Clinical Applications of Frequency-Domain Optical Mammography

Sergio Fantini[a], Oliver Schütz[b], Julian Edler[a], S. Heywang-Köbrunner[c], Linda Götz[c], Maria Angela Franceschini[a], and Horst Siebold[b]

[a] Laboratory for Fluorescence Dynamics, Department of Physics, University of Illinois at Urbana-Champaign, Urbana, IL, 61801-3080

[b] Siemens AG, Medical Technology, Postfach 3260, 91050 Erlangen, Germany

[c] Martin Luther Universitaet Halle/Wittenberg, Institut für Diagnostische Radiologie und CT Magdeburgerstraße 16, D-06097 Halle

ABSTRACT

We present clinical results obtained with a frequency-domain (70 MHz), four-wavelength (690, 750, 788, 856 nm) prototype for optical mammography. The two-dimensional projection images are taken on the slightly compressed breast in craniocaudal and oblique projections, similar to what is done in x-ray mammography. The amplitude and phase images are combined to enhance the contrast and the tumor detectability by reducing the edge effects caused by the breast thickness variations within the scanned area. The analysis of the first set of clinical data (63 patients) has yielded encouraging results. The success rate in the detection of breast cancer was 73%, and specificity was 49%. A comparison of the optical mammograms at the four wavelengths in the range 690-856 nm suggests that spectral information may allow for the discrimination of benign and malignant breast lesions, thereby enhancing specificity.

Keywords: Frequency-domain spectroscopy, near-infrared, optical mammography, breast cancer.

1. INTRODUCTION

Optical mammography has a relatively long history since it was first proposed in 1929 (Ref. 1) and led to diaphanograpy in the 1970's.[2,3] The potential of optical mammography in detecting breast cancer lies in the sensitivity of red/near-infrared light to the hemoglobin concentration and saturation, and to modifications to the tissue architecture. However, the empirical approach of diaphanography resulted to be strongly operator-dependent and yielded a large number of false positive cases.[4] Recent developments in the study of light propagation in tissues have led to improvements in the application of tissue spectroscopy and to the introduction of time resolved methods, where the light emission is not constant with time (as in diaphanography) but is either pulsed (time-domain)[5] or harmonically modulated (frequency-domain).[6] These advances, in conjunction with the use of a physical model to describe light propagation in breast tissue, allows for a more quantitative and rigorous approach to optical mammography.[7-20]

Recent clinical trials of frequency-domain optical mammography performed with a prototype developed by the Carl Zeiss Optics Laboratories[21] have yielded promising results in terms of tumor detectability,[13,22,23] reporting a sensitivity to breast cancer higher than 70%. The clinical data reported in this contribution have been collected with a similar prototype developed at Siemens Medical Technology.[24] The purpose of the analysis of these clinical data is twofold: (1) confirm the previously reported results of sensitivity on an independent clinical data set; (2) investigate the false positive cases to obtain indications about the possible approaches to improve specificity.

2. METHODS

The instrument for frequency-domain optical mammography operates at a modulation frequency of 70 MHz and uses laser diodes at four different wavelengths (690, 750, 788, and 856 nm) as light sources. The breast is slightly compressed between two glass plates. The optical mammogram is obtained by performing a planar tandem scan of the source and detector optical fibers that are located on opposite sides of the breast (transmission geometry). The amplitude (ac) and the phase of the photon-density-wave transmitted through the breast produce two-dimensional projection images at each wavelength. The ac and phase images are combined to minimize the edge effects as previously reported.[25] The resulting image, that we call *N*-image because it reports the dimensionless parameter *N* defined in Ref. 25, is an image of optical attenuation where higher values of *N* correspond to higher values of the optical absorbance. In breast tissue, the optical absorbance is determined by both the absorption and the scattering coefficients, and the *N* image does not allow one to distinguish absorption from scattering perturbations. Therefore, the *N*-images should be considered as a starting point in frequency-domain optical mammography. Our research aims at providing indications on the potential and on future developments of this technique in breast cancer detection.

We report the results obtained studying the frequency-domain optical mammograms collected on 63 patients having tumor-bearing breasts. In each case, we know the size, location, and type of tumor from x-ray mammography and histology. We have divided the patients into five categories according to the kind of breast lesion: (1) carcinoma; (2) ductal carcinoma *in situ* (DCIS); (3) mastopathy; (4) fibroadenoma; (5) other. The first two categories represent malignant tumors, while the last three represent benign breast lesions. The breasts with no tumors have been considered as normal, and have been used to evaluate the *N*-images in normal breasts. Table 1 summarizes the number of cases considered. In some patients, the optical mammograms were available only for one breast. This explains why the total number of breasts is less than twice the total number of patients. The cases of carcinomas have been further divided according to the tumor size (< 5 mm, 5-9 mm, 10-20 mm, 21-50 mm, > 50 mm).

Table 1. Number of cases examined with frequency-domain optical mammography.

Category	No. of Patients	No. of Breasts
Carcinoma	42	42
DCIS	3	3
Mastopathy	8	12
Fibroadenoma	5	5
Other	5	5
Normal	0	39
Total	63	106

The criteria for the interpretation of the optical mammogram are of particular importance. We have considered an optical mammogram to be positive when the three following conditions are met simultaneously:
(1) A region of higher absorption appears in both views (craniocaudal and oblique) of the same breast;
(2) The locations of the suspicious regions in the craniocaudal and oblique views are consistent with each other;
(3) The morphology of the suspicious region is not thread-like in at least one view of the breast.
Usually, thread-like inhomogeneities are assigned to blood vessels. These criteria for interpreting the optical mammograms are similar to those employed by K. T. Moesta in the clinical test at the Humboldt University, Berlin, Germany.[22]

3. RESULTS

Figure 1 reports the frequency-domain *N*-images collected at 788 nm on a 58-year old patient with a 30 mm carcinoma in the left breast. Figure 1 shows the right and left breasts in craniocaudal (cc) and oblique (ob) projections.

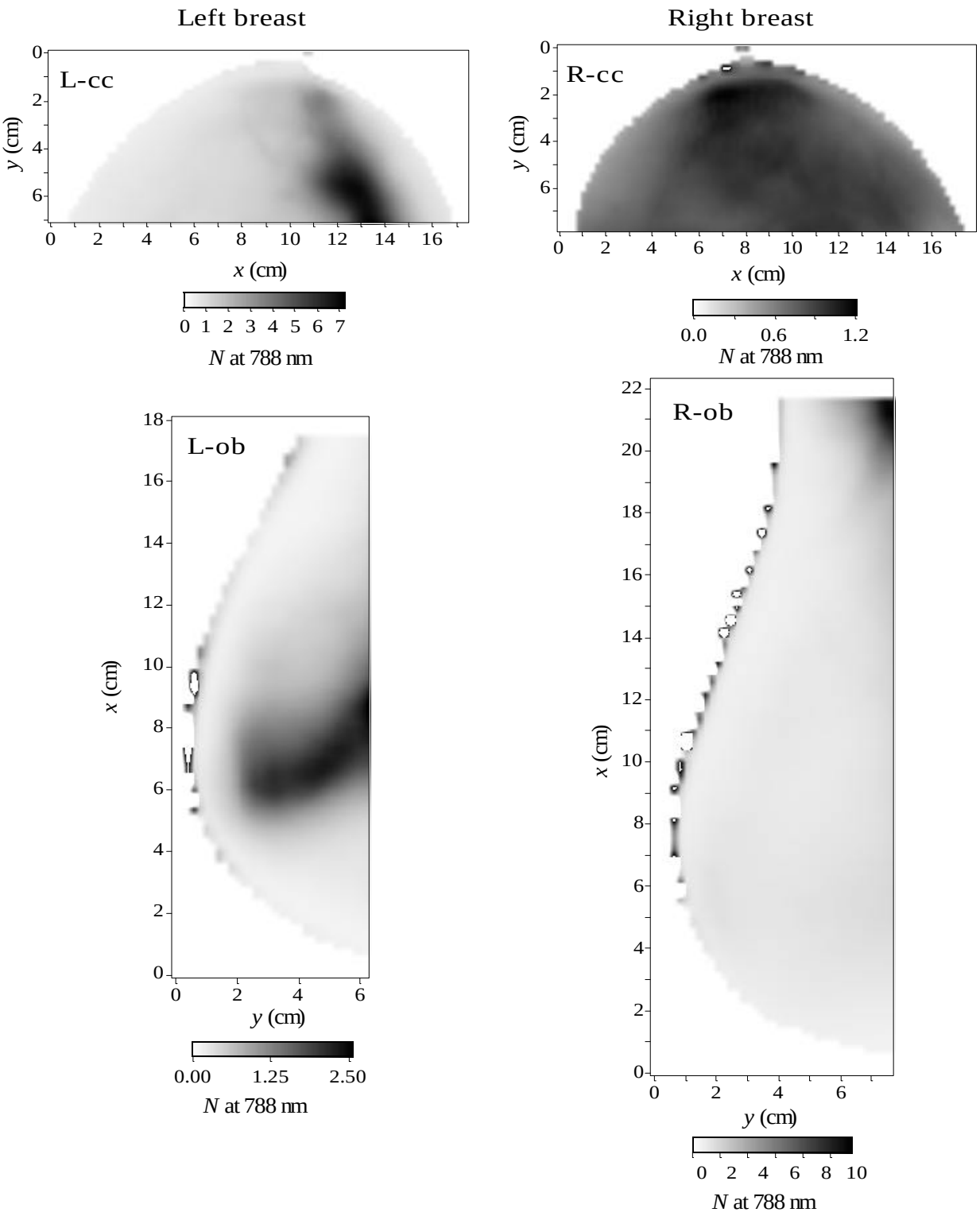


Fig. 1. *N*-images obtained with frequency-domain optical mammography at 788 nm. These mammograms refer to a 58-year-old woman affected by breast cancer (tumor size: 30 mm) in the left breast. The craniocaudal (cc) and oblique (ob) views of the left breast (left two images) show a darker region which corresponds to the tumor. The two views of the right breast (right two images) do not show suspicious areas that are consistent with each other. Consequently, the optical mammogram of the right breast is considered to be negative.

Figure 2 shows a summary of the results of the analysis of the optical mammograms based solely on the *N*-images. Figure 2(a) reports the results obtained on breasts with carcinoma, while Fig. 2(b) shows the results obtained on normal breasts and on breasts with benign lesions. The sensitivity [TP/(TP+FN)] and specificity [TN/(TN+FP)] can be calculated to obtain indications on the performance of the *N*-image approach, even though we should consider that the patient population is not evenly distributed. (TP = true positives; TN = true negatives; FP = false positives; FN = false negative). We found a sensitivity of 73% and a specificity of 49%.

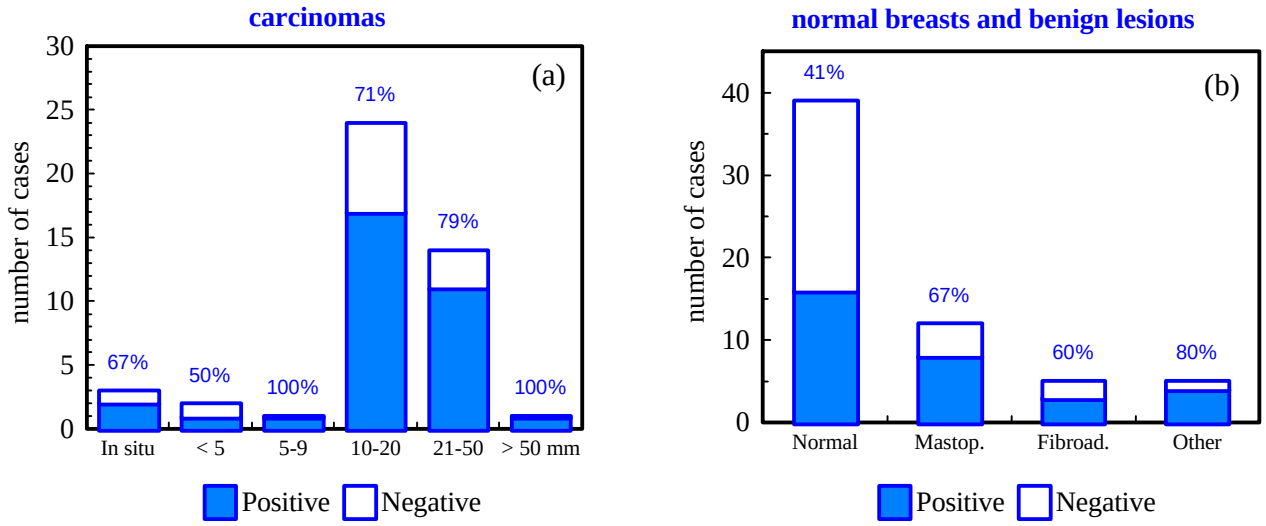
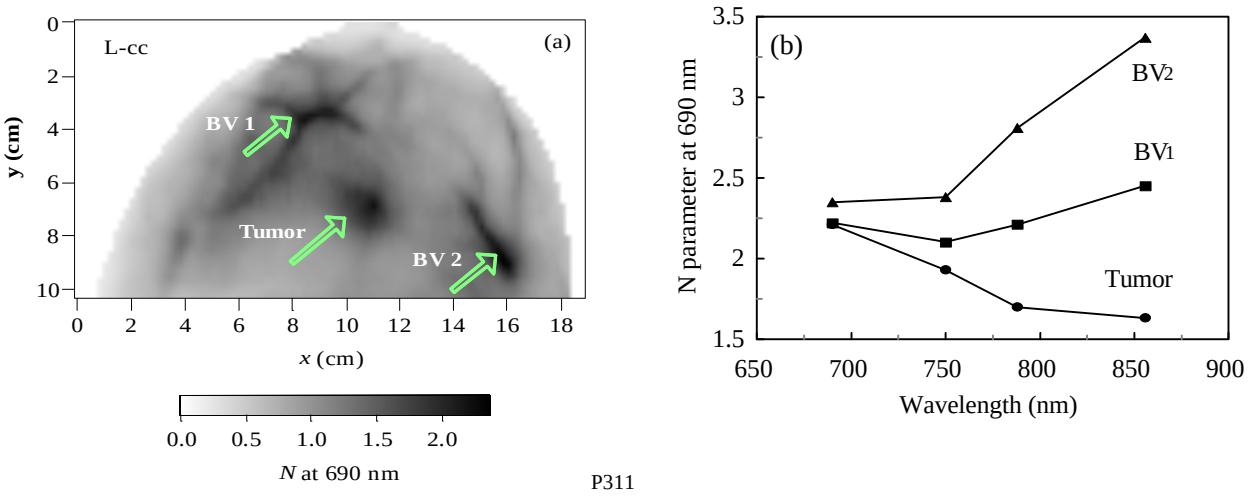


Fig. 2. Summary of the positive and negative frequency-domain optical mammograms (*N*-images) in the cases of (a) carcinomas, and (b) normal breasts and benign lesions.

4. DISCUSSION

The 73% sensitivity of frequency-domain optical mammography is an encouraging result, which is in agreement with the previous findings on an independent clinical data set.[22] However, the reason for the lack of detection of 27% of the carcinomas is still an open question. The 49% specificity should be seen only as a starting point, being based solely on *N*-images (which do not discriminate absorption from scattering inhomogeneities) at one wavelength (therefore without extracting any spectral information). The capability of frequency-domain optical mammography to quantify the absorption and scattering properties of detected tumors has been shown[17], even though we have not applied this capability to this data set, as yet. The (partial) spectral information provided by the four wavelengths employed in this study may help in the discrimination of benign and malignant breast lesions. This possibility is illustrated in Fig. 3, which shows the *N*-image collected at 690 nm on the left breast (in craniocaudal projection) of an 82-year-old woman affected by breast cancer. The tumor, indicated by an arrow in Fig. 3(a), is 25 mm in size. The *N*-image also shows two optical inhomogeneities that, on the basis of their morphology, have been assigned to blood vessels. They are indicated as BV1 and BV2 in Fig. 3(a). Figure 3(b) reports the wavelength dependence of the parameter *N* for the tumor and the two blood vessels. The difference among the three spectral dependencies suggests that the spectral information can be an important factor in discriminating optical inhomogeneities appearing in the *N*-images.



P311

Fig. 3. (a) *N*-image at 690 nm of the left breast (craniocaudal projection) of an 82-year-old woman affected by breast cancer (tumor size: 25 mm). The tumor location is indicated by an arrow in the figure. Two other optical inhomogeneities assigned to blood vessels are indicated in the figure as BV1 and BV2. (b) The different spectral dependence of the *N* parameter recorded at the locations corresponding to the tumor and to the blood vessels.

5. CONCLUSIONS

Frequency-domain optical mammography is an imaging technique that is practically applicable in the clinic. The initial results of sensitivity and specificity in breast cancer detection are encouraging. More work needs to be done to further improve the performance of frequency-domain optical mammography. In this Article, we have explicitly mentioned that (1) the separation of the absorption and scattering contributions,[16-18] and (2) the search for spectral signatures[8,9] are two important research areas to consider. Other promising approaches are being pursued to improve the performance of frequency-domain optical mammography. These approaches include the use of a cylindrical sampling geometry[16,20], more rigorous solutions to the inverse imaging problem,[16,18,19] the use of multi-frequency methods,[14] and the use of amplitude cancellation systems.[15] Being at a stage of development that has already produced encouraging results, frequency-domain optical mammography shows promise as an alternative technique in breast imaging.

6. ACKNOWLEDGMENTS

This work was supported in part by the US National Institutes of Health (NIH), Grant No. CA57032.

7. REFERENCES

1. M. Cutler, “Transillumination of the Breast,” Surg. Gynecol. Obstet. **48**, 721-727 (1929).
2. C. M. Gros, Y. Quenneville, Y. Hummel, “Diaphanologie Mammaire,” J. Radiol. Electrol. Med. Nucl. **53**, 297-306 (1972).
3. E. Carlsen, “Transillumination Light Scanning,” Diagn. Imaging **4**, 28-34 (1982).
4. E. A. Sickles, “Breast Cancer Detection with Transillumination and Mammography,” AJR **142**, 841-844 (1984).
5. E. B. de Haller, “Time-Resolved Transillumination and Optical Tomography,” J. Biomed. Opt. **1**, 7-17 (1996).
6. S. Fantini, B. Barbieri, M. A. Franceschini, and E. Gratton, “Frequency-Domain Spectroscopy,” in *Applications of Optical Engineering to the Study of Cellular Pathology, 1*, E. Kohen, ed., (Research Signpost, Trivandum, India, 1997), pp. 57-66.

7. J. H. Hoogenraad, M. B. van der Mark, S. B. Colak, G. W.'t Hooft, and E. S. van der Linden, "First Results from the Philips Optical Mammoscope," in *Photon Propagation in Tissues III*, D. Benaron, B. Chance, and M. Ferrari, eds., Proc. SPIE **3194**, 184-190 (1998).
8. V. Quaresima, S. J. Matcher, and M. Ferrari, "Identification and Quantification of Intrinsic Optical Contrast for Near-Infrared Mammography," Photochem. Photobiol. **67**, 4-14 (1998).
9. H. Heusmann, J. Kölzer, J. Otto, R. Puls, T. Friedrich, S. Heywang-Köbrunner, and W. Zinth, "Spectral Transillumination of Female Breasts and Breast Tissue-Like Material," Proc. SPIE **2326**, 370-382 (1995).
10. K. Wells, J. C. Hebden, F. E. W. Schmidt, and D. T. Delpy, "The UCL Multichannel Time-Resolved System for Optical Tomography," Proc. SPIE **2979**, 599-607 (1997).
11. D. Grosenick, H. Wabnitz, and H. Rinneberg, "Time-Resolved Imaging of Solid Phantoms for Optical Mammography," Appl. Opt. **36**, 221-231 (1997).
12. R. Cubeddu, A. Pifferi, P. Taroni, A. Torricelli, and G. Valentini, "Time-Resolved Imaging on a Realistic Tissue Phantom: μ_s' and μ_a-Images Versus Time-Integrated Images," Appl. Opt. **35**, 4533-4540 (1996).
13. M. A. Franceschini, K. T. Moesta, S. Fantini, G. Gaida, E. Gratton, H. Jess, W. W. Mantulin, M. Seeber, P. M. Schlag, and M. Kaschke, "Frequency-Domain Techniques Enhance Optical Mammography: Initial Clinical Results," Proc. Natl. Acad. Sci. USA **94**, 6468-6473 (1997).
14. B. J. Tromberg, O. Coquoz, J. B. Fishkin, T. Pham, E. R. Anderson, J. Butler, M. Cahn, J. D. Gross, V. Venugopalan, and D. Pham, "Non-Invasive Measurements of Breast Tissue Optical Properties Using Frequency-Domain Photon Migration," Phil. Trans. R. Soc. Lond. B **352**, 661-668 (1997).
15. S. Zhou, C. Xie, S. Nioka, H. Liu, Y. Zhang, and B. Chance, "Phased Array Instrumentation Appropriate to High Precision Detection and Localization of Breast Tumor," in *Optical Tomography and Spectroscopy of Tissue: Theory, Instrumentation, Model, and Human Studies II*, B. Chance and R. R. Alfano, eds., Proc. SPIE **2979**, 98-106 (1997).
16. B. W. Pogue, M. Testorf, T. McBride, U. Osterberg, and K. Paulsen, "Instrumentation and Design of a Frequency-Domain Diffuse Optical Tomography Imager for Breast Cancer Detection," Opt. Expr. **1**, 391-403 (1997).
17. S. Fantini, S. A. Walker, M. A. Franceschini, M. Kaschke, P. M. Schlag, and K. T. Moesta, "Assessment of the Size, Position, and Optical Properties of Breast Tumors *in Vivo* by Non-Invasive Optical Methods," Appl. Opt. **37**, 1982-1989 (1998).
18. X. D. Li, T. Durduran, A. G. Yodh, B. Chance, and D. N. Pattanayak "Diffraction tomography for biochemical imaging with diffuse-photon density waves," Opt. Lett. **22**, 573-575 (1997).
19. Y. Yao, Y. Pei, Y. Wang, and R. L. Barbour, "A Born Type Iterative Method for Imaging of Heterogeneous Scattering Media and Its Application to Simulated Breast Tissue," Proc. SPIE **2979**, 232-240 (1997).
20. Barbour, R. L., R. Andronica, and I. Soller, "Development and Evaluation of the Iris-Optiscanner: A General Purpose Optical Tomographic Imaging System," *OSA Trends in Optics and Photonics on Advances in Optical Imaging and Photon Migration*, J. G. Fujimoto and M. Patterson, eds., (Optical Society of America, Washington, DC 1998), *in press*.
21. M. Kaschke, H. Jess, G. Gaida, J. M. Kaltenbach, and W. Wrobel, "Transillumination Imaging of Tissue by Phase Modulation Techniques," in *Advances in Optical Imaging and Photon Migration*, Editor R. R. Alfano, Proc. OSA **21**, 88-92 (1994).
22. H. Jess, H. Erdl, K. T. Moesta, S. Fantini, M. A. Franceschini, E. Gratton, and M. Kaschke, "Intensity-Modulated Breast Imaging: Technology and Clinical Pilot Study Results," *OSA Trends in Optics and Photonics on Advances in Optical Imaging and Photon Migration*, R. R. Alfano and J. G. Fujimoto, eds. (Optical Society of America, Washington, DC 1996), Vol. 2, pp. 126-129.
23. K. T. Moesta, S. Fantini, H. Jess, S. Totkas, M. A. Franceschini, M. Kaschke, and P. M. Schlag, "Contrast Features of Breast Cancer in Frequency-Domain Laser Scanning Mammography," J. Biomed. Opt. **3**, 129-136 (1998).
24. O. Schütz, H. Siebold, L. Götz, and S. Heywang-Köbrunner, "Preliminary Imaging Results of a 4-Wavelength NIR Breast Scanner", Oral Presentation at the 2nd Workshop on NIRS & Imaging of Biological Tissue, EC Concerted Action, Florence, Italy, 04/01/1995.
25. S. Fantini, M. A. Franceschini, G. Gaida, E. Gratton, H. Jess, W. W. Mantulin, K. T. Moesta, P. M. Schlag, and M. Kaschke, "Frequency-Domain Optical Mammography: Edge Effect Corrections," Med. Phys. **23**, 149-157 (1996).