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Title

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Permalink

<https://escholarship.org/uc/item/2t73c6mh>

Journal

Annual International Conference of the IEEE Engineering in Medicine and Biology - Proceedings, 6

ISSN

0589-1019

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Publication Date

1997-12-01

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INSTRUMENTATION AND CLINICAL APPLICATIONS IN FREQUENCY-DOMAIN OPTICAL MAMMOGRAPHY

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Abstract—We describe an instrument for frequency-domain light mammography (LIMA), and we present clinical results obtained on patients affected by breast cancer. This instrument uses two laser diodes emitting at 690 and 825 nm. Their intensities are modulated at a frequency of 110 MHz. The amplitude and the phase of the intensity wave are the measured quantities. The breast is slightly compressed between two glass plates and the optical signal is detected in transmission, i.e. on the opposite side of the illuminated spot of the breast. The acquisition time for a full breast image is about 3 minutes. Edge effects (that are mainly due to the breast thickness variability within the scanned area) are corrected by an algorithm of data analysis which enhances the contrast of the optical mammograms. In the clinical applications, we successfully detected 27 out of 37 malignant tumors (73%). This result shows the practical feasibility and the significant potential of frequency-domain optical mammography.

I. INTRODUCTION

Methods employing visible and near infrared light to detect breast cancer have been first proposed in 1929 [1]. These methods have employed continuous wave (CW) light sources and have led to the development of applications known as diaphanography [2] and lightscanning [3]. The shadowgrams produced by these CW techniques have not gained medical acceptance because of the low sensitivity in tumor detection and a relatively high false-positive rate [4,5].

We propose a novel approach to optical mammography which is based on the frequency-domain technique, where the light intensity is modulated at radiofrequency (110 MHz in the application presented here). In this paper, we describe a research prototype for frequency-domain light

mammography (LIMA), and we report its performance in the detection of breast cancer in 37 patients.

II. MATERIAL AND METHODS

The block diagram of the frequency-domain light mammography system (LIMA) is shown in Fig. 1. This instrument works in transmission, i.e. the breast is illuminated on one side and the transmitted light is collected on the opposite side. It performs a tandem planar scan of a dual wavelength laser beam and of an optical detector fiber which sends light to a photomultiplier tube (PMT) detector. As a result, a bidimensional projection image of the breast is produced [6]. The light sources are two laser diodes (LD1 and LD2) emitting at 690 and 825 nm, respectively. Their beams are collimated and made collinear, while their intensities are modulated at a radiofrequency by the signal of an oscillator. The intensity of the 690 nm laser is modulated at a frequency $f_1 = 110 \text{ MHz} + 1000 \text{ Hz}$, whereas the 825 nm laser diode is modulated at $f_2 = 110 \text{ MHz} + 800 \text{ Hz}$. The gain of the PMT is modulated at frequency $f_3 = 110 \text{ MHz}$. In this fashion, the output signal of the PMT contains harmonic components at 800 Hz and 1000 Hz, which correspond to the optical signals at $\lambda = 825 \text{ nm}$ and $\lambda = 690 \text{ nm}$, respectively. These harmonic components are filtered and processed with a digital acquisition method to give the frequency-domain parameters (ac amplitude and phase) at the two wavelengths [7]. The acquisition time per data point, i.e. per image pixel, is 100 ms. This acquisition time enables us to produce a full breast image with pixel size of $1.5 \times 1.5 \text{ mm}^2$ in about 3 minutes. Table I reports the technical specifications for the LIMA system.

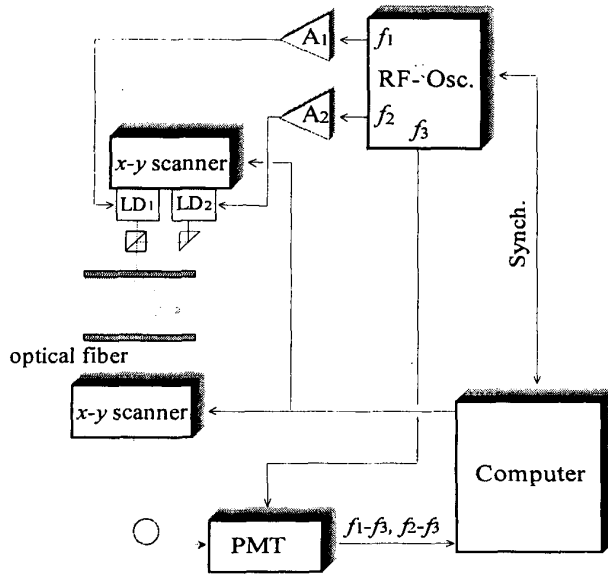


Figure 1. Block diagram of the LIMA system. The technical specifications are reported in Table I. LD1 (LD2) is a laser diode emitting at 690 (825) nm, whose intensity is modulated at a frequency $f_1 = 110.001$ MHz ($f_2 = 110.0008$ MHz) by the RF-oscillator through the RF amplifier A1 (A2). On the opposite side of the breast, the transmitted light is collected by an optical fiber connected to a photomultiplier tube (PMT) detector. The gain of the PMT is modulated at a frequency $f_3 = 110$ MHz. The laser diodes and the optical fiber are simultaneously scanned along the plane of the compression plates (x - y). The RF-oscillator is synchronized with the digital acquisition card in the computer.

TABLE I
TECHNICAL SPECIFICATIONS OF THE LIMA SYSTEM

Wavelengths	690, 825 nm
Average light power	10 mW
Detector	PMT
Beam delivery	direct
Precision in phase	< 0.2°
Precision in amplitude	< 0.1%
Minimum detectable power	< 50 pW
Signal detection	digital lock-in
Modulation frequencies	110, 220 MHz
Acquisition time per pixel	100 ms
Time per breast scan	< 3 - 4 min

As the optical scanner approaches the edge of the breast, several effects (that we call edge effects) have a significant impact on the measured ac and phase. These effects include the decrease in breast thickness, the photon losses through the side of the breast, and changes in the optical coupling with the breast. In pixels close to the edge of the scanned area, these effects overwhelm the changes in the ac and phase that are due to a tumor. Furthermore, edge effects induce a large range of ac and phase values within the image, thus reducing the image contrast and the tumor detectability. We have developed an algorithm for data analysis aimed at correcting for edge effects. This algorithm is described in detail in Ref. [8]. The basic idea is to use the phase information to determine the breast thickness (r) at each image pixel. The dependence of the ac amplitude on r is empirically determined to be $\sim 1/r$ for healthy breasts. At each pixel (x,y), we define a dimensionless parameter (N) as:

$$N(x, y) = \frac{r_0 ac_0}{r(x, y) ac(x, y)},$$

where r_0 is the distance between the compression plates, and ac_0 is the ac amplitude at a particular pixel where $r = r_0$. This parameter N is what we report in our optical mammograms. In healthy breasts its value is about 1 in the whole image, while in the presence of optical inhomogeneities the value of N deviates from the value of 1. In our experience, a tumor always corresponds to a value of N greater than 1, which indicates that tumors cause a stronger light attenuation with respect to healthy tissue.

III. RESULTS

Figure 2 shows the effectiveness of the algorithm for edge effect corrections. The improved image contrast in Fig. 2b (which reports the N parameter at 690 nm) with respect to Fig. 2a (which reports the ac amplitude at 690 nm) allows for a better detection of the breast lesion. It is important to note that the N -image is displayed with a linear gray scale where white (black) corresponds to the minimum (maximum) value of the parameter N in the image. Consequently, the N -based optical mammograms are displayed in real time during the exam, and do not require any additional manipulation by the examiner.

The clinical test of the LIMA system is performed at the Robert Roessle Hospital and Tumor Institute in Berlin, Germany. We have recently reported initial clinical results on two patients affected by breast cancer [9]. Here, we present the results obtained with the LIMA on a larger number of patients. Among 37 cases of patients affected by breast cancer, the LIMA system successfully detected 27 malignant tumors (73%). Each patient underwent surgery, so that we

know the type and size of the tumor for each case. The detectability of breast cancer by LIMA for different tumor sizes is shown in Fig. 3. The results reported in Fig. 3 are based on optical mammograms at $\lambda = 825$ nm. Similar results are obtained at $\lambda = 690$ nm.

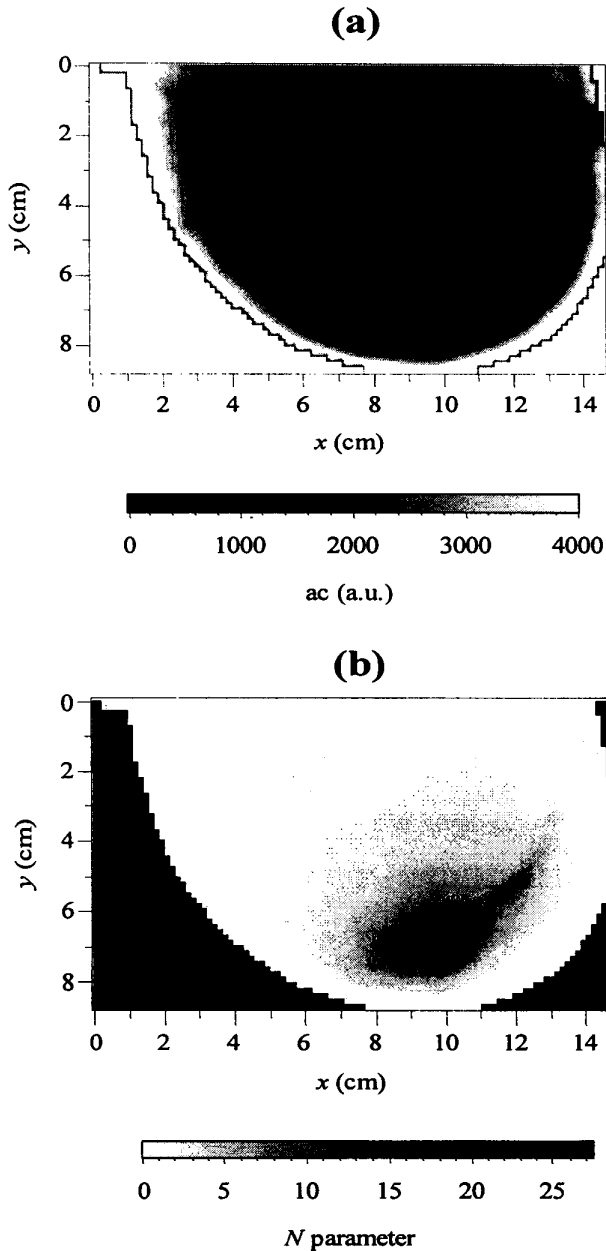


Figure 2. Optical mammograms at 690 nm showing the improved detectability of optical inhomogeneities afforded by (b) frequency-domain optical mammography (N parameter) with respect to (a) simple intensity (ac amplitude) images. In this case, the separation between the compression glass plates (r_0) was 7 cm.

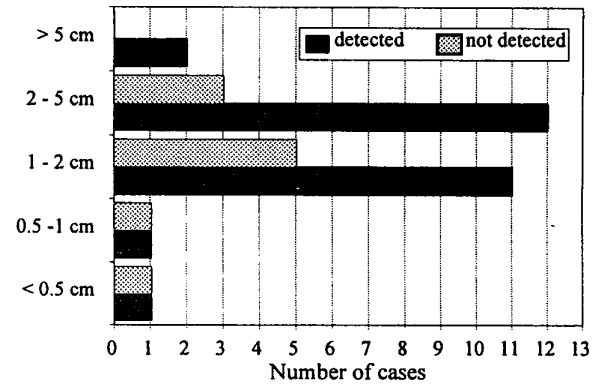


Figure 3. Detectability of the 37 malignant tumors with the LIMA system. The y-axis labels are the tumor sizes in centimeters.

IV. DISCUSSION

Figure 3 shows that LIMA has not detected 10 (27%) out of the 37 malignant tumors. To understand the limitations of our current prototype, we are investigating the possible causes of these false negative results. We discuss three possible reasons for these false negative results.

(1) It is possible that some tumors have optical properties which do not differ enough from those of healthy tissue to permit the detection of the tumor with optical methods. This is a very basic issue, which concerns the intrinsic optical contrast of tumors. A possible way to overcome this potential problem, and to provide a higher sensitivity and specificity of the optical method, is to use extrinsic absorbing or fluorescent contrast agents as tumor markers.

(2) The breast compression geometry used by LIMA is not the ideal configuration to detect tumors that are close to the chest wall. We do not believe that all of the 10 false negative cases are attributable to the fact that the tumor was not in the region of the breast between the compression plates. However, this is certainly a possibility for some of the cases. A different sampling geometry could improve the effectively imaged breast volume. For example, a circular scan of source and detector around the pendulous breast could be a better approach to detect tumors close to the chest wall. Furthermore, this approach would avoid the discomfort caused by breast compression.

(3) The algorithm for edge correction that we are currently using may not be adequate to detect tumors close to the edge of the image. The influence of edge effects can be strongly reduced by embedding the breast in a medium which matches the optical properties of breast tissue. Alternatively, edge effects can also be avoided by using different sampling configurations, such as a circular scanning around the breast.

V. CONCLUSIONS

The frequency-domain approach to optical mammography implemented in the LIMA prototype is yielding promising clinical results. Frequency-domain optical mammography has successfully detected 27 out of 37 malignant tumors (73%). These results indicate that frequency-domain optical mammography has the potential of becoming a useful tool in the clinical environment. Also, the clinical results constitute a crucial input to determine the strengths and the current weaknesses of the LIMA approach, thereby indicating future directions in the instrument development.

ACKNOWLEDGMENTS

The authors thank Dr. G. Gaida for useful discussions, and W. Walch and M. Seeber for technical support. The work at Carl Zeiss is supported in part by the Bundesministerium für Forschung und Technologie, grant 13N6281. The Laboratory for Fluorescence Dynamics is supported by the National Institutes of Health (NIH), grant RR03155 and by the University of Illinois at Urbana-Champaign. This research is also supported by NIH grant CA57032. S. Fantini and M. A. Franceschini acknowledge support from Carl Zeiss for a work visit at Carl Zeiss, Oberkochen, Germany.

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