Chapter 1

Introduction and Motivation

The last ten years have seen a rapid development of new optical techniques for clinical monitoring and diagnosis in medicine. These advances have been fueled by a new understanding of theoretical aspects of light-tissue interactions and substantial technological improvements concerning light sources and light detection systems. One of the most exciting developments in the field of biomedical optics is the possibility to obtain cross-sectional images of the optical properties of various body parts from optical measurements performed on the surface of the body. The spatial distribution of optical properties provides information about the functional and pathological state of various human tissues. This pioneering medical imaging modality is commonly referred to as optical tomography. One of the major remaining problems that need to be solved is the development of accurate and fast image reconstruction algorithms that transform measured data into useful cross-sectional images. This work describes the efforts towards this goal.

1.1 Tomographic Imaging in Medicine

The goal of tomographic imaging in medicine is to obtain a cross-sectional image of internal structures of the human body from measurements performed on the outer boundary. Different types of tomography can be performed. For example, in transmission tomography the body is transilluminated and the transmissive properties are displayed in an image. Scientists speak of emission tomography when the emissive properties of sources within the body are imaged.

Sir Godfrey Newbold Hounsfield, a British electrical engineer, built the prototype for the first computer aided tomography (CAT) scanner in 1972 [Hounsfield73]. An x-ray tube rotated around a specific area of the body and delivered an appropriate amount of x-radiation to the tissue that was studied. The scanner took pictures of the internal anatomy from different angles. Each point on the projected image represented the total absorption of the x-ray along its path from the source to the detector. Cross-sectional images of the x-ray attenuation of the subject were calculated by using the measured projections. Rapid diagnosis in previously inaccessible areas of the body was now possible. The first clinical results meant an immediate breakthrough in x-ray imaging. Up to that point in time, soft tissue characteristics, primarily small density differences between neighboring organs or anatomical sites, were obscured by the much higher contrasts arising from bone or tissue thickness differences. By calculating transverse tomographic images instead of conventional x-ray superposition images, Hounsfield was able to demonstrate disparities in density or x-ray attenuation with higher resolution. For this innovation Hounsfield shared the 1979 Nobel Prize in Medicine with Allan Cormack, who had independently derived and published the mathematical basis of CAT scanning in 1963-64 [Cormack63]. CAT scanning has revolutionized medicine by facilitating the diagnosis of certain conditions, such as brain

and spinal cord disorders and cancer.

The basic ideas employed in tomographic imaging date much further back. The mathematician J.H. Radon proved in 1917 that the distribution of material properties within an object plane can be determined precisely if its line integrals in that plane are given [Radon17]. Regardless of the method of image reconstruction employed, this fundamental concept underlies most tomographic imaging approaches. Radon's mathematical work was not followed up by practical applications for a long time. In particular, no efforts at imaging were reported. Techniques for image reconstruction were first developed by Bracewell in 1956 [Bracewell56]. He reported on experiments in radioastronomy where he calculated two-dimensional images of emitted microwave radiation intensities of the sun's surface from the strip-wise measurements by microwave antennae. Presently, CAT is dealt with on the basis of well-understood linear Radon transform. A more detailed review about fundamental image reconstruction techniques is given by Herman [Herman80] and Natterer [Natterer99].

Another form of imaging that is based on the use of projections is emission tomography. An example for this imaging modality is positron emission tomography (PET), where the emissive properties of isotopes planted within the object are displayed. PET exploits the fact that certain chemical compounds that contain radioactive nuclei have a tendency to affix themselves to specific molecules. The radioactive nuclei used emit positrons upon their decay. Near the source of emission, the positrons combine with electrons to emit two gamma rays in nearly opposite directions. The gamma rays emitted by the decaying isotopes are detected. Upon detection of these two rays, a measurement representing the line integral of the absorption distribution along each path is obtained. Subsequently, the location of the chemical and the associated tissue within the body can be determined [Cho93].

Magnetic resonance imaging (MRI), also called nuclear magnetic resonance (NMR) imaging, is another emission tomography modality. This imaging technique is based on

protons (hydrogen nuclei) possessing a spin that is associated with a magnetic moment. When placed in an external magnetic field, the protons align either parallel or anti-parallel to the static magnetic field. The parallel position is slightly favored, as the nucleus is at a lower energy in this position. Exposure to RF radiation at the *Larmor frequency* causes nuclei in the lower energy state to jump into their higher energy state. When the applied RF signal is removed, the excited nuclei from the high energy state return to their low energy state with characteristic time constants (T1 and T2 relaxation). The transition of the magnetic moments, precessing around the static magnetic field, induces an electromagnetic signal in a RF receiver. The proton density and the environment is determined from the detected signal and can be displayed in an image [Cho93] [Beutel00].

In 1929 Cutler emphasized the potential of optical transillumination in the diagnosis of breast lesions [Cutler29]. F. Jöbsis showed in 1977 that oxygen saturation for cytochrome changes in tissue blood volume and the average hemoglobin-oxyhemoglobin equilibrium can be recorded using near-infrared (NIR) light [Jöbsis77]. Since then optical methods that use visible and NIR light have become increasingly important for non-invasive diagnostics in medicine [Hebden97]. Changes in the optical properties are closely related to physiological and pathological changes of different tissue types. In recent years, many studies have been performed that address the possibilities of using optical techniques for monitoring of blood oxygenation [Kirkpatrick97] [Henson98], detection of hematomas [Gopinath95] [Vahouten96], functional imaging of brain activities [Maki96] [Gratton97] [Hirth97] [Hoshi00], Alzheimer diagnosis [Hock96] [Fallgatter97], breast cancer detection [Franceschini97] [Nioka97], and diagnosis of rheumatoid arthritis [Beuthan96b].

In the early 1990s a non-invasive imaging modality commonly referred to as photon migration tomography (PMT), diffuse optical tomography (DOT), or simply optical tomography (OT), emerged. This new imaging modality is concerned with reconstructing

the distribution of optical properties inside the scattering and absorbing tissue by using NIR light transmission measurements performed on the surface ($\lambda = 650 - 850$ nm). In contrast to conventional imaging modalities, the optical radiation that passes through the body is highly scattered. This poses a substantial problem for the image reconstruction and the feasibility of OT was in doubt. However, development in recent years, including results of the studies presented here, have pushed OT closer to the mainstream of medical imaging modalities and an increasing number of researchers have embraced this technology.

The field of OT has advanced and several groups are currently performing clinical pilot studies to demonstrate the clinical usefulness of this technology [Colak97] [Pogue97] [Eda99] [Hebden99] [Yamashita99] [Schmitz00] [McBride01]. The instrumentation for accurate measurements of photons that have traveled several centimeters through tissue has become widely available. However, a major challenge remains the development of image reconstruction methods, which transform experimental data into images of clinical value. In the following sections we give a brief overview of state-of-the-art optical image reconstruction methods and discuss their usefulness and limitations. This discussion will form the basis of this work, as we derive from it the specific aims of the study.

1.2 Basics of Optical Tomography

As previously mentioned, the main problem in OT is that the radiation used for measurements is highly scattered inside biological tissue. The cell and its organelles, such as the nucleus, have been found to be responsible for light scattering in biological tissue [Mourant98] [Schmitt98]. The cell components vary in their refractive index [Beuthan96a], which causes light to be scattered [Hulst57] [Bohren83]. The parameter used to quantitatively describe scattering in biological tissue is called the *scattering coefficient* μ_s, which

equals the inverse of the average mean free path between scattering events. The scattering coefficients in biological tissue are typically between $20 < \mu_s < 200$ cm^{-1} [Cheong90].

Another parameter used to describe the scattering of light in tissue is the *anisotropy factor* g. If the medium is forward scattering then $0 < g \leq 1$. If light is scattered isotropically then $g = 0$ and if light is strongly backward scattered then $0 > g \geq -1$. Tissues usually have $g > 0.7$ [Cheong90]. Using g and μ_s, a parameter called the *reduced scattering coefficient* $\mu_s' = (1 - g)\mu_s$ is defined.

Besides scattering portions of the incident light can also be transformed into other forms of energy, most notably thermal. This process is called absorption and characterized by the *absorption coefficient* μ_a. The absorption of light is mainly affected by the water content of biological tissue, and natural chromophores such as hemoglobin, myoglobin, bilirubin, the cytochrom pigments of the respiratory chain in the mitochondria, and melanin pigment [Cheong90]. The absorption coefficient μ_a, as well as the scattering coefficient μ_s and the anisotropy factor g, are in general wavelength dependent. The reason for using NIR light for OT is that the absorption is relatively low, therefore allowing light to penetrate relatively thick tissues.

Singer *et al* [Singer90], Grünbaum *et al* [Grünbaum90], Barbour *et al* [Barbour90], and Aronson *et al* [Aronson91] proposed the first ideas of optical image reconstruction from projections. Grünbaum and Singer considered photons undergoing discrete random walks in an optically thick body that was partitioned into little cubes. Absorption and scattering were taken into account by weighting functions. These functions were based on the probability of a photon being absorbed within a cube, or being scattered into one of six directions. Given a particle that entered the object in one cube, the probability of the particle leaving at another boundary cube could be expressed by a system of equations. This could also be considered the *forward solution* for a known set of scattering and absorption

probabilities. Conversely, the *inverse solution* was obtained by computing the absorption and scattering probabilities for all cubes given a set of intensity measurements on the surface.

Barbour and Aronson discussed the principles of a potential imaging scheme, which used the reflected radiation of NIR light and suggested clinical applications. Specifically, they used a Monte-Carlo (MC) method for photon transport to develop a detector response function. Similar to CAT, they employed a *backprojection method* [Herman80] to infer a three-dimensional image of the absorption profile within the scattering medium.

There were several attempts in the field of OT using the backprojection method as implemented for CAT, where multiple scattering events are either neglected or regarded as noise. Applied to OT, average optical parameters were derived and subsequently back-projected along paths determined by weighting functions [Benaron94] [Colak97] [Walker97] [Matson97]. However, these methods had limited success, because the principal difficulty in OT is dealing with the dominant effect of multiply scattered photons. The inverse scattering problem becomes nonlinear and prohibits the direct application of reconstruction methods, such as the backprojection technique. Researchers have dealt with the limitations of the backprojection method by turning over to other methods for solving the inverse problem in OT, which take multiple scattering of photons into account. Currently, the most promising solution methods in OT are the so-called model-based iterative image reconstruction (MOBIIR) schemes.

In general, a MOBIIR scheme attempts to reconstruct the system parameters of a physical model [1] [Hanson98] [Hanson99]. A measurement system model describes the connection between the physical system and the experimental measurements. The system parameters are estimated by minimizing the difference between the predictions, given by

[1] The term *model* is often used throughout this work, such as forward model, inverse model, or adjoint model. In all applications the term model constitutes following meaning as defined by Karl Popper: "*Every system of concepts which satisfies a system of axioms can be called a model of that system of axioms.*" [Popper00].

the physical model, and the measured data obtained from an experiment.

A MOBIIR scheme applied to OT reconstructs the distribution of the optical parameters [Arridge97] [Arridge99a] [Arridge99b] [Hielscher99]. It consists of two major components: (1) a *forward model* for light propagation and (2) an *inverse model*. The forward model predicts the detector readings on the tissue boundary given a source at a specified location and distribution of optical properties inside the medium. In contrast, the inverse model determines the optical parameters inside the tissue, given a set of detector readings and detector predictions on the boundary of the tissue (see Figure 1.1). In the next two subsections we give a brief overview about the forward model and the inverse model used within MOBIIR schemes in OT.

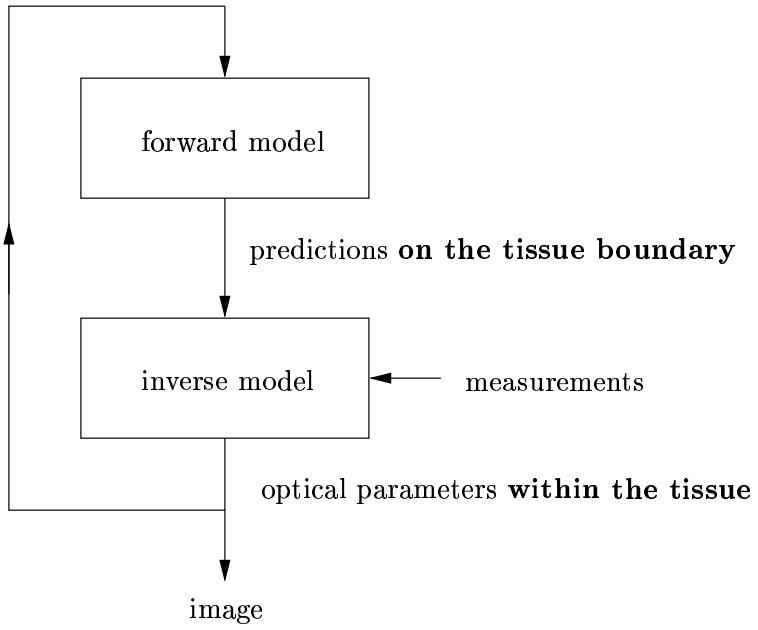

Figure 1.1: Components of the MOBIIR scheme in OT for determining cross-sectional images of the optical parameters. The forward model for light propagation in tissue is iteratively employed to calculate detector predictions. The image is obtained by updating the optical parameters within the inverse model.

1.2.1 Forward Model - Photon Propagation in Tissue

A physical model for light propagation in tissue predicts the intensity signal at the detector positions given an estimated set of optical parameters within the medium [Ishimaru89] [Patterson91]. Problems of radiative transfer similar to those in tissue optics are encountered in many fields of science, such as in planetary and stellar atmospheres, oceanography, and meteorology [Hulst57] [Chandrasekhar60] [Hulst80]. Light transport models dealing with multiple scattering are divided into two main groups: discrete or stochastic models, and continuous or deterministic models [Groenhuis83] [Arridge97].

Discrete models treat the radiation as a stream of single photons. Each photon undergoes individual absorption and scattering events. The most prominent discrete approaches for the flux distributions of light in tissue are the MC method [Groenhuis83] [Wilson83] [Flock89a][Keijzer89] [Jaques92] and the random walk theory (RWT) [Bonner87] [Gandjbakhche93]. The previously mentioned method of Grünbaum is considered to be a Markov random field (MRF) method [Grünbaum92a] [Grünbaum92b]. Patterson *et al* gave a review of various solution methods of radiation transport in tissue [Patterson91].

According to Groenhuis *et al* [Groenhuis83] and Ishimaru [Ishimaru89], deterministic models for light propagation are given by either an analytical theory or transport theory. The analytical theory is based on the Maxwell equations. The scattering and absorption characteristics of the photons are introduced via the material equations. The drawback of the analytical theory is the mathematical complexities involved, and its usefulness for practical applications to tissue optics is limited [Ishimaru97]. The transport theory does not start with Maxwell's equations. Rather, it deals directly with the transport of photon energy through turbid media. This theory has been developed independently of the analytical theory.

Although, the transport theory gives an adequate description of light propagation

in tissue, a general solution to the equation of radiative transfer (ERT) is not known. Solutions are available only for simple cases such as isotropic scattering and infinitely extended geometries [Chandrasekhar60]. Most research groups in OT are pursuing methods that yield approximate solutions to the ERT. One of the most commonly applied approximations is the diffusion approximation. For example, Ishimaru and Duderstadt derive the diffusion equation as an approximation to the ERT [Duderstadt79] [Ishimaru89] [Ishimaru97].

The diffusion equation can be solved analytically for many cases. For homogeneous media and simple geometries, such as slabs, cylinders, and spheres, solutions can be obtained using the method of Green's functions. [Patterson89] [Arridge92]. More complex geometries and heterogeneous media can be solved with numerical methods, such as the finite-element method (FEM) and the finite-difference method (FDM). In FDM the differential operator is replaced by discrete differences and the problem is solved on a regular grid. The diffusion equation in the frequency domain was solved, for example, by Pogue and Jiang *et al* [Pogue95] [Jiang96b], and in the time-domain by Hielscher *et al* [Hielscher99]. The FEM was introduced in OT for time domain, frequency domain, and steady-state by Arridge *et al* [Arridge93] and is widely accepted [Paulsen95] [Model97].

While the diffusion equation can be easily solved, it has its limitations as a forward model. The equation fails to describe the light transport in regions where the mean free path is very large. These regions are also called *void-like* areas, and can be found in the *cerebrospinal fluid* (CSF) of the brain [Hielscher98] [Dehghani99] and in the *synovial fluid* in human finger joints [Prapavat97]. The failure of the diffusion model compared to the transport model was quantitatively investigated by Firbank *et al* [Firbank96] and Hielscher *et al* [Hielscher98].

Some groups have attempted to overcome the disadvantages of diffusion-theory-based forward models. Arridge *et al* presented a hybrid radiosity-diffusion approach for

handling non-scattering regions within diffusion domains [Arridge00]. The method treats light propagation in highly scattering regions with the diffusion approximation and uses a ray-tracing method for the void areas. However, this approach requires *a priori* knowledge about the exact position of void-like regions. Therefore, this approach is of limited use for OT, even though the results of the forward calculations are impressive [Firbank96].

1.2.2 Inverse Model - Reconstruction of Optical Properties

The image reconstruction task in tissue optics involves the solution of an inverse problem. The inverse problem in OT is based on the assumption that, given a set of measurements for different source and detector positions on the surface of the tissue, there exists a spatial distribution of scattering and absorption parameters which yield that set. A solution to the inverse problem is displayed as a cross-sectional image. The most prevalent inverse model within a MOBIIR scheme in OT is the perturbation approach [Schottland93] [O'Leary95] [Arridge95b] [Paulsen95] [Chang96] [Jiang96a] [Jiang96b] [Yao97]. Other methods, which find more interest in recent years, are nonlinear optimization techniques [Davies97] [Arridge98] [Hielscher99] [Roy99].

The perturbation method depends on the fact that the forward model, e.g. the diffusion model, is expanded into a Taylor series around an estimated set of optical parameters. Neglecting all expansion terms higher than the first term yields a linear expression for calculating an update of the optical parameters. The perturbation method requires explicitly or implicitly a difference experiment. Either the difference of measured data of two different states of optical parameters or the difference of the measured data and simulated data with known optical parameters have to be taken. A Jacobian matrix connects linearly the vector of difference measurements with the vector of changes to the optical parameters. The resulting linear system of equations can be solved by an *algebraic recon-*

struction technique (ART) or by techniques that involve matrix inversion [Gilbert72]. A major computational burden is the calculation of the Jacobian matrix by using the forward model.

A difference between several perturbation techniques is how the Jacobian matrix is determined. For example, Chang *et al* [Chang96] derived the Jacobian from a MC model, whereas Arridge *et al* [Arridge95a] and O'Leary *et al* [O'Leary95] calculated the Jacobian using an analytic kernel for several geometries of the turbid medium. The most promising technique is calculating the Jacobian for arbitrarily complex and inhomogeneous geometries of scattering media by using the FEM [Arridge95b].

However, Boas has pointed out that linear reconstruction techniques, such as the perturbation method, offer limited quantitative information of the recovered optical parameters [Boas97]. The success of the perturbation technique depends largely on how close the initial estimate is to the correct solution and that the negligence of higher-order terms in the Taylor series expansion have little effect [Arridge97].

Nonlinear optimization techniques can also be applied to solve the inverse problem. An objective function or error function is defined, which describes the difference between the measured and predicted data. Once the objective function is defined, the task becomes to minimize it. Most commonly applied techniques performing this task are gradient techniques [Arridge98] [Hielscher99] [Roy01]. Once the minimum is found, the final result is the distribution of the optical parameters. These methods require only the knowledge of the gradient of the objective function and are preferable for problems with a large number of unknown optical parameters.

The gradient-based optimization techniques have the advantage that the Jacobian matrix neither needs to be explicitly created nor repeatedly inverted. This is especially important when the ERT is used as a forward model, as opposed to the diffusion equation.

In this instance, the calculation of the Jacobian becomes increasingly time-consuming, as the solution of the ERT is more computationally demanding than solving the diffusion equation.

Several researchers have already worked on the inverse problem concerning the ERT [Larsen81] [Sanchez81] [Larsen84] [McCormick84] [McCormick86] [Larsen88] [Wang89] [Sanchez90]. For example, McCormick provided a review concerning inverse radiative transfer problems limited to the reconstruction of spatially distributed internal light sources, or the estimation of optical thickness of scattering media [McCormick92]. Norton provided an illustration for reconstructing the spatially varying scattering cross-section in a two-dimensional medium by using a nonlinear optimization technique [Norton97]. However, these methods cannot be applied to the transport problems that are typically encountered in biomedical imaging. For this case, Dorn reported an inversion method applied to the time-dependent ERT [Dorn98]. He used the *Frechet derivative* of a residual that is proportional to the difference between the measured and predicted data. The resulting nonlinear system of equations was solved by a nonlinear generalization of the ART, where the optical parameters were iteratively updated. Dorn presented numerical results. However, the inverse model was neither experimentally confirmed nor applied to void-like areas in tissue.

What continues to be lacking is a MOBIIR scheme based on the ERT that can be applied to tissue containing void regions. This is of extraordinary importance for clinical imaging problems, such as the early diagnosis of rheumatoid arthritis in human finger joints. Finger joints contain void areas and thus require the ERT. Until now, no work has been accomplished for reconstructing cross-sectional images of human finger joints that reveal the optical parameters of the synovial fluid within the joint capsule.

1.3 Rheumatoid Arthritis of Finger Joints

A transport-theory-based optical image reconstruction scheme is specifically useful for dealing with void-containing media. Rheumatoid arthritis of finger joints is therefore an obvious candidate for the first clinical application. It is a progressive disease, which has no cure. Rheumatoid arthritis affects mostly human finger joints. The inner membrane of the joint capsule becomes inflamed, which subsequently results in pain, stiffness, swelling, and loss of function in the joint.

The synovial fluid between the bones that lubricates and nourishes the joint tissue is a clear and virtually non-scattering and non-absorbing fluid. It is known that rheumatoid arthritis changes the optical parameters of the inner membrane and the synovial fluid [Prapavat97]. Measuring local changes in the optical parameters of these parts may be used for early diagnosis and monitoring the progression of the disease.

To date, only Xu *et al* [Xu01] reported on the reconstruction of cross-sectional images of the optical parameters in human finger joints. They used a MOBIIR scheme based on the time-independent diffusion equation. However, they did not reconstruct the synovial fluid or the inner membrane within the finger joint. Moreover, the light propagation in void regions such as the synovial fluid needs to be described by the ERT. Until now, there does not exist an optical image reconstruction technique to recover the optical parameters of a human finger joint for the diagnosis of rheumatoid arthritis.

1.4 Objectives

The aim of this work is to develop a MOBIIR scheme for OT that reveals cross-sectional distributions of the scattering and absorption coefficients by performing boundary measurements. The MOBIIR scheme should be applicable to human finger joints. Specific

objectives of this work can be derived from the following problems:

- All existing **forward models** within a MOBIIR scheme that were applied recently to problems in biomedical imaging are based on the **diffusion equation**. The diffusion theory **fails** to describe the photon propagation in **void-like** regions, such as the CSF layer in the brain or the synovial fluid in human finger joints.
- The most prominent **inverse model** within the MOBIIR scheme in OT is a **perturbation technique**. It requires the calculation and inversion of a Jacobian matrix, which is **computationally expensive**.
- There are **no** image reconstruction schemes in OT that recover the optical parameters of human finger joints for the diagnosis of **rheumatoid arthritis**.

We address these problems by focusing on the following issues:

1. We develop a **forward model** based on the time-independent **equation of radiative transfer** that is applied to **tissue-like** media with **low-scattering regions**.
2. We conceive an **inverse model** that is a gradient-based **optimization method**. It minimizes an objective function to recover the optical parameters. The calculation of a Jacobian is not necessary.
3. We introduce an **adjoint differentiation technique** applied to the ERT for calculating the gradient of the objective function.
4. We **experimentally** evaluate both the forward model and the inverse model by using simple **tissue phantoms**.
5. We present for the **first** time cross-sectional **images** of μ_s and μ_a of a **human finger joint**. We show in a numerical study how OT can be utilized for monitoring **rheumatoid arthritis**.

1.5 Outline of the Content

This work describes a MOBIIR scheme based on the ERT. It is structured in three parts: the forward model of the MOBIIR scheme is explained in Part I (Chapter 2-4). The inverse model comprising the numerical optimization method of the MOBIIR scheme and its application to the imaging problem of rheumatoid arthritis is described in detail in Part II (Chapter 5-9). We give a summary and outlook of this work in Part III (Chapter 10-11).

Chapter 2 describes a finite-difference discrete-ordinates method for modeling the light propagation in tissue based on the time-independent ERT. In Chapter 3 we discuss the numerical error of the fluence due to the spatial and angular discretization of the ERT. Chapter 4 deals with experimental studies on tissue-like phantoms that contained void regions.

Chapter 5 describes the nonlinear optimization problem in OT as part of the MOBIIR scheme. A defined objective function is minimized to calculate cross-sectional images of the optical parameters. Different optimization techniques are employed, which use the first derivative of the objective function with respect to the optical parameters to calculate a search direction. In Chapter 6 we describe an adjoint differentiation technique that calculates the derivative of the objective function. The adjoint differentiation technique is a particular numerical implementation of an adjoint model.

The MOBIIR scheme is validated in Chapter 7 by using numerical examples. Furthermore, the performance of different gradient-based optimization techniques is studied. The impact on the reconstruction results of different numbers of source-detector pairs is determined. In Chapter 8, the transport-theory-based MOBIIR scheme is validated by using experimental data from tissue-like phantoms. We focus on typical scattering problems, where diffusion-theory-based reconstruction techniques fail.

The optical image reconstruction problem for the diagnosis of rheumatoid arthritis in human finger joints is addressed in Chapter 9. Moreover, we show the first cross-sectional image of optical properties of a human finger joint.

Finally, a summary of the main results are presented in Chapter 10. An outlook for future work is given in Chapter 11. We address problems of using the time-dependent ERT as a forward model, and discuss an evolution strategy to determine the global minimum of the objective function.