gets absorbed. (3) Light scatters multiple times before being absorbed. (4) Light scatters multiple times before exiting the tissue on the opposite side it entered. (5) Light scatters multiple times but exits on the side it entered.

$$\mu_a(\lambda) = log(10) \sum_{i=1}^{t} \epsilon_i(\lambda) \times c_i \text{ [30]}. \tag{2.1}$$

where t is the total number of absorbing components in the tissue. From this, we deduce that $1/\mu_a$ is the average path length traveled by a photon before being absorbed.

Light entering a tissue can also undergo scattering events, events during which directionality changes occur due to biological structures within the media (Figure 2.1). In the visible to infrared wavelength range, the primary scattering components in biological tissue are protein, fat, and mitochondria [17, 35]. Analogously, the scattering coefficient, μ_s, is defined such that, when a photon propagates over an infinitesimal distance ds, the probability of scattering is $\mu_s \times ds$ [43]. Additionally, we model the probability distribution of scattered photons by an angular function known as the anisotropy factor, g [41]. Since g is based on the scattering angle, the closer to 1.0 g is, the more likely the photon is to be scattered in the forward direction. To account for this anisotropy factor, we define the reduced scattering coefficient, $\mu_s^{'}$, as $\mu_s^{'} = \mu_s(1-g)$ [41]. The average distance traveled by a photon between scattering events is $1/\mu_s$.

2.1.2 Components of Optical Measurement Systems

Optical systems are composed of three elementary blocks: a source that radiates light, a sample through which light propagates, and a detector that measures the light intensity after photons have traveled through the sample [42]. Although there are numerous types of sources and detectors, here, we highlight only the types used in the optical systems developed for this thesis.

light emitting diodes (LED) are devices that radiate light when a current passes through them [42]. They are ubiquitous in modern electronics due to being inexpensive and requiring minimal power to operate. In our Mobile-phone-based Oximeter (MOXI) system, we leverage the white LEDs used for flash photography common in most smartphones. Our Modular Optical Brain Imaging (MOBI) system uses dual-wavelength LEDs chosen to optimize propagation within the brain layers. Arrays of LEDs are used in conjunction with digital micromirrors to project color images from projectors. Our Optical Mammography Co-Imager (OMCI) system uses an LED projector to shine patterns to scan the surface of the breast. For certain applications, it is better to have a light source that does not spread out much, such as Light Amplification by Stimulated Emission of Radiation (LASER). Laser light sources produce very narrow beams of light. In OMCI, we use a laser to input light into a projector to project patterns onto the breast.

Detectors are devices used to measure light. Photodiodes are the reverse of LEDs—they convert light into electrical current [42]. Their cost tends to be relative to their sensitivity. MOXI and MOBI use inexpensive photodiodes chosen to be sensitive to the wavelengths of their associated LEDs. OMCI uses cameras to detect the reflection and transmission of projected patterns. These cameras capture light through a small lens using a tiny array of microscopic detectors.

The measured light, in combination with the known type of source, allows for the determination of biological structure, function, and molecular characteristics of the tissue through which the light propagated. For example, the detection of photons from particular wavelengths allows us to compute concentrations of oxygenated (HbO_2) and de-oxygenated (HbR) hemoglobin in tissue. From this, we can infer parameters such as total hemoglobin concentration and tissue oxygen saturation [30].

2.1.3 Optical Phantom Fabrication

Phantoms are objects with optical properties that mimic human tissues [35]. They are common for evaluating the performance of NIR imaging systems [35]. To mimic NIR light propagation due to components within biological tissue, phantoms typically attempt to mimic the reduced

scattering coefficient ($\mu_s^{'}$) and the wavelength-dependent absorption coefficient (μ_a) in biological tissue [13]. Traditionally, these phantoms are created using recipes that involve a mix of scattering agents and absorbing pigments with a base [24, 16]. The geometry of the phantom is typically created using either mold casting [22, 27] or spin coating [31]. While useful for simple phantoms, these methods fall short in supporting complex geometries needed for phantoms requiring structural and physiological properties, such as when diffuse optical tomography (DOT) is used to image the brain [23, 40]. Thus, a new method to manufacture phantoms with spatially varying optical properties and anatomically accurate geometries is needed to support the system development, calibration, and testing of new imaging protocols [9, 15].

2.2 Imaging Techniques

2.2.1 Pulse Oximetry

Pulse oximetry is used to measure oxygen saturation of hemoglobin in arterial blood and is so widely prevalent it is regarded as the fifth vital sign in medical care [29]. It is based on two principles. The first is that HbO_2 and HbR absorb red and infrared (IR) light differently [6]. Because of this, pulse oximeters tend to emit two wavelengths of light. Traditional (finger-clip) pulse oximeters place light sources and detectors on opposite sides of the finger. The second principle is that arterial blood volume fluctuates with the cardiac cycle while blood volume in veins, capillaries, skin, fat, and bone remains relatively constant [39]. Thus, light that propagates through the finger and is detected by the detector has two components during temporal measurements of the cardiac cycle—a relatively stable and non-pulsatile direct current (DC) component from the constant volume in veins and capillaries, and a pulsatile alternating current (AC) component from the volume fluctuation of the arteries [26]. This detected time trace is called a photoplethysmogram (PPG) [39].

Pulse oximeters use the amplitudes of PPG signals from red and IR light to calculate oxygen saturation (SpO_2) at the finger. SpO_2 is calculated from the ratio of the AC to DC components of the red and IR light. The ratio-of-ratios (RR) is defined as

$$RR = \frac{A_{red,AC}/A_{red,DC}}{A_{IR,AC}/A_{IR,DC}} \tag{2.2}$$

where A is absorbance. At low oxygen saturation, the increased HbR presence leads to a larger relative change in amplitude of red light due to the pulse compared to IR absorbance ($A_{red,AC} > A_{IR,AC}$), resulting in a higher RR value. SpO_2 is calculated from a calibration curve mapping

RR to SpO_2 generated from empirical measurements of RR in healthy volunteers with altered saturations [10].

2.2.2 Functional Near-Infrared Spectroscopy

functional near-infrared spectroscopy (fNIRS) is an emerging neuroimaging technique that uses low-power near-infrared light to measure hemodynamic changes due to brain activities [5]. It is based on three fundamental principles. The first is that human tissue is relatively transparent to light in the near-infrared range allowing photons to propagate [20]. Secondly, hemoglobin has unique absorbing characteristics that allow for oxygenation-dependent quantification of NIR light absorption [20]. The third is the theory of neurovascular coupling, which states that the brain's demand for oxygen is altered by neuronal activation. fNIRS assumes that changes in hemoglobin concentrations are indicators of brain activity [5].

In fNIRS, multiple sources and detectors are placed on the scalp over a region-of-interest (ROI) [37]. The photons travel through the head being scattered and absorbed by the different tissue types [34] (scalp, skull, cerebrospinal fluid, and neuronal tissue) until the non-absorbed components of the scattered light are detected by a detector [7, 25]. The activity-dependent local increase of HbO and decrease of HbR change the absorption rate of neuronal tissue and affect the intensity of light detected [25, 33]. This change in intensity, along with the absorption spectra of chromophores, allows for the calculation of HbO and HbR concentrations via the modified Beer-Lambert law [37].

2.2.3 Diffuse Optical Tomography

DOT is a non-invasive imaging technique for 3-D functional tissue characterization [4]. This is done through the illumination of tissue with an array of light sources and the measurement of the exiting light with an array of detectors [11]. Typically, a source in the array is turned on and the light is measured by all detectors for that source. This is repeated sequentially for each source. A model of light propagation from the source to detector locations is parameterized using unknown scattering and absorption coefficients of the illuminated tissue [1]. The propagation model is then "inverted" to determine the scattering and absorption parameters of the tissue [1]. The inversion of the model is the solution to the question "given my array of sources, what optical parameters must my tissue possess in order to produce the results I measured with my array of detectors?"

Although conceptually simple, in practice, DOT is plagued with difficulties. The use of diffusive light along with the inherent ill-posedness of the inverse reconstruction leads to low spatial

resolution results [2, 18]. Additionally, the sensitivity to tissue-optode coupling coefficients of the course spatial sampling leads to an inaccurate representation of tissue properties [38]. To address low spatial resolution, the use of tissue structural priors (structural data obtained from MRI [32], ultrasounds [45], or x-ray [19, 14]) have been recently used to better constrains the inverse problem and produced higher resolution images [32]. Wide-field illumination (the projection of a pattern image rather than a few spare source points) and camera-based detection (where a pixel in a camera acts as a detector in an array) has allowed for high-density sampling and acceleration of data acquisition [3].

2.2.4 Structured-Light Imaging

One method of improving DOT reconstructions is to further constrain the inverse problem through highly accurate breast surface estimations. However, the two most prominent techniques for 3-D breast surface imaging (stereophotogrammetry and laser scanning [44]), require a large number of cameras and precise installation, making them infeasible in the confined, low-light mammography setting. An emerging, non-invasive 3-D surface imaging technique is structured light illumination (SLI). SLI works by illuminating an object with 2-D spatially varying patterns and using an imaging sensor (e.g. a camera) to capture the illuminated object [21]. The distortion of the specially designed patterns inform of the geometric properties of the object. Calibration of the projector-camera system is easily done by capturing images of a known planar pattern [28]. With the ability to use off-the-shelf components, its use with a single projector and camera, and a robust and simple calibration method, SLI is positioned to be an accurate, fast, and cost-effective breast surface imaging system.

2.3 "-ilities" of Near-infrared Imaging Systems

In general, medical instruments can be approached from multiple viewpoints [42]. They can be classified according to clinical medicine specialties (pediatrics, cardiology, radiology, etc.), the principle of transduction (ultrasonic, electrochemical, capacitive, etc.), or they can be studied separately for each organ system (pulmonary, nervous, endocrine, etc.) [8]. In this thesis, we focus on optical imaging in the near-infrared range. These systems can be classified as a radiology specialty with the principle of transduction being optical measurements perturbed by hemodynamics.

Table 2.1: Near-infrared system attributes

	Pulse Oximeter	MOXI	MOBI	OMCI
Portability	0	↑↑↑	↓	↓↓↓
Adaptability	0	0	↑↑↑	↑
Affordability	0	↑↑	↓	↓↓↓
Complexity	0	↑	↑↑	↑↑↑
Manufacturability	0	↑↑↑	0	↓↓↓
Operability	0	↑↑	↓	↓↓↓
Scalability	0	↑↑↑	↑	↓↓
Maintainability	0	↑↑↑	↓	↓↓↓
Conformability	0	↓	↑	0
Comfortability	0	↓	↑↑↑	↓↓↓

We intentionally have not chosen a particular organ system to focus on so as not to limit the potential application of optical imaging.

Rather, we set the context of the three NIR imaging systems in terms of their positions across "-ility" scales [12]. These "-ilities," or attributes, are essentially interdisciplinary tools used to represent and compare NIR imaging systems. While it is true that any system has a set of design criteria based on signal, environmental, medical, and economic factors that impose constraints based on their specific use, knowing just the fixed requirements is not helpful in understanding the capabilities of NIR systems since we do not know how much each factor can vary. Rather, attributes describe features regarded as inherent characteristics of our systems. Each attribute can vary within the range between possible extremes for that attribute. In design methodology, this is known as a Pugh chart [36]. In this sense, the traditional set of requirements imposed in the design of an imaging system is simply a snapshot or fixed set of factors across attribute scales (Table 2.1).

Below, we closely define each attribute varied in this thesis. **Portability** refers to the ability to be easily moved. If we consider a traditional pulse oximeter as being the center of the scale, then our smartphone-based MOXI is more portable since it only requires a piece of paper and its software can be easily downloaded. Similarly, our OMCI breast imaging system is much less portable than a pulse oximeter due to its size and weight. **Adaptability** refers to whether a system can be used for other applications besides what it was designed for. For example, although designed for stroke recovery monitoring, the features in our MOBI modules allow it to be used in a range of neuroimaging studies without needing re-design. **Affordability** is cost. Compared to a traditional pulse oximeter, our OMCI system is much more expensive than our MOXI system that only requires only a small piece of paper. The reason for not ranking three up arrows for MOXI in affordability

is because it still requires a smartphone, which a user may or may not have in their possession. **Complexity** refers to the intricacy of a system. MOXI, MOBI, and OMCI increase in complexity respectively because, despite all being based on the same near-infrared imaging principle, they use an increasing number of communication protocols, units, and subsystems. **Manufacturability** refers to how difficult a system is to build. While more complex in use, our MOBI modules have very similar optical components and electronics to a pulse oximeter. The same expertise used in designing the circuit and fabricating the physical enclosure of a pulse oximeter clip is needed for a MOBI module. On the other hand, our OMCI system requires not only fabricating circuits but also mechanical assemblies and sensitive optical fibers. **Operability** is similar to usability in that it quantifies how much more (or less) difficult a system is to use and operate relative to a traditional pulse oximeter. While as easy to manufacture as a finger-clip pulse oximeter, our MOBI modules require relatively longer setup times to connect modules and affix a cap onto a user. **Scalability** attempts to quantify the difficulty in increasing the number of users. Since it only requires a piece of paper and is software-based, it is much easier and faster for a new user to obtain a MOXI system compared to manufacturing and shipping a traditional pulse oximeter. While the MOBI system is as simple to manufacture as a traditional pulse oximeter, we ranked it with one up arrow due to its broad range of applications that will likely entice more users than a non-adaptable pulse oximeter. **Maintainability** is the effort and cost needed to keep a system in working condition. Our MOXI system can be easily maintained with regular software updates and replacing its inexpensive pieces of paper. While as simple to manufacture, we ranked the MOBI modules with one down arrow due to the higher number of components (flat-flex cables, caps, master modules) that can potentially break and require replacement. **Conformability** is the ability of the system to physically match the surface it is trying to measure. The reflectance-based design of MOXI relies on the flat surface of a phone camera that is susceptible to motion. OMCI is slightly more conformable than MOXI because it has two surfaces that compress the breast preventing motion. However, the mechanical principle of compressing tissue using two fixed-shaped surfaces is identical to a traditional pulse oximeter in the sense that neither adjusts to different user shapes. The flexible-circuit-based MOBI modules conform easily to the scalp. **Comfortability** refers to long-term use. The silicone covers and wireless capability of the MOBI modules allow them to be used for hours at a time. On the other hand, OMCI requires heavy compression of the breast to minimize the thickness between paddles. This is so uncomfortable that we have to limit the time in compression to less than 3 minutes. The MOXI system, although highly portable, requires the user to actively press onto the camera phone, which can cause discomfort over long-term use compared to the passive design of a traditional

finger-clip pulse oximeter.

2.4 Thesis Aims

CHAPTER 3

MOBILE-PHONE-BASED OXIMETER (MOXI)

This is where the writing goes.

CHAPTER 4

MODULAR OPTICAL BRAIN IMAGER (MOBI)

This is where the writing goes.

CHAPTER 5

OPTICAL MAMMOGRAPHY CO-IMAGER (OMCI)

This is where the writing goes.

CHAPTER 6

3-D PRINTED PHANTOMS

This is where the writing goes.

CHAPTER 7

CONCLUSION

7.1 Mobile-phone-based Oximeter

7.2 Modular Optical Brain Imager

7.3 Optical Mammography Co-Imager

7.4 3-D Printed Phantoms

7.5 “-ilities” Pugh Chart

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