Optical mammography – a new method for breast cancer detection using ultra-short laser pulses

Johannes Swartling and Stefan Andersson-Engels
Department of Physics, Lund Institute of Technology, P.O. Box 118, SE-221 00 Lund, Sweden
Tel. +46 46 222 3894, fax +46 46 222 4250, johannes.swartling@fysik.lth.se

1. Introduction

An alternative method for breast cancer detection is being developed in a joint project involving several research groups around Europe. The method is based on ultra-short (picosecond regime) laser pulses, which are used as an alternative to traditional X-rays to shine through the breast tissue. In analogy with the name for the currently used method – X-ray mammography – the technique has been dubbed optical mammography.

Breast cancer is the most common type of cancer in the female population, accounting for 30% of all cancer cases. One tenth of all women in the Western world develop breast cancer in their lifetime. Screening programs based on X-ray mammograms taken at two or three-year intervals for women above a certain age have been running in some countries for the last decades. Unfortunately, the results of these efforts have been mixed, and screening using X-ray mammography is still a somewhat controversial issue. One of the main problems is that tumors are hard to find in the X-ray images, even with the high resolution of today's systems and despite the experience of trained doctors. The problem is that many tumors have no significant difference in X-ray attenuation compared with the normal tissue, so that no contrast between the tumor and surrounding tissue is seen. Doctors are therefore forced to look for subtle, secondary effects of the cancer, such as miniscule microcalcifications in the glandular tissue. In some cases, especially for younger women with denser glandular breast tissue, the X-ray attenuation is so strong that almost no structure can be discerned in the mammograms.

Another concern is the exposure of ionizing radiation to large groups of the population. Statistically, a few cases of cancer may be expected to occur, which are caused by the X-rays. This problem may be even larger for a small group of women who are genetically disposed for developing breast cancer. These women require X-ray examinations at shorter intervals due to their increased risk of developing cancer, which puts them in the dilemma that the examinations themselves could initiate the disease.

Alternative methods to X-ray mammography have been explored for some time. Ultrasound imaging and magnetic resonance (MR) imaging are both making their way into clinical use, but none of these techniques have proved to be able to step in as general substitute for X-rays. During the last twenty years, there has been a radically increased interest in using lasers and optical spectroscopy for medical diagnostics. This has spurred a quickly growing research into the possibility of using laser light as an alternative to X-ray mammography. A break-through was made in the late 1980's, when ultra-short laser pulses and time-resolved spectroscopy techniques were introduced. Some of that work was pioneered at the Medical Laser Centre at Lund University, where the first image showing the bones inside a hand with high contrast was produced using these methods.

While X-ray mammography suffers from a lack of contrast, the main problem when attempting to detect tumors inside the body using visible or near infrared (NIR) light is the very strong scattering. This leads to very blurry images with poor resolution. The first attempts to use light to diagnose breast cancer were done in the first half the 20th century. The breast was compressed between glass plates and red light was used to shine through the tissue. The method, called transillumination or diafanography, was never successful because many of the tumors could not be distinguished. In the 70's and 80's, research in biomedical optics identified the properties of tissue optics, and a more scientific approach to the problem could be adopted.

A. Tissue optical properties

A prerequisite for being able to detect structures inside several centimeters of tissue using light is that the absorption is sufficiently weak. The main absorbers in breast tissue at visible and NIR wavelengths are hemoglobin, water and fat. The absorption spectra of these substances are shown in Fig. 1. The region between 650 and 950 nm is often called the optical window of tissue, because of the relatively low absorption of all absorbers. This region is most suited for deep-structure detection, and the penetration depth is in the order of a few centimeters. The scattering, on the other hand, is caused by small differences in refractive index at the microscopic level, mainly of fat droplets and structures inside the cell nucleus. The scattering increases for shorter wavelengths, approximately obeying the λ^{-x} law of Mie scattering theory, where x typically is around 1. The scattering, however, is strong even for wavelengths longer that 1 μm.

The advantage of using short-pulse lasers for deep-structure detection comes in two parts. The main advantage is that by us-

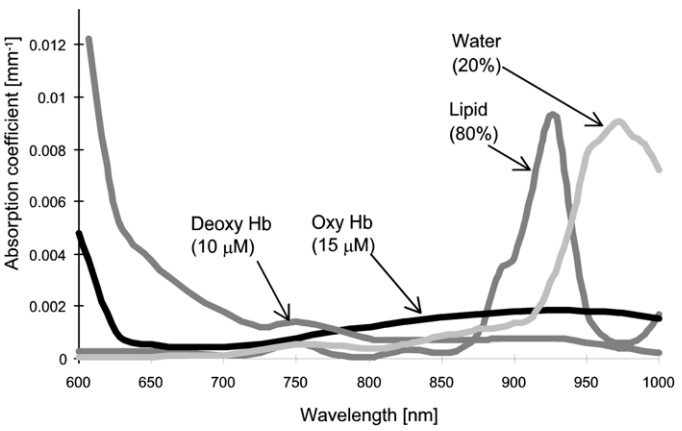

Fig. 1. Absorption coefficients of hemoglobin (Hb), water and fat (lipid) at concentrations typical for breast tissue.

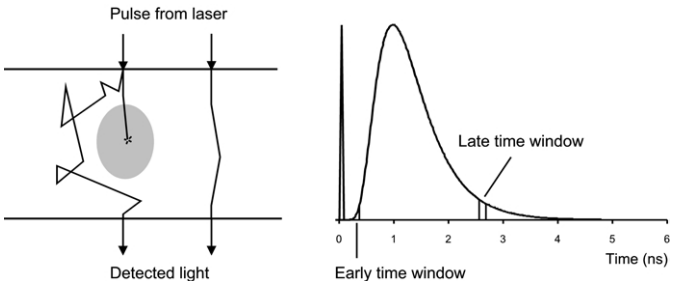

Fig. 2. The principle of time-resolved laser-pulse measurements. The detected light in the early time window has traveled shorter and straighter paths than the light in the late time window. This can be used for better contrast and resolution.

ing time-resolved detection it is possible to select light which arrives at the detector at different time slots. This idea is illustrated in Fig. 2. The light that arrives early has traveled a shorter and straighter path than the late light, which is the principle behind the increased resolution of the time-resolved measurements. In addition, the lasers may be chosen at wavelengths that enhance the contrast between the tumor and the surrounding tissue. This is a classical applied spectroscopy problem, where different compositions of the absorbers give rise to different absorption at various wavelengths. The scattering can also vary between tissue types and wavelengths, which adds another possible parameter that can be used for contrast.

This implies that scattering does not necessarily have to be just an annoyance, but can also be used to an advantage. In the early research, it was suggested that only the light that arrives first at the detector would be used, since this light would have traveled the straightest paths and thus most closely mimics the straight rays of X-ray mammography. Later, is has been established that the first light is usually too weak to be practically useful by its own, and more information can be used from other parts of the detected light pulse.

B. New tomographic methods

Knowledge of the re-emitted pulse is the basis of a new range of tomographic methods that are being developed to suit time-resolved measurements. The object of this type of tomography is to reconstruct an image of both the absorption and the scattering properties inside the tissue, based on measurements at several light-source and detector positions on the skin. To do this, not only the first light, but the whole shape of the detected pulses may be of use.

2. OPTIMAMM

A few attempts to commercialize tomographic techniques for optical mammography have been made, by companies in Europe and North America. In Europe, both Siemens and Philips have built working prototypes, but the development has halted due to both strategic corporate decisions and lack of promising results. With this state of affairs as the background, a joint application for funding within the 5th Framework of the European Commission was organized in 2000. The aim was to force a strong development of the scientific basis and clinical experience of optical mammography that could lead to a direct development of a first generation of optical mammographs for the clinic. A three-year contract was granted starting January 2001, under the official project acronym OPTIMAMM. The participating partners are all centers for biomedical optics research, and most are connected to university hospitals. The project is coordinated by Physikalisch-Technische Bundesanstalt (PTB) in Berlin, with their clinical partner at the Charité hospital. The other groups are with the University of Rotterdam; FORTH in Heracleon, Crete; Politecnico in Milan; University College of London; University of Twente; and the Lund Laser Centre at Lund University (the author's affiliation).

Each group has been assigned different areas of responsibility. For example, the groups in Berlin and Milan are responsible for clinical trials with their prototype mammographs. The group in London is developing tomographic reconstruction algorithms. The group in Lund is responsible for measuring and compiling databases of the absorption and scattering properties of various breast tissue types.

The prototype mammographs in Berlin and Milan are scanning devices, with a measurement geometry that resembles that of X-ray mammographs, see Fig. 3a. Pulsed laser diodes are used as light sources, and so-called time-correlated single-photon-counting detection is used to get time-resolved measurements with a sub-nanosecond resolution. The breast is compressed, and the source-detector optical fibers are scanned, for a series of pointwise measurements. Acquiring data for a whole breast with about 1000 points takes a few minutes. Because of this relatively long time, the breast is not compressed as hard as for X-ray mammography. Another geometry is used in the London prototype, which is depicted in Fig. 3b. The sources-detectors are placed in a conical configuration, more resembling the geometry of conventional tomography.

The key to success for the development of optical mammography likely lies in three areas. The first is finding the optimal geometry for the measurement. The second is the development of efficient tomographic reconstruction algorithms. The third key area is to identify the optimal contrast function for discriminating the tumors, based on the choice of wavelengths and knowledge of the biological processes that determine the tissue composition.

Finding the best geometry is related to the second problem, development of reconstruction algorithms. For example, should

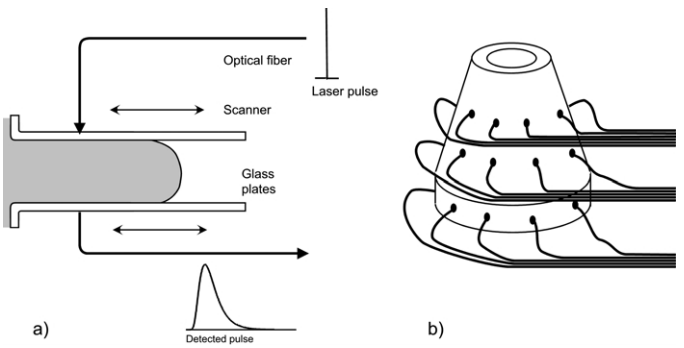

Fig. 3. (a) The scanning configuration used in the Berlin and the Milan systems. The source and detector fibers are usually moved together, but can also be separated for off-axis measurements. (b) The conical configuration used in the London system. There are 32 source fibers and 32 detector fibers (not all are shown in this schematic drawing). Every other fiber is a source fiber, and the others are detector fibers.

the breast be compressed or not, and is it possible to get better results using fluids to match the optical properties between the skin and the detectors, are some of the questions under investigation.

The principle of the reconstruction algorithm is to divide the problem into two parts, the forward and the inverse problem. The forward problem deals with computation of what the detected signal would be, given that the absorption and scattering are known. Light propagation models used for this are usually based on transport theory, where light is seen as an energy flow that is affected by macroscopic absorption and scattering coefficients in the medium.

The inverse problem is the problem of how to use the forward solution to reconstruct the map of absorption and scattering. Since the problem is highly non-linear, the reconstruction is based on iterations. An initial guess of the map is fed to the forward solver, which produces a set of simulated measurements. These are then compared with the real measurements, and the map is corrected accordingly. The process is repeated until the simulated measurements are sufficiently close to the real measurements. The end result is the reconstructed image of the absorption and scattering inside the tissue.

Perhaps the most challenging part is to determine the optimal contrast function that discriminates the tumors. The relative compositions of water, fat and hemoglobin vary not only between tumors and healthy tissue, but also with for example age and hormonal cycles. Furthermore, there is not a single type of breast cancer – tumors vary a lot in composition and structure. All these parameters have to be understood and quantified.

At the Lund Laser Centre, a wide knowledge of how to measure the absorption and scattering of tissue at different wavelengths has been built up. A range of different instruments for measuring these properties is available. The idea behind measuring the absorption and scattering in tissue samples is in principle similar to the reconstruction problem described above. The difference is that an image of the properties is not needed. Only the data in one point is measured, which simplifies the analysis and makes the result much more accurate in absolute terms. This procedure rests on the assumption that the tissue is locally homogeneous around the point where the measurement is done, which may be more or less true.

At this stage in the project, clinical trials are well under way in Berlin, Milan and London. Measurements of the absorption and scattering coefficients of tissue have been carefully prepared in Lund, Heracleon, and Rotterdam, setting up several instruments for both *in vivo* and *in vitro* measurements. The systems have been extensively evaluated on artificial tissue phantoms, mimicking the absorption and scattering properties of real tissue. Measurements on real tissue are under way. By the end of 2003, the OPTIMAMM project will finish, and after the evaluation it will hopefully be possible to judge whether optical mammography has a future in the clinic.

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