Breast lesion detection using diffuse optical imaging
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Chapter 2

INSTRUMENTATION AND CLINICAL APPLICATIONS

Abstract

In this thesis, methods are investigated to improve detection of breast tumors using diffuse optical imaging (DOI). This chapter provides information on instrumentation and clinical application for which new analysis tools are developed and described in later chapters. The first section gives an overview of the 2 instruments built by Philips. The first Philips’ instrument is a diffuse optical tomography (DOT) system. The second instrument combines DOT with fluorescence imaging. The second section describes the diffuse optical spectroscopy (DOS) instrument developed by the Beckman Laser Institute. For each of these 3 systems, experimental procedures are described. Information about the clinical trials from which the data of this thesis are obtained, is included.
2.1 Philips diffuse optical tomography systems for breast imaging

2.1.1 The Mammoscope

In the nineties, Philips Research developed and built an apparatus for breast cancer detection based on optical imaging, the Mammoscope. A description of this instrument has been previously presented elsewhere [1]. Figure presents a picture of the breast scanner: it consists of a bed with in the middle a hole with the measurement cup. The subject can lie on the bed and let one breast hanging freely in the cup containing a matching fluid, described section Matching fluid in section 2.1.1, see Figures 1 and 2. The breast is illuminated sequentially from all sides via 255 optical fibres that are mounted on the surface of the measurement cup. Another 255 fibres are used for parallel probing of the light emanating from the breast for each illumination position. The system uses near-infrared light of continuous wave solid-state lasers to illuminate the breast at three different wavelengths (715 – later changed to 680, 780, and 867 nm). A complete measurement involves therefore 3 breast scans in which transmission data are collected for the three wavelengths. The detected signals can be reconstructed into three-dimensional attenuation images – one image per wavelength. Attenuation images from high-risk patients have already investigating in the past [1]. In this thesis, we are interested in the measured average attenuation of the whole breast which can be obtained from the raw data, i.e. the light transmitted through the breast and collected by the detectors. A detailed description of the technology and the hardware can be found in [2].

Figure 1. The Mammoscope
Instrumentation and clinical applications

Figure 2. (a) Measurement cup. (b) Schematic cross-section of the measurement cup with the positioning of the patient’s breast during the measurement procedure. 255 source-fibres and 255 detection-fibres are mounted around the cup. The breast of the subject is hanging in the cup. The remaining space in between the breast and the cup is filled with a fluid of which the absorption and scattering were chosen to match to the properties of average breast tissue.

Matching fluid

A fluid matching closely the average optical properties of breasts has been developed. A measurement with the Mammoscope always starts with a scan of the cup filled completely with this matching fluid; this is referred to as the reference measurement. This reference measurement is later used in the reconstruction process. Then, the subject positions her breast in the measurement cup and the matching fluid is pumped inside the remaining space between the cup surface and the breast. During a breast measurement, the matching fluid prevents optical short-cut. If air was left between the breast and the optical fibers, then some of the light from the emission fibers would preferentially stay in the air medium and be detected by the closest detection fibers instead of going into the breast tissue. In addition, the matching fluid has to ensure optical coupling between the fibers, at the cup surface, and breast tissue. However, as concluded in chapter 3, the variations in average optical properties of breast between women are very large. As a result, the matching fluid hardly ever matches the average optical properties of the measured breast. As we will explain in section Reconstruction in section 2.1.2, this mismatch affects strongly the quality of the reconstructed absorption images.

Experimental procedures

A measurement session includes a reference scan, subject positioning and a breast scan. To minimize measurement errors, subject positioning has been studied and standardized, as described below. Because the chest is not flat, the subject lies slightly on her side, see Figure 3. Then, to ensure maximum contact of the chest to the bed, the subject’s arm on the side of the breast in the cup is stretched out along the body, see Figure 4. As the subject’s chest is turned on its side, the leg and arm on the opposite side of the measured breast are bent. This position can be comfortably held for the time of the measurement (about 10 minutes) by most of the subjects. Besides,
this position minimizes the motion of the breast in the cup, resulting in more successful measurements.

Figure 3. Subject’s positioning: best way to place the chest on the bed for optimum fit of the breast in the measurement cup

Once the subject is correctly positioned on the bed, the matching fluid is pumped into the cup. The fluid is kept at around 31 °C for subject’s comfort. The breast is scanned per wavelength. A total scan lasts about 10 minutes.

Clinical trial with the Philips Mammoscope

In the course of 1999, a total of 328 women considered as high-risk or referred for further examination based on a screening mammogram have been scanned with the
Philips diffuse optical tomography system at the Academisch Ziekenhuis Leiden-AZL (now called Leids Universitair Medisch Centrum-LUMC). The study was approved by Institutional Review Board (IRB) and consent was obtained from each subject.

Information about the subjects is reported in Table 1. The number of subjects categorized by menopausal status, (PRE – premenopausal, POST – postmenopausal subjects) and by breast disease is given. Because of measurement errors, such as for instance air-bubbles trapped between breast and cup wall and breast motion during the scan, data from 101 subjects were discarded for analysis. It has been noticed that the number of scan artefacts decreases with increasing breast size and age. Indeed large breasts favourably press out the remaining air in-between the measurement cup and the breast, leading to fewer occurrences of air-bubbles compromising the data. Besides, we noticed that large breasts can be brought into a more stable position in the cup and tend to move less when the subjects are breathing. Note that some patients had multiple lesions in their breasts. The breast volumes were estimated based on the bra size.

Table 1: Subjects information (range depicted in brackets)

<table>
<thead>
<tr>
<th>Total number of scanned subjects</th>
<th>328</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of subjects with reliable data</td>
<td>227</td>
</tr>
<tr>
<td>Average age</td>
<td>51 (22 - 81)</td>
</tr>
<tr>
<td>Average estimated breast volume (ml)</td>
<td>387 (105 - 1150)</td>
</tr>
<tr>
<td>Nr of premenopausal subjects</td>
<td>102</td>
</tr>
<tr>
<td>Average age pre menopause</td>
<td>42 (22 - 62)</td>
</tr>
<tr>
<td>Average estimated breast volume of pre menopausal subjects(ml)</td>
<td>376 (105 - 935)</td>
</tr>
<tr>
<td>Nr of postmenopausal subjects</td>
<td>125</td>
</tr>
<tr>
<td>Average age post menopause</td>
<td>59 (30 - 81)</td>
</tr>
<tr>
<td>Average estimated breast volume of post menopausal subjects(ml)</td>
<td>399 (105 - 1150)</td>
</tr>
<tr>
<td>Nr of subjects with a diseased breast</td>
<td>44</td>
</tr>
<tr>
<td>Nr of cystic breasts</td>
<td>20</td>
</tr>
<tr>
<td>Nr of breasts with benign lesion</td>
<td>15</td>
</tr>
<tr>
<td>Nr of breasts with malignant lesion</td>
<td>19</td>
</tr>
</tbody>
</table>

2.1.2 The fDOT system

As mentioned in chapter 1, the low sensitivity and specificity of DOT for lesion detection can be improved using fluorescence imaging. In addition, as mentioned in section Reconstruction in section 2.1.2, the mismatch in optical properties between the fluid and the measured breast result in poor quality of the reconstructed absorption images. The breast-fluid interface is supposedly not seen as perturbation in the reconstruction of the fluorescence data. Performing fluorescence imaging would then overcome the issue of the mismatch, and hence provide better reconstructed images.

A diffuse optical fluorescence tomography system has therefore been designed and developed by Philips Research and Philips Applied Technologies, the fDOT system. It is
an updated version of the Mammoscope, see section 2.1.1. It combines a DOT system and the fluorescent contrast agent Omocianine.

Figure 5. The two modes of the fDOT: a) transmission – endogenous contrast due to different optical properties of the lesion as compared to the normal breast tissue, b) fluorescence – exogenous contrast due to the fluorescence emission of a dye; filters are used to prevent the transmitted light at the fluorescence excitation wavelength from reaching the detectors.

A description of the fDOT system is presented in [3]. As for the Mammoscope, during a measurement, the subject is lying on the optical bed, see Figure 6, with one breast hanging freely in a cup containing an optical matching fluid, see Figure 2. The breast is illuminated sequentially from all sides via 253 optical fibers that are mounted on the surface of the measurement cup. Another 254 fibers are used for parallel probing of the light emanating from the breast for each illumination position. The system uses near-infrared light of continuous wave solid-state lasers to illuminate the breast at four different wavelengths (690, 730, 780, and 850 nm). The wavelength 730 nm is used to excite the fluorescent dye. A complete measurement involves a total of five breast scans: transmission data are collected for the four wavelengths, and fluorescence data for excitation at one wavelength. For the fluorescence scans, the excitation light is filtered out from the fluorescent light emitted by the contrast agent, see Figure 5, (b).

Figure 6. The fDOT system
Finally, the detected signals are reconstructed into three-dimensional absorption images—one image per wavelength, and into a three-dimensional image of the fluorescence emission by the breast.

**System improvement**

The fDOT system is the second generation of breast optical scanner of Philips, the first one being the Mammoscope, described in section 2.1.1. The fluorescence imaging capability has been added to the original scanner to improve lesion detection. The optical imaging part of the fDOT system is to a certain extend similar to the Mammoscope. Nevertheless, newer technology has been implemented in the new system. For instance, stronger and additional lasers are used, more appropriate wavelengths were chosen for the lasers in order to do spectroscopy. Amplifiers were replaced with better and more reliable devices. The computers used are faster, the reconstruction algorithm has been improved. A new matching fluid has been developed for better stability. The design of the measurement cup has been improved to have the optical fibers as close as possible to the breast tissue. Also, 5 variable size cups have been developed (75B, 80B, 80D, 80E and 80 F in the Dutch bra size system) to optimally match the subject’s breast size. The goal is to minimize the amount of matching fluid used during measurements to reduce the effect of the fluid in the reconstruction of the absorption images.

**Reconstruction**

After optical data acquisition, the detected signals are reconstructed into 3D absorption and fluorescence emission images. The reconstruction process of the absorption using a linear reconstruction algorithm based on the first-order perturbation theory has been described in [4, 5]. For each wavelength, 1 absorption image is reconstructed. Using the reconstructed absorption data at the 4 wavelengths, 3-D maps of the chromophore concentrations can be obtained, see section 1.5.3. The 3D fluorescence images are reconstructed using an algorithm based on the first-order perturbation theory [6, 7]. Per measurement, 1 fluorescence image is reconstructed, which depicts the fluorescence emission of the fluorophore after excitation. Because the CW methods employed in the scanner cannot separate scattering from absorption, scattering is assumed homogeneous over the whole breast in the reconstruction of the absorption images. In fact, endogenous variations in the scattering properties in the breast influence the reconstructed absorption images; in other words, features caused by variations in scattering within the breast appear in the reconstructed absorption images.

As it will be shown in chapter 3, the inter-subjects variation of the average attenuation is high. It is therefore unlikely to obtain a match in optical properties between the breast and the fluid. Further, the average attenuation can vary up to a factor 2.5 between women, resulting in a high attenuation mismatch between the breast and the fluid. As the absorption reconstruction method is based on a perturbation approach, a mismatch is interpreted as a perturbation in the reconstruction algorithm. In case of large mismatch, the perturbation from the malignancy will become negligible to the reconstruction process. In addition, the attenuation mismatch occurs in front of the
detectors while the lesion is deeper in the cup. The reconstruction is therefore more sensitive to the perturbation due to a mismatch than to the perturbation due to a malignancy. In this situation, it is very unlikely to observe the lesion in the reconstructed absorption images.

**Fluorescent contrast agent**

Omocianine is non-targeted fluorescent contrast agent, which has been tested for efficacy and safety but it is not yet FDA approved to be used in humans. Omocianine is an indocyanine based NIR fluorescent dye [8], provided by Schering. Figure 7 presents the absorption and emission spectra of omocianine: It has favorable absorption and emission properties for in-vivo use in humans as both spectra are located in the optical window. The wavelength 730 nm of the fDOT system is used as excitation wavelength for the omocianine.

After intravenous injection, omocianine is distributed via the blood stream through the body. Exogenous contrast between healthy and tumor tissue can be seen due to increased blood content in the tumor region. In addition, because of damaged endothelial lining resulting in leaky blood vessels in tumors, the fluorescent dye tends to accumulate and to remain longer at the tumor location.

Figure 7. Normalized absorption, solid line, and emission, dotted line, spectra of Omocianine dissolved in human serum. The 730 nm wavelength used as excitation is indicated by the vertical line.

**Experimental procedures**

The experimental procedures followed for the fDOT system are very similar to that followed for the Mammoscope, see section Experimental procedures in section 2.1.1. A measurement starts with a reference scan in transmission (as for the Mammoscope) and a fluorescence calibration scan. The transmission scan is used as reference scan for the reconstruction of the fluorescence measurement. The fluorescence measurement is obtained by scanning the cup filled with a combination of matching fluid and contrast agent at a certain concentration. The measurement time required for a complete scan with the fDOT system amounts to 10 minutes.
Clinical trial with the fDOT system

In the context of a collaboration between Philips and Bayer Schering Pharma (Berlin, Germany), the combination of optical mammography with the fluorescent dye Omocianine has been investigated in a clinical trial at the Utrecht Medical Center (the Netherlands). The goals of this study were to provide a first clinical evaluation in human of omocianine for breast cancer detection with DOT, and to validate the performance of fluorescence imaging capability of the fDOT system.

A total of 11 patients was included in this clinical trial study. They all received an injection of omocianine after which breast imaging was performed with the Philips optical fluorescence tomography system. Baseline optical images were acquired for both breasts. Then the contrast agent Omocianine was injected intravenously in the patient. After injection, optical images were acquired up to 24 hours, with 8 and 5 imaging time points for the ipsilateral and contralateral breasts, respectively. The ipsilateral breast was scanned immediately, 30 minutes, 1 hour, 1.5 hours, 2 hours, 4 hours, 8 hours, and 24 hours after the dye injection. The contralateral breast was scanned 1 hour, 2 hours, 4 hours, 8 hours and 24 hours after dye injection. It has been chosen to image the ipsilateral breast at many time-points early after the injection of contrast agent at the expense of imaging the contralateral breast.

Results of the clinical trial with the Philips optical fluorescence tomography system and the contrast agent omociane have been presented elsewhere [3]. A total of 5 lesions were detected in the fluorescence images while only 3 lesions were detected in the absorption images. For the 2 lowest dose levels of omocianine, 5 out of 6 lesions were detected in the fluorescence images; the 6th lesion was suspected to be located outside the measurement cup. For the 2 highest dose levels, no lesion was detected. The reconstruction algorithm is based on the assumption that the absorption of the dye is negligible. Therefore, at high dose of omocianine, this assumption may not be valid anymore. The locations of the detected lesions were consistent with MRI. Very distinct pharmacokinetics of the dye in the lesion and in the normal tissue were also observed. The lesion-to-background contrasts were calculated in the absorption and fluorescence image, dividing the mean value in the lesion by the mean value of the background excluding the areola. The optimal lesion-to-background contrasts in the fluorescence images were obtained 8 hours after injection of the contrast agent. These contrasts ranged from 1.8 to 2.8 for the 5 detected lesions in the fluorescence images.

In the absorption images, the mean lesion-to-background contrasts were found at 1.8, 2.6, 1.6, and 1.4, for the wavelengths 690, 730, 780, and 850 nm, respectively. Summarizing the findings of the clinical trial, DOT using a low dose fluorescent agent is feasible and safe for breast cancer visualization in patients. At correct dose levels of the contrast agent, fluorescence imaging improves the sensitivity of optical imaging.

2.2 Laser breast scanner

In 1990, Bruce Tromberg developed a diffuse optical spectroscopy instrument at the Beckman laser institute at the University of California Irvine. The instrument was
multi-frequency photon migration system and was used to recover the absorption and scattering coefficient of known phantoms. The technology of the system has been further developed and improved, and in 1998 the first prototype of the Laser Breast Scanner (LBS) was ready for clinical use. This first LBS system was using a handheld probe. In 2000, broadband spectra measurement was integrated in the system. The frequency domain photon migration (FDPM) component can provide quantitative optical properties for one single wavelength, while Steady-State (SS) spectroscopy can provide relative optical properties over a large range of wavelengths. Combining the 2 methods allow them obtaining quantitative broadband optical properties.

Nowadays, the fifth version of LBS, LBS5, is in use at the Beckman Laser Institute. A picture of this handheld, single spatial point spectroscopic imager based on broadband steady-state frequency domain photon migration (SSFDPM) method is presented Figure 8. The instrument has been described in detail elsewhere [9, 10] and successfully applied to tissue optical property studies [11-16].

**Data processing**

Photon transport theory is used to calculate \( \mu'_s \) and \( \mu_a \) after detecting the phase delay and amplitude demodulation introduced by the tissue for each laser wavelength [10]. The optical properties derived from the FDPM measurement are used to scale the reflectance obtained from the steady state component. By fitting the \( \mu'_s \) to a scattering power law, the full spectrum \( \mu'_s \) in the region from 650-1000nm can be obtained [17]. The absorption coefficient spectrum can then be quantitatively calculated for the same wavelength region using a photon transport model knowing the \( \mu'_s \) spectrum derived from the FDPM data and a scaled reflectance obtained from SS calibration. So in comparison to the CW technique, we recover here independently the absorption and the reduced scattering for each measurement location. Finally, by performing a linear fit of the tissue chromophore spectra in the near infrared range to the recovered absorption spectrum, concentrations of HbO\(_2\), Hb, lipid, and water in the tissue can be quantitatively obtained [10], see section 1.5.3. By acquiring data at multiple spatial locations, DOS can be used to form quantitative maps of local tissue concentrations of HbO\(_2\), Hb, lipid and water.
**Experimental procedures**

A measurement session includes calibrating the instrument, positioning the subject, determining and drawing the measurement grid, and measuring the breast.

The calibration consists of 2 steps: the FDPM sources calibration and the SS source calibration. The FDPM calibration is performed by measuring a solid phantom with known optical properties for each laser diode. The SS calibration is performed by shining the SS light into a reflectance standard (an integrating sphere) with known absorbance and reflectance. The calibration measurements are performed before and after each breast measurement.

The subject is usually placed in a reclined position. Then, depending on breast morphology and area to be scanned, the subject’s arm may be lifted up behind the head and/or a pillow may be placed behind the subject’s back to tilt the chest. Until now, the LBS has never been used for breast lesion screening; only a known region of interest (ROI) was measured. After determination of the ROI, a measurement grid is drawn on the breast. Typically, in case of patients, measurement grids will be defined to cover as much as possible the tumor and normal surrounding breast tissue. The mirrored position on the contralateral breast will be scanned as well. An example is shown in Figure 9 with the lesion in red. Measurements were usually performed in 10 mm (20 mm in case of time restriction) steps in x and y directions.

![Figure 9](image.png)

**Figure 9.** Schematic of an example of a typical measurement situation. The blue dots represent the measurement grid that would be drawn on the breasts. The circular grey shape represents the areolas and the oval red shape represents a lesion.

The breast scans are performed by taking a measurement at each grid point drawn on the breast. Therefore the time of a scan session depends on the lesion and breast size, and on the operator experience. The measurement time for one grid point can be manually changed during a session. It usually varies from 7 s to 10 s depending on the type of probed tissue; for instance, tumorous tissue absorbs more than fatty tissue, then more time will be required to detect enough photons for the data processing. Typically, an experienced operator can scan a ~ 100 mm x 100 mm grid in about 20 minutes.
Clinical trial with the Laser Breast Scanner

The LBS has been validated in many clinical applications. It has for instance been applied to study tissue optical properties, monitor the healing of tissue after biopsy taking, to investigate differences in lesions and healthy breast tissue, and to monitor chemotherapy response [11-13, 15, 16, 18]. The patient data used in this thesis were obtained within 2 IRB approved protocols (1995-563 and 2002-2306). The goals of these studies were to characterize normal and cancerous tissue, and to monitor neo-adjuvant chemotherapy response. The patients were informed and consented. More details on the study populations can be found in the corresponding chapter, chapter 6.

2.3 Conclusion

The analyses presented in this thesis, are based on data collected with 3 diffuse optical imaging systems: one diffuse optical tomography system using continuous-wave techniques, one fluorescence diffuse optical tomography system using continuous-wave techniques and one diffuse optical spectroscopy system using a broadband frequency domain photon migration method. The two CW systems used to obtain tomographic measurements of the female breast were similar. In addition to using newer and better technology, the latest scanner provides also fluorescence imaging. A drawback of the CW technique is that it cannot yet separate the scattering from the absorption, and therefore, only relative values of absorption and chromophore concentrations were obtained. On the other hand, these tomographic CW systems provide 3D maps of the breast using affordable technology. The third technique employed for the study described in this thesis, broadband FDPM spectroscopy, provides quantitative functional information from breast tissue by quantitatively separating light absorption from scattering. By adding a steady-state component, the full absorption and scattering spectra can be recovered. However, the spatial content is limited to a single measurement point as compared to the tomographic capability of the 2 Philips systems. The use of the different instruments in the outline of this thesis is as follows: chapter 3 reports results from a study about the average tissue optical properties based on data acquired from more than 300 subjects collected with the prototype DOT system described in section 2.1.1. In chapters 4 and 5, data acquired with the fluorescence DOT system, described in section 2.1.2, are used to develop 2 different tools aiming at improving sensitivity and specificity for lesion detection. Finally, in chapter 6, data acquired with the DOS system presented in section 2.3 are used to validate the optimization of an algorithm for lesion identification.
References


