Chapter 1

Introduction

The potential to acquire information about tissue optical and dynamical properties non-invasively offers exciting possibilities for medical imaging. For this reason, the diffusion of near infrared photons (NIR) in turbid media has been the focus of substantial recent research [1, 2, 3, 4]. Applications range from pulse oximetry [5, 6, 7, 8, 9, 10] to tissue characterization [11, 12] to imaging of breast and brain tumors [13, 14, 15] and to probing blood flow [16, 17, 18, 19]. Presently, pulse-time [4, 12, 20], amplitude modulated [3, 21, 22, 23], and continuous wave sources of light [7, 24, 25] are used to probe turbid media for optical anomalies such as tumors and hematomas.

These procedures are complicated by the fact that light does not travel ballistically through turbid media. Rather, photons experience many scattering events prior to their absorption or transmission through boundaries. For many biological tissues, the absorption length for NIR light is much longer than the scattering length. Furthermore, the scattering length is much smaller than the dimensions of the sample. In this case the migration of photons is accurately described as a diffusional process. These conditions are met in breast tissue for which the reduced scattering coefficient, μ_s' (which is the reciprocal of the photon random walk step), is approximately 10 cm^{-1} and the absorption coefficent, μ_a (which is the reciprocal of the photon absorption length), is approximately 0.03 cm^{-1} [26, 27].

An intensity modulated source of light produces a wave of light energy density which propagates spherically outwards from the source through the turbid medium.

This intensity wave is called a diffuse photon density wave (DPDW) [3, 21, 22, 23]. Although microscopically the photons are diffusing and have thus lost memory of their initial direction, macroscopically the photons combine incoherently to produce a scalar wave of light energy density with a well defined phase front. The wavelength of the DPDW depends on the optical properties and source modulation frequency and is around 10 cm for typical biological samples and modulation frequencies ($\sim$ 200 MHz). The optics of DPDW's have been well defined in the recent literature [3, 21, 22, 28, 29, 30, 31, 32, 33]. In particular, studies of the distortion of DPDW's by optical inhomogeneities demonstrate that heterogeneities may be found and characterized by measuring distortions in the DPDW wavefront [28, 29, 30, 31, 34, 35].

In a different vein, when a photon scatters from a moving particle, its frequency is Doppler-shifted by an amount that is proportional to the speed of the scattering particle and dependent on the scattering angle relative to the velocity of the scatterer. Under certain conditions it is possible to measure these small frequency shifts caused by Doppler scattering events. Thus it is possible to non-invasively measure particle motions and density fluctuations in a wide range of systems. Applications include measuring the Brownian motion of suspended macromolecules [36, 37, 38, 39], velocimetry of flow fields [40, 41, 42, 43], and *in-vivo* blood flow monitoring [44, 45, 46].

Methods for using light to measure flow and density fluctuations have appeared with numerous names including Photon Correlation Spectroscopy [47], Dynamic Light Scattering [38, 39], Quasi-Elastic Light Scattering, and Diffusing Wave Spectroscopy [48, 49, 50, 51]. These methods basically fall into two categories: Doppler methods and speckle methods. The Doppler methods measure the Doppler broadening of the laser light linewidth directly using tunable optical filters. Speckle methods monitor the intensity fluctuations that arise from the beating of electric fields with slightly different frequencies. This is analogous to the acoustic beat notes that a musician uses to tune a musical instrument. The two different methods essentially give access to the same information, as is discussed by Briers [52].

Intensity and Doppler/speckle probes of random media are connected since they

both rely on the behavior of the migrating photons. The two different probes require different equipment since the first measures the average intensity and the other indirectly measures the light coherence properties, but I show that the measured signals can be accurately predicted and quantified using analogous diffusion models.

Spectroscopic intensity probes have been used since the 1930's to measure blood oxygenation non-invasively and to detect hematomas and various breast cancers. Non-invasive monitoring of average blood oxygenation is successful and widely accepted. Detection of hematomas and cancers has also been successful but is not widely accepted because of the inability to accurately characterize the anomalies. To improve anomaly characterization it is necessary to have models which accurately predict the migration of photons through turbid media with spatially varying optical properties. The photon diffusion model has been shown to work well [4, 28, 29, 53] as I will show in this dissertation.

Photon correlation spectroscopy (specifically speckle probes but including Doppler probes because of their similarity) is successfully used in industry and biology for measuring and monitoring particle size, aggregation, gelation, and flow in optically dilute and concentrated samples. Medical applications include monitoring blood flow and diagnosing the viability of burned tissue. Quantification of correlation signals from turbid samples has been limited to systems with spatially uniform optical and dynamical properties. The models I present here, which permit the quantitative analysis of signals from samples with spatially varying properties, increase the range of applicability for photon correlation spectroscopy.

The work I present here is a unification of intensity and speckle probes of turbid media. By treating them with similar theoretical models, ideas and concepts developed for one probe to be easily applied to the other probe. Chapter 2 reviews the photon diffusion model, discusses macroscopic scalar wave solutions that arise in this model (otherwise known as diffuse photon density waves) including the scattering of diffuse photon density waves from macroscopic heterogeneities, and experimentally demonstrates the validity and accuracy of this model. Chapter 3 presents a signal-to-noise

analysis which reveals the power and practical limits to the detection, localization, and characterization of optical inhomogeneities using diffuse photon density waves. Chapter 4 presents a diffusion equation for correlation and experimentally demonstrates its validity and accuracy for turbid media with spatially varying Brownian motion, flow, and optical properties. Chapter 5 discusses two biomedical applications for correlation diffusion, monitoring blood flow, and probing tissue burn depths. Chapter 6 describes the experimental methodology used throughout.