Time-resolved optical spectroscopy and imaging of breast

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A fully automated system for time-resolved reflectance and transmittance spectroscopy from 610 to 1010 nm was developed and applied to the optical (absorption and scattering) characterization of breast tissue in vivo. From absorption spectra, information is derived on tissue content of oxy-, deoxyhemoglobin, water and lipids, while scattering spectra provide knowledge on tissue structure. A portable system for breast imaging at four wavelengths (683, 785, 912, and 975 nm) was also developed and is being tested in clinics for the detection and characterization of breast lesions (optical mammography).

Keywords: absorption, optical mammography photon migration, reflectance, scattering, time-resolved imaging, time-resolved spectroscopy, tissue, transmittance.

1. Introduction

Time-resolved reflectance and transmittance spectroscopy allows the optical characterization of turbid media, such as biological tissues, through the simultaneous measurement of the absorption and reduced scattering coefficients (μ_a and μ_s, respectively). This is achieved non-invasively, so it can be exploited in vivo not only with the aim of characterizing biological tissues, but at least in principle also for medical diagnosis, as changes in the optical properties may reflect the onset of pathologic conditions.

In particular, we have developed a spectroscopy system operating continuously over a broad spectral range (610–1010 nm). Its main application is the in vivo assessment of the optical properties of biological tissues, with the aim of correlating the optical properties with physiological parameters and the changes occurring with the onset of pathology.

We are also testing time-resolved transmittance imaging as a possible means for the detection and characterization of breast lesions, namely for optical mammography.

2. Time-resolved reflectance and transmittance spectroscopy

2.1. System set-up

The system for time-resolved reflectance and transmittance spectroscopy is fully automated to allow measurements to be performed in vivo.

To cover the spectral range from 610 to 1010 nm, two laser sources are used for illumination: a synchronously pumped dye laser (below 700 nm, with computer-controlled wavelength tuning) and an actively mode-locked titanium:sapphire laser (above 700 nm). For the latter source, which is more critical, also the laser pulse duration and power are automatically optimized at each wavelength by PC-controlled optimization of the cavity length.

The two sources are alternatively coupled to an illumination fiber. The illumination power is controlled at each wavelength with a variable attenuator. The light transmitted through (or diffusely reflected by) the sample is collected with another fiber and sent, through a scanning monochromator, to the detection chain. A small fraction of the illumination beam is split off. Part of it is sent directly to the detector, to provide the system response function at each wavelength, which is a basic feature for data analysis, and part provides the reference signal to an electronic chain for time-correlated single photon counting.

The system response has a FWHM of 120–160 ps, depending on wavelength, and the time-drift was minimized. The acquisition parameters change with the specific measure to be performed. Typically, the illumination power never exceeds 10 mW, data are acquired every 5 nm, with an acquisition time of 4 s, and a dead time of 2 to 4 sec for laser optimization and wavelength tuning.

Data analysis is performed on-line and consists in the interpretation of the time-resolved curves with the diffusion theory or Random Walk model for an infinite homogeneous medium and display of the measured absorption and reduced scattering spectra wavelength by wavelength, during the measurement.

A second level of data analysis is then performed off-line. As displayed in Fig. 1, in the red the absorption of
tissue is dominated by deoxyhemoglobin (Hb) which shows also a typical absorption peak at 760 nm. On the contrary, in this spectral range oxyhemoglobin (HbO2) has no main spectral features, just a very broad band beyond 800 nm. Water has a main peak around 970 nm, while lipids are clearly visible in the typical sharp peak at 930 nm. To derive information on tissue composition, the absorption spectra of tissue are best-fitted with the absorption line shapes of the main constituents absorbing in the red and NIR, namely Hb, HbO2, water and lipids. This allows us to evaluate the total hemoglobin content (THC), the oxygen saturation Y, and the percentage content of water and lipids in tissues.

Information on a tissue structure can be obtained by interpreting the scattering spectra with a very simple empirical approximation of Mie theory, where tissue scatterers are described as spheres that behave independently. The scattering coefficient is described as \( \mu_s = ax^b \), where \( x \) is a shape factor depending on the equivalent radius \( r_e \) of the scattering centres, the index of refraction \( n_m \) of the medium, and the wavelength \( \lambda_0 \), \( a \) and \( b \) are the constant factors related to the density and equivalent radius of the scattering centres, respectively, which can thus be derived from the best fit of the reduced scattering spectrum (as shown in Fig. 2).

2.3. Experimental results

In interpreting any experimental results, we need to take into account the effects of the measurement geometry. Tissues are usually heterogeneous media and time-resolved reflectance/transmittance measurements – interpreted using a homogenous model – provide effective values of the optical parameters, averaged over the probed volume, i.e., the volume traversed by photons in their propagation. However, by properly choosing the measurement geometry, we can change the shape of the probed volume, thus probing different tissue regions.

As an example, two absorption spectra of the same breast measured in different geometry are reported in Fig. 3. In reflectance geometry, the region of most probable photon propagation is a banana-shaped volume, mostly confined in the superficial layers of breast. So, the optical information comes mostly from those layers. This is confirmed experimentally, as the spectrum obtained in reflectance geometry is characterized by a strong contribution from Hb and HbO2 at short and intermediate wavelengths, in agreement with the fact that blood vessels, both veins and arteries, lie quite superficially in the breast.

In transmission geometry, photons propagate mostly in a fuse-shaped region, broader in the inner layers of breast, which are thus better probed. Experimentally, in transmitt-
This is confirmed quantitatively. In reflectance, we measure a higher THC (60 µM vs. 47 µM), due to superficial blood vessels, but the oxygenation is lower (68% vs. 75%). This seems to indicate that the information comes mainly from venous vessels that are even more superficial than the arterial ones. Reflectance data are also more sensitive to the presence of lipids in subcutaneous layers (31% vs. 16%), while, as we have seen already from the spectral shapes, they are less sensitive to the high water content in the inner glandular tissue (41% vs. 63%).

In the measured scattering as well, we observe some dependence on the measurement geometry (Fig. 4). There is no significant difference in the absolute value of the scattering coefficient, but the slope of the spectrum is smaller in reflectance geometry, implying bigger scattering centres (0.28 µm vs. 0.23 µm), and consequently more forward-oriented scattering events. This seems to suggest that lipid-rich tissues are characterized by bigger scattering centres, and measurements performed on other tissues, such as the arm and the abdomen, have confirmed this hypothesis.

If optical methods are to be used for diagnostic purposes, first of all it is necessary to characterize the tissue of interest in physiologic conditions, so that pathologic changes can reliably be identified. Moreover, the overall quality of optical images depends not only on the optical contrast between lesion and surrounding healthy tissue, but also on spatial resolution and on signal to noise ratio, and in turn both these parameters change with the optical properties [1,2].

In particular, in view of the use of optical methods for mammography, systematic measurements were performed over two following months and showed a systematic dependence of the optical properties of breast on the menstrual cycle [3]. Moreover, as expected, based on physiologic changes occurring in the breast with age, significant differences in the estimated optical properties were observed for measurements performed on subjects of different age. The most significant change with age reflects the progressive reduction in fibro-glandular component and increase in adipose tissue leading to reduced absorption of water at 970 nm and significantly increased absorption of lipids at 930 nm [4].

All the information collected on the optical properties of breast and the changes they undergo in physiologic conditions contributed to the design of a portable system for time-resolved optical mammography.

3. Time-resolved transmittance imaging

3.1. Imaging procedure

Transmittance data are obtained from point measurements. To obtain an image, we need to build a 2D matrix of point measurements, and this is achieved through a raster scan over the region of interest. Specifically, the breast is slightly compressed between parallel plexiglas plates, and an illumination fiber and a collection bundle are scanned in tandem.

Different optical images, with potentially different informative and diagnostic content, can be obtained depending on the quantity that is plotted to build an image. Advantage can be taken from the link between the optical parameters and the composition and structure of tissue. However, care should be taken in interpreting scattering and absorption plots, because, as described above, in order to have a simple analytic solution of the problem, the tissue is described as a homogeneous medium, and only average values of the optical properties are thus estimated.

Our imaging procedure relies on the random walk model [5] for the estimation of the effective reduced scattering coefficient which is plotted as a function of the measurement position. To build maps sensitive to the absorption properties, we obtained better results with the method of dynamic time-gating. The light transmitted in steady state depends on both absorption and scattering properties of the traversed medium, and the two contributions cannot be separated. On the other hand, the discrimination between the two is possible if photons are collected only within a time-window suitably delayed with respect to the illumination pulse. In particular, an early gate, on the rising edge of the transmittance pulse, is more sensitive to the pulse delay, which means to the scattering properties, as the scattering events delay the photon arrival. A late gate, on the tail, is sensitive essentially only to absorption changes, as in the tail we detect photons that remained longer in the medium and thus experienced a higher probability to be absorbed. Specifically, we use the light intensity collected in a late gate to track absorption variations as a function of position.
To illustrate the results achieved, optical images acquired from a tissue phantom of the known geometry and optical properties are shown in Fig. 5. The phantom is 5 cm thick, with $\mu_a = 0.05 \text{ cm}^{-1}$ and $\mu_s = 10 \text{ cm}^{-1}$ to simulate the compressed breast imaged with NIR light. Four 1-cm cylindrical inclusions are embedded in the medium. The two on the upper (lower) row differ from the background in scattering (absorption). The plot of the effective scattering allows the detection of the scattering inclusions and is only slightly affected by the absorption contributions. On the other hand, the absorption inclusions are easily localized in the map of the late gated intensity, which is essentially insensitive to the scattering inhomogeneities.

Generally, in vivo optical imaging is performed at red or NIR wavelengths, so that enough light is transmitted through the compressed breast. In order to maximize its diagnostic potential, optical mammography should be sensitive to the main tissue constituents. In this spectral region, four main absorbers are present and this led us to set-up a portable system for clinical imaging at four wavelengths: 683 nm to detect Hb, 785 nm to enhance the contribution of HbO₂, 912 for lipids, and 975 for water.

### 3.2. System set-up

As described above, the breast is slightly compressed between plane parallel plates, and the system works in a transmission geometry. The plates can be rotated to allow image acquisition in different projections, as routinely done in x-ray mammography.

Continuous scanning and data acquisition are performed, storing data every 25 ms, which corresponds to a scan step of 1 mm. This leads to a typical acquisition time of approximately 5 min for an entire in vivo image.

A multi-channel driver controls four picosecond pulsed diode laser heads at the different wavelengths. The two shorter wavelengths are optically delayed with respect to each other, and the same is done with the two longer wavelengths. Then, the four beams are coupled together and collimated, so that a 3-mm diameter illumination spot is shined on the surface of the compressed breast. Both the illumination fiber and a collection bundle are scanned in tandem, under computer control. The bundle has bifurcated distal ends to separate the path of the shorter wavelengths from that of the longer ones. Suitable filters, variable attenuators and focusing optics are placed in front of two compact PMTs. The amplified signal is then sent to two PC boards for time-correlated single photon counting.

Simple on-line data analysis is performed estimating gated intensity images and scattering plots at one wavelength (683 nm) with analysis time of 10 ms/point. Detailed off-line analysis is then performed and images are displayed simultaneously at all four wavelengths for easier comparisons, and image processing can be performed (filtering, correction, histogram equalization, etc.) to make lesion detection and characterization easier.

### 3.3. Experimental results

The system is presently used in a multinational clinical trial, supported by the EU Project “Optimamm” aiming at testing the diagnostic potential of time-resolved optical mammography.

An example of optical images acquired in vivo is reported in Fig. 6, which displays x-ray and optical images (oblique view) of a breast bearing a cyst. The breast is quite adipose and the mammary gland can hardly be identified in the conventional mammogram. On the contrary, in the gated intensity images (used to identify absorption changes), it appears dark at 975 nm. This implies that fewer counts are collected, due to strong absorption at 975 nm. The explanation for this behaviour can be found in the higher water content of fibro-glandular tissue as compared to the surrounding adipose tissue. The high lipid content is
confirmed by the intensity image at 912 nm, generally uniform and dark, suggesting that the whole breast volume is strongly absorbing at this wavelength, which is close to the absorption maximum of lipids. Small regions of significant absorption are detected also close to the nipple at 683 and 785 nm, probably due to high blood content.

The cyst is opaque to x-rays and can be easily detected as a round opaque area, while it cannot be reliably identified in the gated intensity images, except for a slightly lower absorption at 912 nm.

On the contrary, it is readily localized in the scattering plots, thank to its liquid nature, which makes its scattering lower than that of the surrounding tissue at all wavelengths. The breast structures in a healthy breast cause no main features in the scattering plots, which, in the absence of lesions, usually appear quite flat. The dark ring at the border is caused by the “edge effects” that are not corrected for. The “edge effects” are due to the variable thickness of the breast in the boundary region, which is not taken into account by the theoretical model and lead to artificially low values of the estimated scattering coefficient.

For what concerns the detection and identification of malignant breast lesions, some promising preliminary results have been obtained. The tumours detected up to now were characterized by strong absorption at 683 and 785 nm, probably due to the neo-vascularization associated with the tumour development, which increases the blood absorption, effectively probed at those wavelengths. The neoplastic masses were also characterized by low scattering, at least at short wavelengths. More data need to be acquired, especially from malignant lesions, to determine whether they can still be detected even in the absence of neo-angiogenesis.

4. Conclusions

In conclusion, time-resolved reflectance and transmittance spectroscopy can be profitably applied for the in vivo optical characterization of breast as well as other tissue types. As the absorption and scattering properties of tissue depend on its constituents and structure, information can be derived on the physiological conditions of tissue. Monitoring changes in the optical properties can also bring diagnostic information, as the onset of pathology, causing morphologic and functional alterations, is expected to affect also the optical features of tissue.

In this line, time-resolved transmittance imaging is presently investigated in clinics as a possible means for optical mammography. In particular, work is in progress to develop more accurate theoretical models to better quantify the local optical properties, instead of averaging over the entire probed volume.

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