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

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Chapter 7

CONCLUSION

Diffuse optical imaging (DOI) non-invasively provides biochemical molecular information on in vivo biological tissue. DOI is sensitive to functional information, such as the amount of hemoglobin, water or lipid, contained in the probed tissue. In addition, it uses no ionizing radiation as compared to other imaging modalities, enabling repetitive measurement over time. Moreover, DOI is relatively inexpensive. These advantages make optical imaging an ideal candidate for population wide screening programs, following high-risk subjects or monitoring diseases.

In this thesis, the application of DOI for breast imaging was investigated using 2 techniques: tomography (diffuse optical tomography, DOT) and spectroscopy (diffuse optical spectroscopy, DOS). Tomographic imaging samples a high number of measurement points in space; spectroscopic imaging samples a large amount of spectral information in a single measurement point.

Even though DOI has many advantages that make it suitable for clinical use, its application in breast imaging is still a challenge due to, among others, the complexity of human breast tissue. For instance, chapter 3 reports on the high inter-subject variability in breast tissue optical properties. Fibro-glandular tissue contains high vascularity, resulting in highly attenuated transmitted NIR light. On the contrary, fatty tissue does not absorb as much NIR light. The total average absorption of breasts will thus depend on the fat and glandular content of the breasts. In chapter 3, we showed that the average optical attenuation of breasts was statistically correlating to age and breast volume. However these correlations were not strong; the breast tissue optical properties vary highly between women. The mean average attenuation of breasts at 780 nm was found at 108 m$^{-1}$ (with a standard deviation of 19 m$^{-1}$, minimum value of 66 m$^{-1}$ and maximum value of 159 m$^{-1}$). In addition, the results show that the presence of a lesion did not statistically affect the overall average attenuation of breasts. As the changes of chromophores content are an indication of malignancy, this means that no absolute threshold in the optical images can be used to detect lesions.
In addition to the high inter-patient variability reported in chapter 3, the changes of chromophores due to malignancy are not specific to malignancy, which makes lesion detection an even tougher task. Moreover, the low spatial resolution of DOI added to the low contrast of malignancies as compared to the background features results in low sensitivity and specificity for lesion detection. These limitations of DOI have been addressed in chapters 4 to 6.

In chapters 4 and 5, we have investigated the use of fluorescence imaging to compensate for the limitation in sensitivity of DOT. Chapter 4 investigates a statistical method to combine fluorescence and optical tomography using phantom measurements. This combination improved the lesion contrast to noise ratio. In addition, by training adequately the statistical tool, the phantom-lesions were identified with sensitivity and specificity of nearly 100%. Then, chapter 5 investigates the combination of fluorescence and optical tomography in a scatterplot using phantom and patient measurements. Plotting the absorption, fluorescence and blood volume data in the scatterplot, improved lesion detection and better discrimination between malignant and healthy structures was obtained in patients. The work achieved in these 2 chapters shows that adding fluorescence imaging to DOT not only improves DOT sensitivity for lesion detection but also has a great potential to increase DOT specificity.

One of the reasons of the low contrasts of lesions in the imaged breasts using the fDOT system is the use of a sub-optimal scattering fluid between the measurement cup surface and the breast. This scattering fluid, matching the overall average optical properties of breasts, is used to optimize the contact between the optical fibers and the breast. However, as observed in chapter 3, the average optical properties of breasts vary tremendously between women (about 18 % variations in absorption at 780 nm). Consequently, the scattering fluid will not match the optical properties of the probed breasts. This mismatch creates high perturbations at the surface of the breast and close to the detectors, which becomes an issue as we are trying to detect tumors within the breast. For instance, a large mismatch in optical properties located at the breast surface can overwhelm small perturbation in optical properties due to a potential tumor, even if it is located in the middle of the breast. As a result of this mismatch, the reconstructed optical images will contain many artifacts and a low sensitivity for tumor detection. Therefore, we would recommend exploring the use of a patient specific scattering fluid. Optimizing the match in optical properties between the fluid and the breast would significantly reduce the noise level. Consequently, the perturbation due to lesions will show up in the whole measurement field of view and would result in better lesion detectability. The resulting increase in sensitivity might be comparable to the sensitivity of fluorescence imaging; the reconstruction of the fluorescence images is not influenced by the scattering fluid used between the optical fibers and the breast surface.

A future improvement for DOI may be the combination of anatomical information obtained by other imaging modalities with the functional information of DOI. As a first attempt, to compensate for the low spatial resolution of DOT, the combination of a whole-breast 3-D ultrasound imaging system and optical tomography was explored in the work presented in Supplement 1. A bed system using three 3-D transducers and
resembling an optical tomography bed used for DOT only was developed. The frequency of the ultrasound transducers was tuned to image the breast shape for registration with the optical images and to visualize also the content of the breast as much as possible. Furthermore, a clinical trial was conducted to explore the potential performance of the ultrasound system to detect lesions. Over the 19 benign lesions and the 10 malignant lesions, 12 and 2, respectively, were visualized in the ultrasound images. In addition to detecting a low number of lesions, the ultrasonic image quality was low. This result can be partly explained by the fact that, to achieve sufficient penetration depth, the frequency of the transducers was chosen relatively low as compared to the conventional ultrasound breast transducer, resulting in a loss of image resolution. The transducers cannot be used at the same frequency for detecting the breast surface (high frequency) and imaging the content of the breast (low frequency). Thus, instead of using the ultrasonic data for lesion detection, we recommend 3-D whole-breast ultrasound imaging in combination with DOT to construct co-registered images of anatomical structure and optical absorption. Ultrasonic data could also support DOT by incorporating the anatomical information from ultrasound as prior constraints into the DOT reconstruction algorithm.

Chapter 6 addresses the issue of the low contrast in chromophores concentration between tumor and normal breast tissue; increased blood and water, and decreased lipid is non-specific to malignancy. Chapter 6 explores minute shifts in the absorption spectra of tumor containing breast tissue. These shifts originate from different molecular dispositions that are specific to malignancy. They are isolated by taking the residual to the fit of the absorption spectrum of tumor breast tissue to the known basis spectra for the breast chromophores. The residual is also corrected for individual biochemical variations in normal tissue. In this chapter, the assumption of the uniqueness of the shifts to malignancy was tested in 10 patients. In order to account for the inter-patient variability, the tumor absorption spectrum was subtracted from the normal tissue absorption spectrum. We showed that any type of normal breast tissue, for instance fatty, dense or normal tissue from the ipsilateral breast, used to reference the tumor absorption spectrum does not affect the shifts observed in the tumor absorption spectra. It was confirmed in these 10 patients that the shifts observed in the tumor absorption spectra are specific for malignancy. The results also suggests that lesions located in dense breast tissue could be detected using this method.

By looking at the residual of the fit of the tumor absorption spectrum to the chromophores spectra, we assume that an additional component is present in the breast tissue. By accounting for normal breast tissue, we isolate the tumor part of this component. This quantity is therefore called specific tumor component (STC). It is associated with molecular disposition. While in chapters 4 and 5 the abundance of chromophores was used to identify tumor contrast, in chapter 6 the tumor contrast is given by the molecular disposition of these chromophores. Similar work as the STC is performed in the MRI community using the water component \([1]\). Even though the chromophore abundance is not as specific to malignancy as the molecular disposition is, more work still needs to be achieved on the STC to accurately quantify (and thus image) it, and to understand what it means biologically.
The current DOS system presented in this thesis measures breasts at single locations. The system uses a handheld probe that an operator moves along a grid drawn on the breast to take subsequent point measurements. The method has thus far not been adapted for screening application. A solution to this problem would be a continuous measurement with potentially a tracking device to record the probe position. This technique is currently being tested and shows promising results.

DOI has the ability to image breast cancer. However, to make a difference, DOI needs to be able to deal with low contrast lesions whose detection is still critical using the current imaging modalities. Different issues of DOI were addressed along this thesis with the primary goal of enhancing the optical contrast for lesion detection. In addition, two different DOI instruments, using DOT and DOS, were used for this purpose. Both instruments have their own benefits and limitations. Ideally, a newer prototype based on these 2 instruments would bring better lesion contrast. For instance, a multi-channel broadband FDPM instrument would generate multi-view, quantitative, high resolution absorption and reduced scattering spectra. Various source-detector distances on the different channels would provide depth imaging, and parallel data acquisition would permit quicker and wider breast tissue area imaging. Such device would provide quantitative tomographic maps of tissue volume when combined with image reconstruction techniques. This would certainly offer better insight on the probed breast tissue.

Recently, research groups have been focusing on the development of new contrast agents that would bind to cancer-associated targets. Such targeted contrast agent would optimize tumor enhancements and reduce non-specific enhancements from surrounding normal tissue. This would result in very high contrast images. However, other clinical applications in breast cancer will always certainly benefit from DOI without the use of a contrast agent. For instance, DOS has showed its potential for differential diagnosis: using the technique described in chapter 6 in another study, DOS was able to discriminate benign from malignant tumors in 40 patients with a sensitivity of 91% and a specificity of 94% [2]. Furthermore, because it is relatively inexpensive, fast and non-invasive, DOI is the perfect candidate for measuring subjects repeatedly and for monitoring lesions, for instance during chemotherapy. Some research groups already showed the potential predictive value of DOI for neo-adjuvant chemotherapy response [3-5]. Supplement 2 describes also a pilot study that investigates the pre-chemotherapy spectral heterogeneity of the tumor as an indicator for chemotherapy response. Baseline DOS measurements seem to provide enough information on the biology of the tumor tissue to predict the response of the neo-adjuvant chemotherapy. Finally, broadband DOS has been shown to detect components unique to cancer and potentially specific to the cancer type [2], possibly allowing for differential diagnosis. DOI is thus a very promising technique that has the potential to make a difference in the breast cancer field.
References


