A DIFFUSE OPTICAL TOMOGRAPHY SYSTEM COMBINED WITH X-RAY MAMMOGRAPHY FOR IMPROVED BREAST CANCER DETECTION

Chapter 1

Introduction

Breast cancer has the highest incidence (30%) of all female cancer cases in the United States. About 10% of American women will develop breast cancer during their lifetime. An estimated 175,000 new cases will be diagnosed and 43,000 deaths will occur because of breast cancer each year [1]. Even small improvements in the early diagnosis and treatment of breast cancer would likely save thousands of lives annually.

X-ray mammography and clinical breast examination (CBE) are the current gold standards of breast cancer screening. Ultrasound and MRI are also used as secondary screening tools to elucidate suspicious findings from the X-ray mammogram. Other non-optical imaging techniques include positron emission tomography (PET), electrical impedance tomography (EIT), and thermal imaging [2,3]. Recent advancements in x-ray mammography offer great promise including digital mammography and tomography. Some of these non-optical techniques rely on specific intrinsic characteristics of breast tissue to image the breast or to identify lesions within it, while others employ exogenous tracers or contrast agents [2]. Similarly, some are useful in screening while others are useful only in diagnosis. These various methods have demonstrated success in cancer

screening and diagnosis [2]. While the sensitivity of X-ray mammography appears to be greater than 80% in women over 50 and less for younger women, there is still a need to detect cancers earlier for treatment and to detect cancers missed by mammography. Furthermore, mammographic specificity is known to be limited [2]. Methods that measure changes in functional processes, as opposed to those that measure structural changes, show the greatest promise for future improvements [4-13]. Functional MRI and PET do assess function, but their high cost and invasiveness have prevented their widespread deployment in breast screening and diagnosis.

X-Ray mammography represents the current standard of care and has contributed to a significant reduction in breast cancer mortality [1,2]. It is inherently limited, though, as it is incapable of direct observation of physiological information relevant to the "functioning of cancer," which ultimately limits the specificity and prognostic value of X-ray mammography.

There has been considerable interest, recently, in applying diffuse optical tomography (DOT) to breast cancer detection [4-14]. Diffuse optical tomography exploits the intrinsic contrast of hemoglobin in breast tissue to provide information on the function and evolution of cancer, in particular, angiogenesis and hemoglobin oxygen saturation. The development of tomographic optical breast imaging (TOBI) has been progressing steadily for the last 10 years, and has been propelled by its promise of providing physiological information directly relevant to the functioning and evolution of cancer, information not readily obtainable from traditional widely available imaging techniques.

Diffuse optical tomography suffers, however, from limited spatial resolution relative to X-Ray, and this inhibits structural guidance and interpretation of the obtained images [4-13]. The central thesis of this dissertation proposes that this obstacle can be overcome by acquiring diffuse optical and X-Ray mammographic images "simultaneously" to produce a new multi-modality imaging method with enhanced specificity and prognostic value. This co-registered multi-modality imaging method has the potential to overcome the limitations of X-ray mammography, limited by specificity, and optical imaging, limited by resolution.

A Time-Domain Optical Breast Imaging System has been developed that promises to advance the clinical utility of tomographic optical breast imaging by co-registration of diffuse optical tomography with digital X-ray mammographic tomography (known as Tomosynthesis). This multi-modality imaging method integrates structural (adipose and glandular tissues, micro-calcifications) and functional information (angiogenesis, metabolic activity/oxygen consumption) relevant to the screening and diagnosis of breast cancer [14]. This combination of imaging modalities offers the promise of better differentiation of tumors through angiogenic and metabolic markers known to have prognostic value.

The Time-Domain Optical Breast Imaging System incorporated a scanned, pulsed Ti:Sapphire laser as the source subsystem, and a gated, image-intensified CCD (ICCD) camera as the detection subsystem. Background optical properties were determined by treating the breast or breast phantom as a homogeneous medium, with the assumption that the perturbations due to heterogeneities were small relative to the background. The time-domain system had 150 source fibers scanned serially and 313 detection fibers read

out in parallel. The particular advantage of using the ICCD in conjunction with the high performance, custom designed objective was that all the detection fibers were read out simultaneously. Typically, between 5 and 10 discrete time gates would be obtained for a given clinical measurement. At least two wavelengths would be used for the determination of hemoglobin saturation. The laser system was capable of providing any wavelength within the range spanning from 750 nm to 850 nm.

A unique source probe was developed, comprised of a source fiber array plate that was positioned within a modified compression plate attached to an X-ray detector or film box and a detection fiber array plate, positioned within a modified compression plate that attached to the X-ray system in the normal position. The breast or breast phantom was positioned between two modified compression plates. Quick-release features could allow both fiber array plates to be removed from their respective modified compression plates for co-registered X-ray image capture within seconds of the optical image capture. The X-ray contrast could be correlated with the optical contrast and provide information about boundaries to aid the optical reconstruction. The marriage of the structural information from the X-ray and the functional information of the DOT images promises to provide the clinician with a powerful new imaging modality for the screening and potential diagnosis of breast cancer.

Chapter 2 reviews the DOT theory as applied to time-domain imaging. The anatomy of the breast and that of benign and cancerous lesions of the breast are reviewed in Chapter 2 to provide insight into the requirements of the optical system and optical models of photon transport in breast tissues.

Chapter 3 presents a comparison of time-domain, frequency-domain, and continuous wave instrumentation techniques. Time-domain techniques are regarded as having the greatest information content of practical instruments. Chapter 3 also reviews the literature with respect to other time-domain instruments that could have potential application to breast imaging. No other system was found in the literature that combined the speed and 3-dimensional spatial resolution capabilities of the Time-Domain Optical Breast Imaging System described in this dissertation.

Chapter 4 presents the design details of the Time-Domain Optical Breast Imaging System. The key features of the fiber source Multiplexer are discussed that enable it to provide an unprecedented 300 μsec fiber switch time, which is 3 orders of magnitude better than systems described in the literature. The design and performance of the wide field, high numerical aperture camera objective that enables the massively parallel detection of 313 fiber positions is presented. The methods and instrumentation used to develop both homogeneous and heterogeneous breast tissue phantoms are presented.

A critical review of the literature with regard to noise theory of ICCD systems revealed that no comprehensive noise treatment existed. Thus, a comprehensive noise theory for an ICCD time-domain optical imaging system was developed as presented in Chapter 5. The noise theory provided the tools necessary to obtain insight toward the optimization of the time-domain system in the context of time limitations posed by a clinical measurement.

Chapter 6 provides a detailed characterization of the system. The most critical finding was that the ICCD system was subject to saturation effects in two regimes; at low gains the system suffered from photocathode saturation and at high gains the system

suffered from intensifier gain saturation. The magnitude of these effects was shown to be very dependent on the configuration of the measurement, such as average laser power, the background optical properties of the tissue or phantom, the gain voltage, integration time, etc. Thus, it was shown to be incumbent on the operator to characterize the saturation effect, specific to their system parameters, in order to apply appropriate correction factors, if needed.

Chapter 7 discusses methods for improving the image contrast-to-noise within the limits of time and maximum permissible skin exposure relevant to clinical measurements. Specific recommendations for system improvements are outlined in Chapter 8 along with general closing remarks.

Chapter 1 References

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