CHAPTER 1

INTRODUCTION

Early screening, detection and precise diagnosis are indispensable in today’s world, to reduce the morality of tumor disease. Highly developed imaging systems compete as a key in the process of proper detection and diagnosis. The tumor detection is complex and initial stage finding directs to improved chances of effective treatment, thereby increasing the survival rate. All categories of imaging methods are highly meant for investigative applications in medical and industrial fields. Industrial process tomography is an emerging field which has numerous imaging applications in industrial process monitoring system as well as material characterization in non-destructive evaluation.

1.1 SOFT TISSUE IMAGING MODALITIES

The initiation of imaging model was followed by the invention of X-ray radiography with the help of electromagnetic radiation. X-ray which penetrates through human body is absorbed or scattered leads to the production of attenuation or reduction of the beam. The absorption level varies with different parts of human body thus the penetration of photon light level differs for each and every organ. Based on this major concept, imaging techniques were introduced. The X-ray radiography initiates the biomedical imaging (John Webster 2003) and provides a single dimensional image of bony structures in a photographic film X-ray. It could give the image of bony defects, but the recognition of soft tissue tracks are attained by the direction of
contrast agents or dyes. High density tissue having high attenuation seems to be light grey or white on radiograph, while low density tissue having low attenuation seems to be dark on radiograph. The advanced version of X-ray radiography is digital radiography, which offers a single plane image along with extra attributes such as data collection, processing, display and storage system. The memory is introduced to store the patient’s data for future use. X-ray limitations are high frequency electromagnetic radiation and harmful dye usage. But large variations in soft tissues can be detected only by those dye injection.

The X-ray computed tomography carries out the organ imaging at multiple angles; using mathematical expression the image is rebuilt and exposed on the monitor. In the examination of a soft tissue, contrast images are produced when the dye fluids are forced into the ventricles. The X-ray noise rises naturally over the square root of the dose and therefore the dose must be boosted to conserve the same amount of noise. Therefore, over dosage leads to dangerous side effects such as skin allergy. The disadvantages are ionizing radiation, lack of portability and relatively high cost.

Nuclear Medical Imaging (NMI) (John Webster 2003) employs the energy of radioisotopes for imaging. Appetite amount of radioactive material is injected into the arm vein; later on the amount of radioactivity of the organ is examined using the radiation detectors. NMI has Emission Computed Tomography which exhibits the single plane slice of the object with radioactivity, similar to X-ray computed tomography. In Single Positron Emission Tomography, a three dimensional representation of the radioisotope injected organ is visualized using gamma camera. Positron Emission Tomography (PET) imaging demonstrates the biological function, physiological and pathological characteristics with the help of the cross sectional images of positron emitting isotopes. Allergic reactions are created
due to the injected radioisotope and it takes hours to be cleared from the blood, hence the process is time consuming process. PET utilizes ionizing radiation with high equipment cost and meticulous care while handling radioactive materials.

Magnetic Resonance Imaging (MRI) uses high radio frequency signals and strong magnetic field in the range of 0.5 to 3 Tesla, to obtain the anatomy and physiological process of the human body as cross sectional images. The subject is needed to be still while imaging. In case of movement, it blurs the output image. MRI causes highly ionized radiations which are harmful; it is time consuming for complete examination, cost inefficient and has high auditory noise level for early tumor detection. The Ultrasonic imaging system applies ultra high frequency sound waves between 1-15MHz for obtaining images of internal organs in the abdomen, liver, kidney, spleen and pancreas. Tissue interface produces various degrees of sound wave reflection namely hyper-echoic and hypo-echoic. When it penetrates through the human body, it is completely reflected at boundaries with gas and there is a serious restriction in investigation of gas containing structures. The ultrasonic waves cannot penetrate through bony structures and therefore impossibility of imaging the brain.

Mammogram or advanced X-ray is used as simple breast cancer screening test. They are low dose X-ray (~15-25KeV) in mammogram but in breast tomo-synthesis a high dose is used for 3D image reconstruction of breast imaging. Limitations of mammogram are false-negative mammogram that appears to be normal even though breast tissue is affected by cancer and false-positive mammogram which appears to be abnormal in the absence of cancer in the breast. It uses ionizing radiations as gamma rays hence harmful for health. Microwave Tomography (MWT) is a new emerging Electromagnetic (EM) tomography. A non-ionizing EM spectrum is used in
contrast to ionizing radiation used in CT imaging and nuclear medicine. MWT imaging is associated with high cost, high computing power, more complicated, nonlinear and high dielectric contrast inverse problems of 3D diffraction tomography.

1.2 DIFFUSE OPTICAL TOMOGRAPHY

Diffuse Optical Tomography (DOT) (Jacques et al. 2008, Gibson et al. 2005) is a non-invasive imaging technique which uses the near infrared light in range of 700nm-1000nm (Arridge et al. 1999). It is a non-ionizing radiation which causes no harm or side effects. It has its main application of imaging the soft tissue organs such as the brain and breast for diagnosing tumor using the biological parameters (Arridge et al. 1997, Dehghani et al. 2009) such as oxygenation etc. The brain and breast tumor or lesion can be detected by examining the oxygenated, deoxygenated hemoglobin, water and lipids (proteins). DOT imaging (Gibson et al. 2009) provides a number of advantages, such as reduced size set-up in turn led to portability, real-time imaging, low instrumental cost and less time consumption when compared to the other imaging techniques but it is generally known to have a low image resolution which limits its further clinical application. Table 1.1 Compares Biomedical Imaging Modalities such as Computer Tomography (CT), Magnetic Resonance Imaging (MRI), and Positron Emission Tomography (PET) with DOT. The parameters namely cost, imaging time, size, sensitivity and specificity are compared.

The main absorbers of near-infrared (NIR) light in blood-perfused tissues are Oxy-hemoglobin, de-oxy hemoglobin, Lipids (Bulk proteins) and water. NIR Spectral Window absorption spectra between 650 and 1000 nm shown in Figure 1.1 is obtained from compiled absorption data for water (Hale & Querry 1973) and hemoglobin (OMLC (2012)).
Table 1.1 Comparisons of Biomedical Imaging Modalities

<table>
<thead>
<tr>
<th>Parameters</th>
<th>DOT</th>
<th>CT</th>
<th>MRI</th>
<th>PET</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cost</td>
<td>$150,000</td>
<td>$300,000</td>
<td>$1,000,000</td>
<td>$1,446,546</td>
</tr>
<tr>
<td>Imaging Time (mins)</td>
<td>15 – 20</td>
<td>45 – 60</td>
<td>45 – 70</td>
<td>75 – 90</td>
</tr>
<tr>
<td>Size</td>
<td>60 x 45 cm</td>
<td>50 x 50 cm</td>
<td>4x4m</td>
<td>25x36x17cm</td>
</tr>
<tr>
<td>Sensitivity</td>
<td>50%</td>
<td>90%</td>
<td>91%</td>
<td>93%</td>
</tr>
<tr>
<td>Specificity</td>
<td>100%</td>
<td>56%</td>
<td>71%</td>
<td>70%</td>
</tr>
</tbody>
</table>

Therefore, light in this spectral window penetrates deeply into the tissues, thus allowing for non-invasive investigations. The depth of NIR light penetration in the tissues is limited by the hemoglobin absorption at shorter wavelengths and water absorption at longer wavelengths.

Different systems in DOT are Continuous Wave (CW) imaging (Dehghani et al. 2009), Time Domain (TD) and Frequency Domain (FD). Continuous imaging is the study of hemodynamic and oxygenation changes in superficial tissues. It requires a source of constant intensity modulated at low frequency. Measuring the intensity of light transmitted between two points on the surface of the tissue is economical. Optimum sensitivity is achieved by a number of distinct sources and detectors. Intensity measurements are sensitive and unable to distinguish between the absorption and scattering effects.

Time Domain (TD) system uses photon counting detectors slowly but sensitively. The temporal distribution of photons is produced in short duration.
Figure 1.1 Absorption spectra of deoxy-hemoglobin (Hb), Oxy-hemoglobin (HbO₂), Lipids and water

Short pulses of light are transmitted through a highly scattering medium known as a Temporal Point Spread Function (TPSF). Frequency Domain (FD) (OMLC (2012)) system is relatively inexpensive, easy to develop and provides fast temporal sampling up to 50Hz. The system acquires quick measurements regarding the amplitude and phase of scattering and absorption in the frequency domain at high detected intensities.

1.3 REQUISITE FOR FUNCTIONAL DIFFUSE OPTICAL TOMOGRAPHY

The NIR light propagation through the biological soft tissues in turbid medium is described by analytical RTE (Radiative Transfer Equation) or deterministic Diffusion Equation or statistical Monte Carlo simulation is known as forward model. The Boltzmann Transport Equation (BTE) is referred as the Radiative Transfer Equation (RTE) which states that energy is balanced within a boundary volume element in a scattering medium. The RTE solution is computationally complex and therefore it is only possible by approximation as well as it is cost effective. Accordingly, DOT uses the Diffusion Equation (DE), which has described the forward problem as the
NIR light transport in a biological soft tissue. The solution of diffusion equation for the transport of photons in a tissue medium is computationally efficient and can be examined efficiently, as the NIR light diffuses inside the soft tissue.

The methods employed to provide numerical solution are Finite Difference Method (FDM), Finite Element Method (FEM), Finite Volume Method (FVM) and Boundary Element Method (BEM). The functionality of the source detector placed on the tissue geometry boundary predicts the optical requirement of parameters from the forward model. To solve the Diffusion Equation, Finite Element Method was employed. Numerical Solution for FEM is provided by boundary value problem to determine the optical flux distribution in a tissue medium. Diffusion equation incorporates Robin boundary conditions in order to evaluate the photon flux. In the inverse model, the forward model solution was applied to optical flux approximate equation. This flux equation is solved using conjugate gradient function consecutively to calculate the Jacobian matrix.

The inverse problem is the tissue image reconstruction from the absorption, scattering coefficient and optical flux of tissue, which in turn determined from the light measurements on the phantom surface of the boundary. The forward model data suffers due to ill-posed problem and therefore to solve the ill-posed problem, regularization methods are used to convert the non-linear data to linear data. The spatial resolution images are obtained by diffuse optical imaging technique. The ill-posed problem is removed by different regularization techniques. Among them, Levenberg-Marquardt method (LM) is most commonly utilized.

1.4 DIFFUSE OPTICAL TOMOGRAPHY INSTRUMENTATION

Advancement in optoelectronics leads to DOT instrument development. Pulse oxy-meter was useful in measuring patient arterial
oxygenation level. Applying the similar spectral features, absorption, scattering and optical flux for soft tissue is estimated to reveal the hypoxia in tumor.

**DOT instrument can be categorized as**

**1.4.1 Continuous Wave**

DOT instrument continuously emits light as probing signal and measures the relative attenuation of light through tissue. It is relatively inexpensive and portable. Continuous measurements are difficult to calibrate and add with coupling errors (Boas et al. 2001). To obtain the imaging points, there is non-uniqueness problem in the data sets. The functional parameters are calculated from the absorption estimation at multiple wavelengths assuming scattering as constant. The continuous wave instrument applies for brain monitoring without using image reconstruction algorithms (Tromberg et al. 2005, Cerussi et al. 2007, Leff et al. 2008).

**1.4.2 Time Domain**

Pulsed Laser source signals are used to transmit light through the tissue. At the detectors TPSF is measured to estimate the time of flight through the tissue. The measurement is directly related to absolute transport scattering coefficients of the tissue. In time domain techniques, Time Correlated Single Photon Counting (TCPSC) and pulsed laser requires temperature and current control that adds to the complexity of the system (Gibson et al. 2005) which are very expensive.

**1.4.3 Frequency Domain**

The laser light is modulated in the range of 50-500MHz to produce an intensity modulated or frequency domain. The attenuation of modulated
amplitude and phase shift are measured at the detector. Frequency domain systems are relatively inexpensive compared to time domain and capable of obtaining the data modulated over wide frequency range.

DOT instrument with low cost prototype model of time domain system was developed with laser sources and avalanche photo-detectors. Laser source and detector signals are controlled by MOSFET switches and ATMEL89C51 microcontroller. The measured scattering voltage data is displayed using PROTEUS tool. Tumor presence is detected based on the scattering voltage range.

1.5 MODELING TECHNIQUES

1.5.1 Analytical Model

Analytical model has fast computation and the Green’s function is applied for modeling the diffusion equation or RTE analysis. The Green’s function provides a solution when the source is a spatial and temporal function. It is commonly used to solve the forward problem for image reconstruction, specifically for the fast imaging techniques. In analytical model, the optical properties are modeled by green’s function (Gibson et al. 2005) for a slab structure representing the homogeneous background along with an additional perturbation term representing the spherical insertion.

1.5.2 Statistical Model

The individual photon with Poisson error is incorporated in the statistical model. Monte Carlo method is a gold standard statistical technique in diffuse optics. The geometry of the model is defined by $\mu_a$, $\mu_s$, the refractive index and the photon trajectories. Light propagation in non-diffusive domains is calculated by Monte Carlo techniques.
Random walk theory provides a distinct approach, in which photon transport is modeled as a series of steps on the discrete cubic lattice. Random walk theory (Chernomordik et al. 2000) is particularly suited to model time-domain measurements. The random walk extension technique has been developed for modeling media with anisotropic optical properties, maintaining the cubic lattice.

1.5.3 Numerical Model

Numerical techniques have the potential for modeling complex geometries. Finite Element Method (FEM) (Schweiger et al. 1995) is used to represent the inhomogeneous distribution of the optical properties in an arbitrary geometry. Finite Difference Method (FDM), Finite Volume Method (FVM) and Boundary Element Method (BEM) (Gibson et al. 2005) are used in more specialized applications. Finite Element Method divides the reconstruction domain into finite element meshes. The optimal computational efficiency of FEM depends on the smallest number of elements to represent the internal field by a finite element mesh. The mesh is adaptively refined by placing more elements when the field changes rapidly.

1.6 COMPUTATIONAL CHALLENGES OF DIFFUSE OPTICAL TOMOGRAPHY

Computational has remarkable development in power desktop computers to perform intense computations within fraction of second. DOT image recovery is difficult to solve from mathematical point of view.

The challenge is due to non-linear transport in forward model, ill-posed condition in inverse model and the under determination of detection strategies.
**Non-linear**: The linear changes in optical properties do not provide linear changes in detected signal.

**Ill-posed**: The small changes in detected signal rise to large changes in estimated optical properties. The estimation error increases with availability of noisy data.

**Under-determined**: The ill-determined problem is due to less number of independent equations compared to the number of unknowns.

Features imply that there is no unique solution for a given detected signal. The non-uniqueness problem results in a need to constrain the solution space using mathematical methods known as regularization. The non-linear problem solved by a set of optical properties creates constraints on computational methods in real-time.

Developing a novel design of DOT instrument for immediate detection of tumor is based on the optical property measurement. Advanced regularization method namely SURE (Stein’s Unbiased Risk Estimate) regularization with unbiased estimation and minimum MSE (Mean Square Error) removes ill-posed problem. In this vein, BEM (Boundary Element Condition) has been explored and tested its significance in optical imaging systems.

1.7 **RATIONALE OF THE THESIS**

The major contribution of the thesis consists of four main parts.

1.7.1 **Signal Extraction from Soft Tissue**

The experimental set-up designed using laser diodes OPV310 (850nm), D7805I (780nm) and the avalanche photo-detectors OPT101 exhibits
the forward model. The scattering voltage from the photo-detector was processed using Lambert–Beer Law to evaluate the intensity and attenuation. The absorption and scattering coefficients were determined at different fractional volumes and areas of tissue geometry. The fluence rate was evaluated in different boundary conditions namely spherical, slab and cylindrical structures using boundary element method. The diffuse reflectance was estimated on the boundary of the geometrical structure.

1.7.2 Forward Model Analysis

The Response Surface Method (RSM) using Box-Behnken Design (BBD) optimization was adopted for forward model design due to minimum residual error percentage. The forward model numerical solution was assessed by Radiative Transfer Equation (RTE) and Diffusion Equation solved by Finite Element Method (FEM).

1.7.3 Regularization Techniques

The ill-posed problem in image reconstruction is removed by providing a unique solution using various regularization techniques such as Tikhonov Regularization, Exponential Regularization, Adaptive Regularization, Model based Regularization and Stein’s Unbiased Risk Estimate (SURE) Regularization.

1.7.4 Inverse model analysis

Inverse model performs image reconstruction from photonic flux subjected to boundary conditions of the tissue medium with the help of Levenberg-Marquardt regularization reconstruction method and the Split-Bregman method.
1.8 ORGANIZATION OF THESIS

The thesis deals with the optical property extraction in soft biological tissues to detect carcinoma cells using the designed DOT instrument. The absorption coefficient, scattering coefficient, photon flux and diffuse reflectance of tissue medium were analyzed in three boundary conditions. The numerical solution for forward and inverse model was evaluated using image reconstruction algorithms. The thesis is organized as follows:

**Figure 1.2 Research Flow**
Figure 1.2 Depicts the research flow for DOT instrumentation interfaced with image reconstruction algorithms for detection of sarcomas.

**Chapter 1** presents general introduction of the thesis with various imaging modalities along with applications and limitations. Diffuse optical tomography applications, advantages and comparison with other imaging modalities are conversed. Requisite for diffuse optical tomography, history of DOT instrumentation with computational methods and modeling techniques are discussed.

**Chapter 2** deals with the literature review from existing research work for optical property extraction of soft tissue phantom, forward model, inverse model, regularization, image reconstruction and image segmentation.

**Chapter 3** proposes a design of diffuse optical tomography instrumentation system with design of laser sources and detectors experimental setup interfaced with the personal computer. The device performance is optimized by the regression method called Box-Behnken design using ANOVA.

**Chapter 4** determines the optical property extraction of soft tissue for carcinoma cell detection using Diffuse Optical Tomography under boundary element condition. The optical property extracted from soft tissue is absorption coefficient, scattering coefficient, diffuse reflectance and optical flux obtained in three structural medium under boundary element condition. On evaluation of optical properties based on the absorption and scattering coefficient value, the normal or cancer patient identification is performed on actual measured data.

**Chapter 5** establishes numerical solution for forward Model Diffuse Optical Tomography System with various angular and spacing arrangements of laser sources and detectors in NIR wavelength. Diffusion equation solved using
Finite Element Method determines the optical flux. The regularization method removes the ill-posed problem. The Tikhonov regularization, exponential regularization, adaptive regularization, model based regularization and Stein’s Unbiased Risk Estimate or (SURE) regularization improves the resolution of reconstructed image. The SURE estimate is nearer to the Mean Squared Error (MSE), hence providing a better estimate for the non-linear data. Numerical solution for Image Reconstruction was provided with Levenberg-Marquardt Method and Split Bregman method. The reconstructed image was segmented using fixed grid wavelet network (FGWN), Graph Cut Algorithm (GCA) and Genetic Algorithm (GA).

Chapter 6 presents the conclusion that the designed diffused optical tomography system is a cost efficient model for sarcoma detection. The boundary detection of tumor at cellular level promotes the detection and identification at earlier stage. The future scope of the research work was discussed to promote the experimental device in the form of equipment for the tumor detection in patients.

1.9 SUMMARY

This chapter provides introduction for optical tomography in biomedical field and industrial field. The soft tissue imaging modalities namely X-ray, CT, PET, NMI, MRI, EMT, MWT and Mammogram were discussed with their advantages and limitations. DOT benefits and its gain on comparison with other imaging modalities were communicated. The absorption coefficient of tissue parameters were plotted in NIR wavelengths. Need for DOT with DOT instrument design in different domains, modeling techniques and their computational challenges were discussed. Further the major contribution and organization of the thesis were conferred.