Breast lesion detection using diffuse optical imaging
Leproux, A.

Citation for published version (APA):
Leproux, A. (2012). Breast lesion detection using diffuse optical imaging
Chapter 1

INTRODUCTION

Abstract

Breast cancer is recognized as a major health problem worldwide. This chapter introduces the disease and its impact on women. It provides information on the current methods of detection and presents newer methods that are still under research. Diffuse optical imaging (DOI), which is a subset of molecular imaging, is introduced as a potential modality to image breast cancer. More research is yet to be carried out for DOI to play a role in breast cancer imaging. The following chapters, outlined at the end of this introduction, present my contribution to this effort.
1.1 Breast cancer statistics

Worldwide, breast cancer is the second leading cause of cancer deaths in women (after lung and bronchus cancer) and is the most common cancer among women (World Health organization); more than 1.2 million women are diagnosed every year with breast cancer (World Health organization). According to the Centraal Bureau voor de Statistiek, the Netherlands has among the highest rates of breast cancer death in Europe (after Denmark, Ireland and Iceland). The American Cancer Society estimated that in 2010 only in the United States (USA):
- About 207,090 new cases of invasive breast cancer would be detected in women
- About 54,010 new cases of carcinoma in situ will be found
- About 39,840 deaths will occur in women from breast cancer

Table 1: Incidence of breast cancer by age in the USA (Breast Cancer Facts & Figures 2011-2012, American Cancer Society [1])

| Probability of developing invasive female breast cancer in the next 10 years |
|------------------|------------------|
| By age 20        | 1 in 1,681       |
| By age 30        | 1 in 232         |
| By age 40        | 1 in 69          |
| By age 50        | 1 in 42          |
| By age 60        | 1 in 29          |
| By age 70        | 1 in 27          |
| Lifetime risk    | 1 in 8           |

According to the American Cancer Society, age is the most important risk factor for breast cancer (after being a female). Table 1 presents woman’s risks of being diagnosed with breast cancer at different ages. These probabilities are averages for the whole USA population, concern women free of cancer at the beginning of the age intervals, and are based on cases diagnosed between 2004 and 2006. Other risk factors for breast cancer include family history of breast cancer, personal history of breast cancer, breast feeding, ethnicity, dense breast tissue, certain benign breast conditions, and lifestyle. Currently, a woman living in the USA has a 1 in 8 lifetime risk of being diagnosed with invasive breast cancer.

Table 2: Survival rate by age in the USA (American Cancer Society)

<table>
<thead>
<tr>
<th>Five year survival rate by age</th>
</tr>
</thead>
<tbody>
<tr>
<td>Younger than 45</td>
</tr>
<tr>
<td>Ages 45-64</td>
</tr>
<tr>
<td>Ages 65 and older</td>
</tr>
</tbody>
</table>

Breast cancer at young age is less common than at older age (Table 1). However, breast cancer in younger women tends to be more aggressive and less likely to respond to treatment [2-3]. It is therefore of importance to detect effectively early breast cancer in young women. Unfortunately, there is no effective breast cancer screening tool for young women; diagnosing breast cancer in younger women is more difficult because their breast tissue is generally denser than the breast tissue in older
women. So by the time a lump in a younger woman's breast can be felt, the cancer is often advanced, which explains why survival rates are lower among younger women (Table 2). Early detection and prompt treatment would significantly improve a woman's chances of surviving breast cancer [1]. Breast cancer in younger women has therefore become a new focus in breast cancer research.

Breast cancer mortality increases with tumors stage and size [1]. Therefore, it is of importance to detect early small tumors that may be aggressive. Breast cancer screening has been shown to reduce breast cancer mortality: tumors are detected earlier and can therefore be treated earlier resulting in lower rate of breast cancer mortality [4]. In the USA, death rates from breast cancer in women have been declining since 1990, due in large part to early detection by mammography screening and improvements in treatment. Currently, about 65% of breast cancers are diagnosed at a lymph node negative stage, for which the five-year survival rate is 99% [1].

1.2 Breast anatomy

The female breast consists of glandular, fatty and fibrous tissue located over the pectoralis muscles of the chest wall and attached to these muscles by the Cooper’s ligaments, see Figure 1. The lobules (or glands), which produce the milk for breast feeding, are linked by a network of milk ducts. A layer of fat surrounds the breast lobules and extends throughout the breast. The glands produce the milk when stimulated by special hormones and the ducts transfer the milk from the glands to the nipple. Surrounding the nipple is a slightly raised circle of pigmented skin called the areola. The nipple and areola contain muscle fibres.

Figure 1. Lateral view of the female breast showing the inner composition. Copied with permission from http://www.breastcancer.org/pictures/types/


1.3 Breast cancer types

There are different types of breast cancer; the most common are ductal carcinoma and lobular carcinoma \([5]\). Breast cancers can be either non-invasive (in situ) or invasive. In situ breast cancer refers to a cancer that is located where it first originated, Figure 2 (b). On the other hand, invasive breast cancer refers to a cancer that has invaded the surrounding normal fatty tissue of the breast, Figure 2 (c).

Figure 2. (a) Example of normal cells in a duct. (b) The cancerous cells in ductal carcinoma in situ are located in the ducts. (c) The cancerous cells in invasive ductal carcinoma are invading the surrounding tissue. Copied with permission from http://www.breastcancer.org/pictures/types/

The major types of non-invasive breast cancer are:

- Ductal Carcinoma In Situ (DCIS): abnormal cells were formed within the milk ducts and are still contained there. It is an early-stage breast cancer and is considered as a precancerous condition. Indeed, if not treated it can progress to form an invasive breast cancer.
- Lobular Carcinoma In Situ (LCIS): abnormal cells were formed within the lobules of the breast and are still contained there. It is a precancerous condition but it is not clear whether LCIS is an early-stage breast cancer. LCIS is a risk factor of developing breast cancer and therefore can be left untreated with a yearly mammographic follow up.

As said above, invasive breast cancers refer to cancer cells that have invaded the surrounding normal fatty tissue of the breast. Invasive breast cancers can also metastasize through the blood stream or lymphatic vessels to other parts of the body. The major types of invasive breast cancer are:

- Invasive Ductal Carcinoma (IDC): it represents the majority of breast cancers. Cancer cells from the milk duct invade the surrounding breast tissue.
- Invasive Lobular Carcinoma (ILC): this type of cancer is less common than IDC and is often more difficult to diagnose on mammogram and by palpation (there is no breast lump). It initially forms within the milk lobule and invades the surrounding breast tissue.

There are also other less common breast cancer types that do not originate from a duct or lobule. For instance, Paget’s disease of the breast is a rare form of in situ cancer that is often accompanied by an invasive cancer or a DCIS. Paget’s disease is located in the skin of the nipple and areola and is often confused with skin conditions, such as eczema. Another uncommon type of breast cancer is the sarcoma that comes from connective tissue such as nerves, fat, fibrous tissue, or blood vessels of the
breast; or locally advanced breast cancer that is growing into the skin or chest wall or where there are enlarged lymph nodes. Breast cancer is a heterogeneous disease with several different subsets, or several different categories of breast cancer determined by the molecular characteristics of the tumor cell. These molecular characteristics determine the behavior of the cancer cells; for instance, the likelihood that the cancer cells spread away from the primary site.

The breasts can develop other types of disorders. The majority of breast conditions are not cancerous:
- Fibroadenoma: it is a fibrous, benign growth of breast tissue. Fibroadenomas are solid, usually painless lumps not attached to any structure in the breast. They can be removed surgically, but also can disappear by themselves.
- Cyst: it is a fluid filled sac. Often cysts are not harmful, but they can be painful. They can disappear by themselves or the liquid can be drained with a needle.
- Fibrocystic breast disease: it is a benign clinical condition characterized by an increase in the fibrous and glandular tissue in the breast, which results in small nodular cysts, noncancerous lumpiness and tenderness.
- Breast abscess: it is a collection of pus resulting from an infection. The treatment consists of antibiotic therapy and/or drainage.

1.4 Current breast imaging techniques

X-ray mammography is currently the primary technique for breast screening and is routinely used in the clinics. Lesion identification relies on the imaging of radiographic density differences between different tissue types. Radiographically, benign lesions are usually less dense than malignant lesions, and they have smooth outlines while malignancies have irregular outlines. Overall, malignant lesion can be observed as characteristic masses and/or specific patterns of micro-calciﬁcation in x-ray images. Breasts mainly composed of fat are more transparent to the x-ray beams than breasts with glandular tissue. Breast cancer screening with mammography has been shown to decrease mortality [1]. However, it is still debated whether young women (under 50) should be screened [6]. Young women tend to have radiographically more dense breasts, which results in a drastic decrease of sensitivity of mammography.

Even if X-ray mammography is the most commonly used imaging modality for breast cancer screening, it has known limitations, such as rather high false-positive rate (resulting in many true negative biopsies), poor sensitivity in women with radiographically dense breast tissue, discomfort due to breast compression, and a slight risk of inducing cancer due to the ionizing radiation exposure [7].

New imaging techniques including digital mammography, x-ray computed tomography (CT) ultrasound (US), magnetic resonance imaging (MRI) and positron emission tomography (PET) are emerging to overcome the limitations of mammography, and some of them are already used as adjunctive screening tools [8].
Digital mammography was first developed to overcome the low sensitivity of screen-film mammography in dense breasts. Post-processing can be performed on the digital mammographic images and may increase lesion contrast. Computer-aided detection can also be used easily with digital mammography and has shown to improve the specificity of conventional mammography [9].

By imaging the breast in 3 dimensions, CT aims at reducing the overlaps of structures present in the 2 dimensional images and thus at enhancing the ability of mammography to detect cancer [10]. In addition, CT provides better information on the location of the lesion. It however suffers from the poor contrast differences between fibroglandular tissue and malignant tissue and therefore requires iodine contrast-media.

In clinics, the primary role of US is the evaluation of breast abnormalities found with mammography or by physical examination and is a close companion of mammography in the daily work up of breast radiologists. US imaging is known to detect and characterize benign tumors with very high accuracy. In addition, it has been shown that ultrasound imaging can detect clinically occult tumors that were missed by mammography [11]. US is also used for guidance of interventional procedures, such as biopsies. However, the current ultrasound examination is too time-consuming to be used for screening, and is very operator dependent.

MRI is currently mainly used for women who may be at increased risk for the development of breast cancer. It provides similar spatial resolution as x-ray mammography but with greater contrast resolution in soft tissue. The sensitivity of MRI in dense breast is greater than that of mammography. Combined with a contrast agent, gadolinium, [12] reports for fluorescent MRI (fMRI) (CE MRI, contrast enhanced MRI) a sensitivity in dense breast of 81 % against 60 % for mammography in high risk women. Therefore MRI appears to be more appropriate for younger women. However MRI specificity is much lower than mammography, resulting in many more negative surgical biopsies. For instance, [12] reports a positive predictive value in dense breast of 71 % in MRI against 78 % in mammography. MRI has 3 other major limitations: it uses a contrast agent, it is time consuming, and it is too expensive to be used routinely for screening.

PET relies on the overexpression of a certain type of glucose by the breast cancer cells as compared to normal tissue. Glucose molecules (FDG - fluorodeoxyglucose), combined with a radioactive tracer, are injected intravenously prior to the scan. The uptake of FDG allows clinicians tumor visualization and differential diagnosis. PET is currently used to detect breast metastasis.

Lesion identification in X-ray mammography and US is based on morphological information of breast tissue. However, tumors have distinct compositions that differ from healthy breast tissue. Fibroadenomas, for instance, have a high stromal content and lower blood vessel density as compared to IDC that have a high epithelial content. Therefore, there is an increased interest for imaging techniques that can give functional and molecular characteristics specific to tumors, e.g. MRI and PET. Optical imaging is another technique that provides functional and molecular information. The development of optical breast imaging techniques is attractive because, in addition to being safe, non-invasive and cost-effective, optical imaging can reveal contrast between normal and diseased tissue that is not available with the conventional methods.
1.5 Optical imaging

Near-infrared (NIR) optical imaging methods are a subset of molecular imaging techniques which image the underlying biological processes or functional state of living cells, tissues, and organs. In the domain of breast cancer research, NIR optical imaging methods provide a non-invasive tool to characterize the bulk composition of breast tissue. Optical methods have been shown to be safe, and effective for in vivo imaging. Briefly, they involve the detection of photons that propagate through the breast (in transmission or reflection), and, using light propagation models, reconstruct the optical properties of the illuminated breast.

1.5.1 Light propagation in biological tissue

Light propagation in tissue is determined by scattering, described by the scattering coefficient $\mu_s$, and absorption, described by the absorption coefficient $\mu_a$, both of which are dependent on cellular structure and molecular composition of the tissue [13, 14]. The reciprocal of both coefficients describe the average pathlength the photons travel before being scattered or absorbed. Because of refractive index discontinuities between and within cells, most biological tissues have an inhomogeneous structure and are therefore highly scattering. Within the NIR wavelength range, the probability of a scattering event is much larger than the probability of an absorption event. After a sufficient number of light scattering events, the propagation direction of the photon has become independent of the propagation direction of the incoming photon. When the ratio $\mu_s' / \mu_a$ is high enough (larger than 10) and the source-detector distance is larger than $1/\mu_s'$, the diffusion equation becomes applicable to characterize light transport and the tissue optical properties can be determined. Scattering in biological tissues is then characterized in terms of reduced scattering coefficient $\mu_s'$, which is defined as the product of the scattering coefficient and one minus the anisotropy factor (1-g). The anisotropy factor g is defined as the average of the cosine of the scattering angle. The optical methods examining biological tissues for this regime are then referred to as diffuse optical methods.

The NIR spectral region from 600 to 1000 nm is considered as an optical window. Indeed in this region, the tissue attenuation is at its lowest and therefore the light can penetrate deepest. For instance, NIR light can be detected after it has been transmitted across several centimeters of breast tissue. The NIR wavelength range is predominantly sensitive to the following absorbers: melanin, hemoglobin in its oxygenated (HbO$_2$) and deoxygenated (HHb) states, water and lipid. Melanin is the main absorber of biological tissue, but in case of breast tissue, it is contained only in a thin layer of skin and has therefore a minimum effect on the total absorption of the breast. Therefore, in case of spectroscopy in breast tissue, the main breast chromophores are assumed to be hemoglobin, water and bulk lipid. Because of the wavelength-dependent intensity of light penetration into biological tissue and of the difference in wavelength dependence of the chromophore absorptions, NIR optical imaging methods can characterize the composition of breast tissue and therefore the functions of tissue, see section 1.5.3. The contrast between healthy and cancerous
tissue is due to vascularisation of tumors and can therefore be observed most significantly in hemoglobin content [15]. Note that in addition to probing endogenous contrast, optical techniques can detect exogenous contrast when using an optical contrast agent [16, 17], e.g. fluorescence of contrast agents as described in section 1.5.4.

### 1.5.2 Diffuse optical techniques

Two major diffuse optical techniques can be cited: Diffuse Optical Tomography (DOT) and Diffuse Optical Spectroscopy (DOS). While DOT focuses more on the spatial content of the measurement at the expense of the spectral content (producing 3D maps of the breast), DOS typically samples a lower number of spatial locations with a higher spectral bandwidth. The number of measurements provided with DOT is equal to the number of sources times the number of detectors.

Within the field of optical imaging and spectroscopy, three distinct instrumentation techniques have been developed, based on frequency-domain [18], time-domain [19], and continuous-wave (CW) or steady-state [20] methods. Briefly, for the frequency domain method, the light sources are intensity modulated at high frequencies. The detected light that is absorbed and scattered will be attenuated and phase shifted compared to the input light. These amplitude changes and phase shift are related to the tissue optical properties [21]. Time domain methods use short pulses (picosecond) as light source to illuminate the breast. When propagating in tissue the pulses are broadened. The delay between and attenuation of the incoming and detected pulses and the broadening of the pulses are related to the optical properties of the tissue [22]. The results of time-domain method are the Fourier transform of the results of frequency-domain method. However, time-domain has more data and is more time consuming than frequency domain. Steady state methods use CW light as light source and measure the attenuation of light across the breast. Steady-state devices are known for their inability to separate absorption from scattering, resulting in inaccurate quantification of the amount of absorbers in the breast [23].

In this thesis, the presented data have been obtained with 3 instruments using 3 different diffuse optical methods: CW DOT, CW DOT combined with fluorescence imaging and frequency-domain DOS combined with broadband steady-state measurements. Chapter 2 presents detailed descriptions of these instruments, their main applications and results obtained during clinical trials.

### 1.5.3 Spectroscopy

In DOI, lesion detection and localization are enabled by endogenous optical property contrast (i.e., absorption and scattering) between tumor and normal breast tissues [24-26]. By employing multi-spectral approaches, along with model-based analysis of NIR light transport in tissues, the concentrations of the 4 main chromophores in breast tissue, i.e. hemoglobin (oxygenated and deoxygenated), water and lipid, can be determined. Increased hemoglobin concentrations in tumor relative to normal breast tissues have been widely observed in the literature; these increases are understood to
be a direct result of tumor angiogenesis [15, 27-31]. In addition to chromophore concentrations, optical indices have been developed to condense information content. For example, tissue hemoglobin saturation and total hemoglobin concentration, depending upon tissue oxy-hemoglobin and deoxy-hemoglobin concentrations, are hemodynamic indices that are widely employed. Other functional indices, such as the tissue optical index (TOI) derived from the concentrations of water, lipid and deoxy-hemoglobin have been developed in order to increase lesion-to-normal contrast [15].

In case of DOT, 3D absorption maps can be recovered for the (typically limited number of) wavelengths used. In case of broadband DOS, for each measurement point, absorption spectra are recovered for a spectral range. To recover the concentration of the main absorbers contained in the probed breast tissue, we assume that the total absorption of the sample is a summation of the absorptions by all the absorbers present in breast tissue and that absorption in breast is caused mainly by the following four absorbers: deoxy-hemoglobin (HHb), oxy-hemoglobin (HbO$_2$), water and lipid. The concentrations of the main chromophores of the breast can therefore be obtained with:

\[
\mu_a(r, \lambda) = \sum_{i=1}^{4} \mu_{a_i}(r, \lambda) \quad (1)
\]

\[
\mu_{a_i}(r, \lambda) = c_i(r) \cdot \varepsilon_i(\lambda) \quad (2)
\]

\[
\bar{c}(r) = \left[\varepsilon(\lambda)\right]^{-1} \cdot \bar{\mu}_a(r, \lambda) \quad (3)
\]

In equation (1), $\mu_a(r, \lambda)$ is the recovered absorption coefficient as a function of wavelength $\lambda$ and spatial location $r$, $i$ refers to individual absorbers (HHb, HbO$_2$, water or lipid), so $\mu_{a_i}(r, \lambda)$ is the attenuation contribution for a given chromophore as a function of wavelength and spatial location. The probed absorption is a linear combination of the chromophores absorption. Each chromophores absorption can be described as in equation (2), where $c_i(r)$ refers to the concentrations of the given absorbers at the location $r$, $\varepsilon_i(\lambda)$ is the molar extinction coefficients of the given chromophores as a function of wavelengths, see Figure 3. The vector of concentrations of the 4 chromophores, $\bar{c}(r)$, is then obtained by solving the matrix equation (3), where $\left[\varepsilon(\lambda)\right]$ is the matrix of molar extinction coefficient of the 4 chromophores per probed wavelengths.

Since we assume that the breast is composed of 4 main absorbers, a minimum number of 4 wavelengths are required to recover the concentrations of these 4 absorbers. In case of broadband DOS, many more wavelengths are measured than chromophores and a least-squares fit is performed to recover the concentration of the absorbers.
From the concentrations of deoxy-hemoglobin and oxy-hemoglobin, the total hemoglobin concentration ($THb$) and tissue hemoglobin oxygen saturation can be determined, using: $THb = c_{HbO2} + c_{HHb}$, and $stO2 = c_{HbO2}/THb$ respectively, with $c$ referring to concentration of the chromophore. A tissue optical index (TOI) representing the tissue metabolism can also be obtained: $TOI = c_{HHb} \times c_{H2O}/c_{lipid}$. In general, higher hemoglobin and water concentrations and lower lipid concentration are observed in tumors, resulting in high TOI values in malignancies. The TOI is typically used to identify the spatial location of tumors [15, 33].

### 1.5.4 Fluorescence imaging

Some clinical studies have shown that for breast cancer detection, the intrinsic optical properties and chromophore concentrations in breast tissue are not sufficient for stand-alone lesion detection and for discrimination of malignant from benign tumors [34-37]. Indeed, the endogenous contrast from the increased vascularisation in small tumors or tumors in dense breast tissue is expected to be low. Besides, this endogenous contrast is nonspecific to cancer. Also, breast cancer mortality increases rapidly with tumors size whereas diffuse optical imaging has a known low spatial resolution (in the order of 5-10 mm). The low contrast and spatial resolution of DOI result in limited sensitivity and specificity for lesion detection and characterization, especially in case of small and non-palpable lesions or lesions in dense breast tissue. The use of fluorescent contrast agents may increase the sensitivity and specificity [38, 39] of lesion detection and hence could provide better and earlier diagnosis. The injected fluorescent molecule may preferentially accumulate in diseased tissue because of increased blood content due to tumor angiogenesis [40] and leaky blood vessels in tumors due to damaged endothelial lining. Alternatively, the agent may have different decay properties in diseased tissue, which could be used to localize tumors independently of the concentration of the fluorescent molecule [41].
targeted contrast agents may significantly improve the contrast between tumors and surrounding healthy tissue. Indeed, targeted contrast agents target receptors specific to cancer cells [42, 43].

In breast cancer research, the fluorophore Indocyanine Green (ICG) is often used for fluorescence imaging. In [17], they found in 3 patients that the ICG contrast was 3 to 4 fold higher than the total hemoglobin contrast in the tumor. [44] found that 3 different pathologies (fibroadenoma; adenocarcinoma; invasive ductal carcinoma) in 3 patients had different pharmacokinetics of ICG. This suggests that fluorescence imaging with ICG can improve the specificity of DOI. [45] succeeded in imaging the lymphatic drainage pathways and sentinel lymph nodes (which are the first lymph node to receive drainage from cancer) using ICG. In [46], they claim that they can discriminate benign from malignant lesions looking at their contrast to normal tissue in fluorescence signal after the dye is almost fully eliminated from the body.

1.6 Thesis goals and outline

The main focus of this thesis is the investigation of methods to improve breast lesion detection using optical imaging. The motivation was introduced in the first sections of this introductory chapter. The two main facts are that breast cancer mortality increases with tumors size and that breast cancer is difficult to detect in dense breast using conventional mammography [1]. Therefore, it is of importance to detect small tumors and tumors in dense breasts. Diffuse optical techniques utilize light in the near infrared spectral range to measure tissue physiology noninvasively and can be applied for breast cancer imaging. However, due to diffusion of light in tissue, the spatial resolution in optical techniques is rather low. Besides, the functional contrast of lesions in breast tends to be low as well, due to the presence of fibroglandular tissue. At last, in case of DOT, image reconstruction is using many approximations that result in limited image quality. Therefore optical imaging has low sensitivity and has not shown yet the potential to be a standalone imaging modality for lesion detection in breasts. This thesis aims at validating new methods to improve detection of breast tumors using optical imaging.

Each of the result chapters 3, 4, 5, 6, and 7, are organized as individual papers in which there is an introduction, a description of the research methods, the presentation and discussion of the results and finally the conclusion. Motivation for the specific studies is laid out in the introduction of each chapter. The following will briefly describe each study and how it fits with the overall goal of the thesis.

The second chapter of this thesis gives background information on the 3 optical instruments used to collect the data for this thesis. Their main applications and the results of clinical trials using these systems are also presented.

Chapter 3 is an introductory study for the thesis. It describes a demographic study of the averaged optical attenuation of the female breast. The results of this study give insight into the biological variations between women that impact the sensitivity and specificity of diffuse optical techniques.
Chapters 4 and 5 are investigations of the effect of the combination of DOT and fluorescence imaging on lesion detection. Some clinical studies have shown that for breast cancer detection, the intrinsic optical properties and chromophore concentrations in breast tissue are not sufficient to discriminate malignant from benign tumors [34-37]. The use of a contrast agent may increase the specificity [38, 39] and hence provide differential diagnosis, i.e. allow the differentiation between malignant and benign tumors. Chapter 4 presents the results of a statistical analysis used to combine the absorption and fluorescence data. Phantom measurements mimicking breasts are used to validate the statistical method. In chapter 5, we investigate the combination of absorption, blood volume and the fluorescence signal into a graph, the scatterplot, both for phantom and patient measurements. In chapters 4 and 5, we aim at enhancing the information contained in fluorescence and absorption images by combining these two sources of information. The goal of this exercise is to detect smaller lesions and better characterize the different structures in the breast for diagnostic purpose.

DOS has proven its ability to quantitatively characterize breast tissue composition [15, 47]. Recent advances have shown that broadband DOS can be used to image molecular disposition of water and lipid in breast tissue using a differential method. Molecular dispositions of water and lipid seem to be highly sensitive to malignancy and therefore may compensate for the frequent poor functional tumor contrast. The sixth chapter investigates the capability of broadband DOS to image specific tumor components of breast cancer using a self-referencing method. The published studies on lesion detection with optical techniques use the contralateral normal side for referencing. However, in certain case, the contralateral side cannot be measured or even used as normal tissue (e.g. in case of bilateral lesions). Chapter 6 focuses therefore on self-referencing on the ipsilateral breast to image the specific tumor components.

Chapter 7 gives a conclusion and an outlook on the different methods investigated in this thesis, to improve lesion detection of breast cancer using diffuse optical imaging. Finally, supplements 1 and 2 present the results of two additional studies, which are slightly out of the scope of this thesis, but present two other ways to optimize the way DOI is used. The feasibility of 3-D whole-breast ultrasound imaging is investigated in supplement 1. The goal is to combine the anatomical information from ultrasound with the physiological information of DOT to improve lesion visibility. Supplement 2 presents DOSI in a different context than breast cancer detection. The self-referencing method presented in chapter 6 is used to investigate breast cancer spatial heterogeneity as a predictor to neoadjuvant chemotherapy.

References


