Spatial and Spectral Information in Optical Mammography

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This article reviews our research activities in the area of optical mammography and relates them to the historical developments and the current state and trends in the field. The guiding threads for this article are the roles played in optical mammography by spatial and spectral information. The first feature, spatial information, is limited by the diffusive nature of light propagation but can take advantage of the exceptionally high optical contrast featured by blood vessels and blood-rich areas in the breast. We describe a method to correct for edge effects, a spatial second-derivative algorithm, and a two-dimensional phased-array approach that enhance the image contrast, the spatial resolution, and the depth discrimination in optical mammograms. The second feature, spectral information, is the most powerful and unique capability of optical mammography, and allows for functional measurements associated with hemoglobin concentration and oxygenation, water concentration, lipids content, and the wavelength dependence of tissue scattering. We present oxygenation-index images obtained from multi-wavelength optical data that point to the diagnostic potential of oxygenation information in optical mammography. The optimization of the spatial and spectral information in optical mammography has the potential to create a role for this imaging modality in the detection and monitoring of breast cancer.

Key words: Optical mammography; Diffuse optical imaging; Near-infrared spectroscopy; Frequency-domain; Breast cancer; and Oxygenation.

Introduction

The applicability of visible and near-infrared light to the detection of breast cancer has a relatively long history, with first explorations in the late 1920’s (1). Refinements of the methods in the 1970’s and early 1980’s (2-5) led to the development of commercially available equipment for diaphanography or lightscreening (as optical mammography was referred to at the time), which prompted a number of pilot clinical studies in the 1980’s. Some of these studies reported promising data and projected a positive attitude about the potential of diaphanography and lightscreening (6-11), while others were critical and raised questions about its clinical viability (12-17). In the late 1980’s, a multi-center clinical study on a population of 2,568 women concluded that “lightscreening in its current form is inferior to standard mammography” (18), suggesting that further developments were needed before optical imaging of the breast could play a clinical role. In fact, the conceptually simple idea of trans-illuminating the human breast and basing the detection of breast cancer on the increased optical attenuation (shadows) typically associated with it, proved to be feasible but not sufficiently sensitive and specific to play a role in the clinical practice. Starting in the late 1980’s, more quantitative approaches to describing light propagation inside biological tissue (19, 20), together with the development of time-resolved exper-

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imental techniques, either in the time-domain (20-23) or frequency-domain (24-26), led to new developments, in the 1990’s, in the areas of continuous-wave (27-29), time-domain (30-32), and frequency-domain (33-39) optical mammography. Specific areas of research have included the solution of the inverse imaging problem to produce quantitative spatial maps of the optical properties of the breast (40-42) and the search for an optimal instrumental configuration (43) among the options of a planar breast compression (27, 31, 34), a circular arrangement of illumination/collection optical fibers around the pendulous breast (36, 44), the use of optical matching fluids (28), and reflection measurements obtained by applying a hand-held optical probe on the breast (35, 37, 45). The late 1990’s have also witnessed the emergence of novel approaches that involve the combination of optical and ultrasound techniques either by complementing the information content of the two imaging modalities (46-48), or by using a focused ultrasound beam to label or tag photons that have traveled through the ultrasound focal volume (ultrasonic tagging of light) (49), or by using photoacoustics to generate pressure wave as a result of localized areas of increased optical absorbance (50-53). Several groups have also proposed to combine optical imaging of the breast with other existing diagnostic imaging modalities such as magnetic resonance imaging (MRI) (54-57) and x-ray mammography (58). Finally, one of the newest and potentially powerful developments involves the introduction of extrinsic optical contrast agents (55, 59).

On the one hand, combining optical mammography with other imaging modalities (especially MRI and x-ray mammography) or with extrinsic contrast agents provides a richness of information that is invaluable for research purposes, as well as the promise of enhancing the sensitivity and specificity for cancer detection and diagnosis. On the other hand, it introduces significant complications that undermine one of the very reasons for the attractiveness of optical mammography, namely its non-invasiveness, safety, relatively compact instrumentation (suitable for doctor’s office use, bedside use, and even home use), and cost-effectiveness. These features allow for a high repetition frequency of the optical measurements, which points to a potential niche for optical mammography in the area of therapeutic follow-up (60). Another niche for optical mammography in breast cancer diagnostics is the investigation of relatively young women, for whom x-ray mammography is not applicable because of the high density of glandular breast tissue. Ultimately, the greatest promise for clinical applicability of optical mammography lies in the feasibility of basing it on the intrinsic optical contrast provided by breast cancer. For this reason, much research has been devoted to characterizing such optical contrast and identifying ways to maximizing it by studying the optical features of breast tissue in vitro (61-65), in vivo (66-68), and breast tumors in vivo (69-74), developing optical indices that correlate with the presence of cancer (75), and by measuring the changes in the breast optical properties associated with aging, hormonal activity, and the menstrual cycle (76-79), or across subjects (80, 81).

The oxygen saturation of hemoglobin is one of the specific sources of intrinsic contrast to which optical mammography is uniquely sensitive. However, it is not well-established whether oxygenation measurements can provide an enhanced performance of optical mammography. In fact, while spatially-resolved studies of the partial pressure of oxygen (pO2) have shown that breast cancer has lower average values of pO2 with respect to benign breast lesions and normal breast tissue (82, 83), in vivo optical measurements of hemoglobin saturation of breast cancer have not given an unequivocal indication. Some case studies have reported a lower oxygenation of breast cancer compared to benign tumors and healthy breast tissue (71), some have found a higher oxygen saturation at the cancer location with respect to the background (41), while others have not always found a statistically significant or unidirectional oxygenation contrast associated with breast cancer (72, 84, 85). This point is arguably one of the most critical open questions in optical mammography, as near-infrared imaging is highly sensitive to the oxygen saturation of hemoglobin, a functional indicator that is not directly measured by other existing diagnostic breast imaging modalities.

This article reviews our research efforts in the area of optical mammography. These research activities include an edge-correction approach to enhance image contrast leading to an improved detectability of breast cancer, and a comparison with x-ray mammograms (34, 86) (in collaboration with Enrico Gratton at the University of Illinois at Urbana-Champaign, and Michael Kaschke at Carl Zeiss, Germany), a systematic analysis of a clinical data set of optical mammograms collected on 131 patients (39, 87) (in collaboration with Horst Siebold and Oliver Schütz at Siemens AG, Medical Solutions, Germany, and with Sylvia Heywang-Köbrunner at Martin Luther University, Germany), further developments in image processing of optical mammograms based on a spatial second-derivative algorithm (88) the combination of multi-wavelength data to generate oxygenation images (89), and a novel 2-D phased-array scheme for enhanced spatial resolution and depth discrimination (90, 91). In the spirit of the above introductory paragraphs, our research objectives have been focused on developing a robust approach to optical mammography to enhance the diagnostic information content of the optical images on the basis of intrinsic contrast (but the principles and methods developed lend themselves to detecting extrinsic contrast as well), by optimizing the spatial information content, the image contrast associated with the vasculature and with breast lesions, and the functional information associated with the oxygen saturation of hemoglobin.
Instrumentation: Frequency-domain Breast Imager

The optical mammograms presented and discussed in this review were obtained with two research prototypes developed by Carl Zeiss, Oberkochen, Germany (33, 34), and by Siemens AG, Medical Solutions, Erlangen, Germany (38, 39), respectively. The Zeiss instrument is shown in Figure 1(a), and the Siemens instrument is shown in Figure 1(b). Both instruments operate in the frequency-domain with an intensity modulation frequency that is 110 MHz in the Zeiss instrument and 70 MHz in the Siemens instrument. The wavelengths are 690 and 810 nm for the Zeiss instrument, and 690, 750, 788, and 856 nm for the Siemens instrument. Both devices work in a transmission geometry through the slightly compressed breast, and acquire a 2-dimensional projection image by tandem-scanning the illumination and collection optical fibers (which always remain collinear with each other) over the breast area. The spatial sampling rate is 0.67 mm\(^{-1}\) for the Zeiss instrument (translating into an image pixel size of 1.5 \(\times\) 1.5 mm\(^2\)) and 0.50 mm\(^{-1}\) for the Siemens instrument (translating into an image pixel size of 2\(\times\)2 mm\(^2\)). The total scanning time per optical mammogram is in the order of a few minutes. Similarly to x-ray mammography, the breast is imaged in two projections, craniocaudal (cc) and either oblique (ob) or mediolateral (ml).

Correction for Edge Effects in Planar Projection Imaging

The planar geometry associated with the light compression of the breast between glass plates determines a range in the thickness of the breast between the plates. Anterior and lateral tissues, closer to the edge of the projected breast image, are thinner than the base closer to the chest wall. The frequency-domain optical data (amplitude and phase) collected closer to the breast edge are significantly affected by such reduced tissue thickness, which causes a higher optical transmission (by several hundred percent) and a smaller phase delay (by tens of degrees) with respect to the central part of the breast. These geometrical effects on the optical data compete with the much smaller effects (typically 1-10% in the amplitude and up to a few degrees in the phase) induced by cancer and other optical inhomogeneities in the breast. Because these geometrical factors are important in areas close to the edge of the breast, they are referred to as edge effects. Taking advantage of frequency-domain data, we have combined the amplitude and phase data to obtain edge-corrected images, which enhance the contrast of breast lesions and extend the useful imaging area to the whole breast (86). Figure 2 illustrates the approach to edge correction by comparing the raw-data images (amplitude and phase) and the edge-corrected image (\(N\)) of the right breast of a 74-year-old patient (reference number: 184). The arrows in the optical mammograms of Figure 2 indicate the position of a 2.5 cm invasive ductal carcinoma. The basic idea for edge correction is to use the phase data to estimate the tissue thickness (\(r\)) at any given pixel (\(x,y\)) and correct the amplitude (\(A\)) for the variable tissue thickness across the image. This procedure leads to an edge-corrected parameter (\(N\)) defined as \(N(x,y) = r_0 A_0/[r(x,y)A(x,y)]\), where \(r_0\) is the maximal breast thickness, and \(A_0\) is the amplitude at a reference pixel in the central area of the breast. Because the phase measured in the frequency-domain is equivalent to the mean time-of-flight measured in the time-domain, this edge-correction procedure lends itself to being applied in the time-domain as well (31).

Second-derivative Algorithm for Enhanced Spatial Information

To improve the visibility of the vasculature and breast lesions, we have introduced an algorithm based on a spatial second-derivative operator (88). While this algorithm is for-
mally similar to commonly employed edge-detection algorithms, it nevertheless plays a unique role in diffuse optical imaging. In fact, while the width of the optical transmission valley associated with an absorbing inhomogeneity measured by spatial scanning is relatively insensitive to the size and structure of the inhomogeneity (92), its shape (and therefore its spatial second derivative) is affected by geometrical and structural details. To generate the second-derivative images, we first smooth the original $N$-image with a low-pass spatial filter. Next, at each pixel we calculate the discrete second-derivative along four directions ($\hat{x}$, $\hat{y}$, $\hat{x}+\hat{y}$, $\hat{x}-\hat{y}$) and we take the minimum of these second derivatives to enhance the visibility of directional structures such as blood vessels. In the second-derivative images, we display pixels associated with a negative second-derivative (i.e., attenuation peaks) in grayscale, while pixels associated with a positive second derivative are set to white and the outside of the breast is set to black. The enhanced display of spatial structures within a normal breast can be appreciated in Figure 3, where second-derivative images ($N''$) are compared to the original edge-corrected images ($N$). The spatial information content of the second-derivative images allows for a clear visualization of the vasculature within the breast as well as any breast lesions that are associated with an optical contrast. Such a spatial information display in the optical images relies on a relatively fine spatial sampling that is impractical to achieve with an instrumental setup based on a set of fixed optical fibers, while it can be obtained with a spatial scanning approach as implemented by the Zeiss and Siemens prototypes, or by the fine spatial sampling featured by detector arrays.

Reproducibility of Optical Mammograms Measured in Planar Projection

The optical mammograms shown in Figure 3 were collected on the left breast of a healthy 53-year-old subject over a period of twelve days. The first measurement session (top panels) was on January 9, the second session (middle panels) was on January 15, and the third session was on January 21 (bottom panels). These three measurement sessions give an insight on the level of reproducibility of the two-dimensional planar projection approach to optical mammography. There is spatial congruence in the vasculature seen in the images collected in the three measurements session; not just the major blood vessel that dominates the edge-corrected mammograms, also finer details that can be visualized in the second-derivative mammograms (see for examples the circled structures in Fig. 3). Of course, the spatial congruence is not absolute because of the deformation of the breast under slight compression. Such deformation may affect the spatial location of the blood vessels along the $x$-$y$ plane (which accounts for the variability in the location of some vascular structures in the images of Fig. 3), as well as along the $z$ coordinate (which accounts for the variability in the contrast level of some blood vessels in the images of Fig. 3). Nevertheless, the well-defined geometry featured by the planar breast constraint, and its excellent level of reproducibility, are two positive characteristics of planar projection imaging of the breast. It is important to point out that the projection images of Figure 3 are not able to provide information about the depth (or $z$ coordinate) of the displayed blood vessels. Such important information may be obtained by applying methods that afford depth discrimination, such as the one described in Two-dimensional Phased-array Approach for Enhanced Spatial Information and Depth Discrimination.

Multi-wavelength Optical Data for Oximetry

The second-derivative, $N''$-images in Figure 3 show much more structural detail with respect to the corresponding edge-corrected, $N$-images thanks to an enhanced contrast and resolution. In particular, second-derivative images show with unprecedented contrast and resolution the network of major blood vessels within the breast, exploiting the strong optical contrast provided by blood (the near-infrared absorption coefficient of blood is $\sim 5 \text{ cm}^{-1}$, which is 2-3 orders of magnitude greater than that of the surrounding breast tissue). Even by itself, this is a significant result, taking into account the fact that “abnormal vascularity is probably at least as important as light absorption in the detection of breast cancer” (9). However, the additional spatial detail does not necessarily allow for the discrimination of cancer and benign.

**Figure 3:** Edge-corrected mammograms ($N$) and second-derivative mammograms ($N''$) of the left breast in craniocaudal projection (lcc) of a 53-year-old healthy subject. The top, middle, and bottom images were acquired in three different measurement sessions, each six days apart from the previous one (see the dates indicated in each panel). The more detailed spatial information of the second-derivative images allows one to appreciate the level of reproducibility of the optical mammograms (for example, notice the corresponding circled structures in the three second-derivative images).
lesions or normal tissue inhomogeneities. Additional steps may be required to differentiate the various structures that are visible in the second-derivative images. This can be done by using multi-wavelength information, which can be translated into a level of blood oxygenation, which in turn is determined by the balance between the local supply and demand of oxygen. It is well-established that the oxygen saturation of hemoglobin can be quantitatively determined by measuring the absorption coefficient of hemoglobin at two wavelengths (93). In near-infrared spectroscopy of tissue, where hemoglobin is the dominant source of tissue absorption, absorption measurements at two wavelengths can provide absolute readings of hemoglobin saturation in tissue (94, 95). However, the breast imagers presented in this review (Fig. 1) are not designed for quantitative absorption measurements. Therefore, we have devised an approximate method that takes advantage of the spectral sensitivity of the transmitted intensity to hemoglobin saturation, but does not attempt to determine an absolute value of oxygenation. Specifically, we have performed a least-square fit of the second derivative data ($N'$) at four wavelengths with a linear combination of the absorption spectra of oxy-hemoglobin and deoxy-hemoglobin (89). This fit provides a relative measurement of hemoglobin oxygenation on an arbitrary scale, and therefore we refer to the result of the fit as an oxygenation index rather than the oxygen saturation of hemoglobin (96). The oxygenation index is only calculated at pixels where the $N'$-value is negative at all four wavelengths, which indicates a peak in attenuation. The combination of second-derivative images at four wavelengths to generate an oxygenation-index image is represented in Figure 4. The region corresponding to the tumor location, indicated by the arrow in Figure 4, is consistent with the hypoxic area as indicated by the low oxygenation index values (blue/green in the color palette of Fig. 4). The second-derivative mammograms at four wavelengths (690, 750, 788, and 856 nm) shown in Figure 4 allow one to visually appreciate the spatial dependence of the wavelength behavior of the optical contrast. In fact, the cancerous area (indicated by the arrow in the 690 nm image) shows a contrast that decreases with wavelength (consistent with a low oxygenation level), while most of the blood vessel structures show a contrast that increases with wavelength (consistent with a high oxygenation level). The fact that the optical contrast featured by breast cancer typically decreases with wavelength has also been demonstrated by recent research studies (73, 74).

The complementary information provided by oxygenation index images, and their potential diagnostic power, is illustrated in Figures 5 and 6. Figure 5 reports the edge-corrected ($N$), second-derivative ($N''$), and oxygenation-index images collected on the left breast of a 53-year-old patient (reference number: 215) in both craniocaudal (lcc) and oblique (lob) projections. The imaged breast bears a 3.0 cm invasive ductal carcinoma whose location, as identified by x-ray mammography, is indicated by the arrow in Figure 5. In the craniocaudal projection (lcc), the cancer location is associated with a higher optical absorbance in the $N$ image, a denser blood vessel network in the $N''$ image, and a relatively low oxygenation index values in the oxygenation index image. By contrast, in the oblique projection (lob) the cancer is not readily identifiable in the $N$ and $N''$ images, whereas it stands out as a hypoxic area in the oxygenation index image. Figure 6 reports optical mammograms collected on the left breast of a 62-year-old patient (reference number: 174) in craniocaudal and oblique projections. The imaged breast bears a 1.5 cm benign mastopathy whose location, as identified by x-ray mammography, is indicated by the arrow in Figure 6. In the craniocaudal projection (lcc), the mastopathy location is associated with a higher optical absorbance as visible in the $N$ image and in the $N''$ image, and a relatively high oxygenation index values in the oxygenation index image. In the oblique projection (lob) the mastopathy does not stand out in the $N$ and $N''$ images, and no suspicious hypoxic areas appear in the oxygenation index image. These two representative cases show how the information content of edge-corrected images (displaying areas of increased optical absorbance), second-derivative images (displaying spatial details of the blood vessel network and other optical inhomogeneities), and oxygenation-index images (displaying relative oxygenation values within the breast) complement each other in the diagnostic interpretation of optical mammograms.

**Two-dimensional Phased-array Approach for Enhanced Spatial Information and Depth Discrimination**

The refined spatial information content of the second-derivative images, with a special emphasis on the breast vasculature, suffers from a major limitation of two-dimensional projection imaging, namely the lack of depth discrimination. In fact, depth discrimination capabilities become especially important in conjunction with spatially refined information such as that provided by second-derivative images. Depth resolution can be achieved by circular arrangements of optical fibers around the breast (28, 36, 44), or by using off-axis collection/illumination in a planar geometry (85). To complement the spatial information content of second-derivative images with depth discrimination capabilities, we propose a two-dimensional source/detector array approach that extends the previously conceived concept of phased-arrays in diffuse optical imaging (97, 98). The basic idea is to arrange multiple source and/or detector elements in a planar configuration, and then combine the normalized intensities ($I/I_0$, with $I_0$ reference intensity) measured by each source-detector pair to yield a phased-array intensity ($I_{PA}$) that provides enhanced imaging information. If we conceptually group the sources (or detector) elements along lines (labeled as directions $d_j$),
Figure 4: Second-derivative images at four wavelengths (690, 750, 788, and 856 nm), and resulting oxygenation-index image for the same case reported in Figure 2 (craniocaudal view of the right breast of patient N.184, 74 years old). The location of a 2.5 cm invasive ductal carcinoma, known from x-ray mammography, is indicated by the arrow. The cancer location corresponds to the hypoxic area in the oxygenation-index image.

Figure 5: Edge-corrected ($N$), second-derivative ($N''$), and oxygenation-index images collected on the left breast of a 53-year-old patient (reference number: 215) in both craniocaudal (lcc) and oblique (lob) projections. The location of a 3.0 cm invasive ductal carcinoma, known from x-ray mammography, is indicated by the arrow. The cancer location is associated with relatively low oxygenation values in both craniocaudal and oblique projections.

Figure 6: Edge-corrected ($N$), second-derivative ($N''$), and oxygenation-index images collected on the left breast of a 62-year-old patient (reference number: 174) in both craniocaudal (lcc) and oblique (lob) projections. The location of a 1.5 cm benign mastopathy, known from x-ray mammography, is indicated by the arrow. The mastopathy is associated with relatively high oxygenation values in both craniocaudal and oblique projections.
the phased-array intensity associated with a specific detector (or source) element is defined as (91):

\[ I_{PA} = \max_{d_j} \left\{ \sum_i A_i^{(d_j)} I_{norm}^{(d_j)} \cos(\alpha_i^{(d_j)}) \right\} \]  

where \( A_i^{(d_j)} \) and \( \alpha_i^{(d_j)} \) are the amplitude and phase factors, respectively, for the \( i \)-th array element along direction \( d_j \) (90). To be specific, we can consider a linear array of three sources along the \( x \) direction, with an inter-source separation of 1 cm, amplitude factors of \( A_1 = A_3 = 1, A_2 = 2 \), and phase factors of \( \alpha_1 = \alpha_2 = \alpha_3 = \pi \). This yields the following expression for the three-element (along \( x \)) phased-array intensity:

\[ I_{PA(x)}^{(x)} = I_{1,\text{norm}}^{(x)} - 2I_{2,\text{norm}}^{(x)} + I_{3,\text{norm}}^{(x)} \]  

This expression is formally similar to a discrete spatial second derivative (with the notable difference that it refers to data from three adjacent sources rather than from three adjacent scanning positions), and indeed achieves a similar enhancement in spatial resolution and information content as that obtained with second-derivative image processing (90). This increase in spatial resolution is determined by a narrower sensitivity function for the phased-array intensity \( (I_{PA}) \) with respect to the central source intensity \( (I_2) \) (single source-detector case). This is illustrated in Figure 7, which reports the sensitivity function for the single-source case [panel (a)] and for a linear phased array along \( x \) [panel (b)], normalized at \( x = 0 \), \( i.e., \) at the line joining the central source and the detector. More formally, if we identify with \( \Delta I_2(x,z) \) and \( \Delta I_{PA(x,z)} \) the changes induced by a small absorbing perturbation located at \( (x,z) \) in the central-source intensity and phased-array intensity, respectively, the sensitivity functions of Figure 7 are defined as \( (\Delta I_2(x,z)/\Delta I_2(0,0)) \) [panel (a)] and \( \Delta I_{PA(x,z)}/\Delta I_{PA(0,0)} \) [panel (b)]. At any depth \( z \), the region of sensitivity of the phased-array intensity is narrower than that of the single-source intensity, accounting for an improvement in spatial resolution, even though it presents two side lobes that expand the region of sensitivity toward the source array side.

In addition to an enhanced spatial resolution (similar to second-derivative imaging), the phased-array intensity provides depth discrimination as a result of the dependence of its sensitivity function on \( z \). This can be appreciated in Figure 8, where the sensitivity functions for the single-source case [panel (a)] and source array [panel (b)] are now normalized at a fixed point \((x = 0, z = 0)\). Figure 8(a) shows that the region of sensitivity of the single source-detector intensity is symmetrical with respect to the midplane \( z = 0 \) [which is perpendicular to the plane of Fig. 8(a)]. By contrast, in the case of the phased-array intensity, the sensitivity close to the source-array is much greater than that close to the detector [Fig. 8(b)]. The reason why the contrast is higher close to the source array is that the intensities detected from the individual sources become increasingly similar for objects closer to the single detector, and they tend to cancel each other out in the phased-array intensity of Eq. \[2\]. By taking advantage of the asymmetric character of the phased-array sensitivity, it is possible to discriminate structures at different depths in the medium (91).

**Figure 7:** Spatial distribution of the sensitivity function on the \( y-z \) plane for the case of one detector located at (0,3) and (a) one source at (0,-3), (b) a linear, three-source array with sources at (-1,-3), (0,-3), and (1,-3). In each panel, the sensitivity function is defined relative to its value at \( (0,0) \). The optical absorption and reduced scattering coefficients used to calculate these sensitivity functions using a perturbation analysis and diffusion theory are 0.03 \( cm^{-1} \) and 14 \( cm^{-1} \), respectively. The phased-array region of sensitivity is narrower than that of the single-source intensity.

**Figure 8:** Same as Figure 7, with the only difference that the sensitivity functions for (a) the single source case, and (b) the phased-array case, are normalized to their value at \((0,0)\). The phased-array sensitivity shows a \( z \)-dependence [panel (b)] that is not featured by the single-source case [panel (a)].

**Discussion**

Optical mammography is a diffuse optical imaging modality. To probe the whole human breast, near-infrared light diffuses over a large tissue volume, and as a result the spatial resolution of optical mammograms is intrinsically limited. While optical mammography has the potential to yield spatial information of diagnostic value, it is generally acknowledged that the biggest promise of optical mammography rests on its sensitivity to functional and metabolic parameters, which may in turn provide specificity to tumor detection. These features of optical mammography (limited spatial resolution, sensitivity to functional parameters) contrast with x-ray mammography, whose most valuable feature is its high spatial resolution, but which only provides structural
information on breast tissue. For this reason, the information content of optical mammograms and x-ray mammograms may effectively complement each other. This review has touched on both aspects of optical mammography, namely its capability to provide spatial and functional information, the latter mostly through spectral measurements.

**Spatial Information**

While the spatial resolution of diffuse optical imaging is never going to compete with that of x-ray mammography or MRI, at least not for deep structures within tissue, several approaches have been proposed to improve it. Previously proposed methods to enhance the spatial resolution include time-gating in the time-domain (99, 100), using high frequencies of intensity modulation (101) or two-element phased-arrays (97) in the frequency-domain, or identifying optimal wavelengths in continuous-wave approaches (102).

Here, we have presented a digital image processing approach based on a spatial second-derivative algorithm, which achieves two results: (i) it enhances the visibility of superficial and deep structures in the breast and (ii) it enhances the spatial resolution with respect to edge-corrected images of optical attenuation. It is important to note that while the spatial resolution for deep structures is relatively poor (~cm), the detectability of small (~mm) deep structures is feasible provided that they feature a sufficiently high optical contrast. This is the case for blood vessels, which provide a 100 to 1,000 fold absorption contrast with respect to the background breast tissue. The high visibility of blood vessels provided by second-derivative images adds to the spatial information content of optical mammography, and may help in the detection of breast cancer, as well as in the follow-up of cancer therapy, as a result of the role played by angiogenesis in conjunction with the metabolic demand of cancer. It is important to stress that the second-derivative images do not simply enhance the visibility of structures in the edge-corrected N-images, but they also provide complementary information. In fact, the contrast in N-images is dominated by high attenuation structures, while the contrast in second-derivative images is dominated by spatially peaked structures. As a result, a dominant feature in the N-image (high attenuation) may appear with limited contrast in the second-derivative image (broad spatial peak). Conversely, a weakly visible feature in the N-image (low attenuation) may appear with high contrast in the second-derivative image (sharp spatial peak). In this sense, the information content of the N-images and second-derivative images is complementary.

The second-derivative method can be implemented by the three-element phased-array approach described by Eq. [2], but the real value added by the phased-array approach described here is its depth discrimination capability. Such a capability is particularly relevant in conjunction with the refined spatial information content provided by the second-derivative images. Ultimately, depth discrimination relies on off-axis detection, by generalized triangulation methods (85) or the application of independent component analysis (103). The basic idea of the spatial-array approach is the differential sensitivity to structures that are close to the array (of either sources or detectors) with respect to structures that are close to the single element (either detector or source). The details of the method for depth discrimination (91) point to the robustness of the method, even though the depth discrimination afforded by this method is limited to the resolution of three layers (one on the array side, one on the single-element side, and a central one), and structures that are symmetrically located in the outer layers cannot be distinguished from structures in the central layer. However, even with these limitations, such depth information is complementary to that of second-derivative images, and further enhances the spatial information content of optical mammograms.

**Spectral Information**

The potential of optical mammography in providing functional and metabolic information represents its greatest promise for diagnostic imaging, and distinguishes it from x-ray mammography and ultrasonography of the breast. Functional and metabolic information is obtained from multi-wavelength data, and ideally from the collection of continuous optical spectra. The major contributions to the near-infrared attenuation spectra in breast tissue come from the absorption spectra of deoxy-hemoglobin, oxy-hemoglobin, water, and lipids, and from the overall scattering spectrum of breast tissue. Within the spectral region considered in optical mammography, which is typically within the 600-1,000 nm wavelength range, the absorption of deoxy-hemoglobin decreases with wavelength, with the exception of a peak at ~758 nm (104); the absorption of oxy-hemoglobin shows a broad valley with a minimum at ~692 nm, and a broad peak with a maximum at ~924 nm (104); the absorption of water shows a relatively strong peak at ~975 nm (105); and the absorption of lipids shows a peak at ~924 nm (32, 80, 106). The scattering spectrum of breast tissue is featureless and decreases with wavelength, with a wavelength power dependence, typically in the range $\lambda^{-0.4} \sim \lambda^{-1.5}$ (77, 79, 107), that is a weaker wavelength dependence than the Rayleigh limit for particles much smaller than the wavelength ($\lambda^{-4}$) (108). Near-infrared wavelengths below ~850 nm, like the ones used by the instruments reviewed here (Fig. 1), are weakly sensitive to lipids, and they mostly probe hemoglobin-related parameters such as the blood volume and blood oxygenation. Thus, the single-wavelength edge-corrected images and second-derivative images shown in this article are mostly representative of the hemoglobin concentration, while the oxygenation-index images are represent
sentative of the hemoglobin saturation. However, if spectral measurements are extended beyond \( \sim 850 \text{ nm} \), the power of spectral information in optical mammography goes beyond providing indications on hemoglobin-related parameters, and involves water concentration, lipids content, and scattering wavelength dependence. With regards to hemoglobin parameters, it is well-established that cancer is associated with a higher concentration of hemoglobin (37, 41, 60, 70, 71, 84, 109), while, as mentioned in the Introduction, it is still unclear whether hemoglobin saturation provides a universal intrinsic source of contrast for cancer. With regards to water and lipids, case studies have indicated that cancer, relative to healthy breast tissue, typically has a higher water concentration (60, 71) and a lower lipids content (60).

The four-wavelength approach reported in this article aims at providing oxygenation information since the wavelengths used (690, 750, 788, and 856 nm) are mostly sensitive to oxy- and deoxy-hemoglobin (with some contribution from water absorption), while they are weakly sensitive to lipids content. The representative cases of Figure 5 (cancer) and Figure 6 (benign mastopathy) point to the diagnostic potential of oxygenation information. It is important to obtain reliable, reproducible, and absolute measurements of oxygenation to fully explore the potential of oximetry in optical mammography. The oxygenation index images of Figures 5 and 6 do not provide absolute measurements, and are based on the spectral shape of the transmitted intensity rather than the tumor absorption spectrum. We have recently proposed an oximetry approach based on identifying two (or more) wavelengths at which the intensity perturbation caused by the tumor is the same (110). The idea behind this approach is that regardless of the tumor size, shape, location, and background inhomogeneity, the tumor oxygenation uniquely determines such iso-intensity-perturbation wavelengths. This may result to be a robust and effective approach to tumor oximetry to complement the detection of breast lesion (based on spatial information) with diagnostic oxygenation measurements (based on spectral information).

**Conclusion**

The general idea of optical mammography, namely to use visible and near-infrared light to image the human breast, is not new, as it has been first proposed in the late 1920’s and further explored and developed throughout the 1970’s and 1980’s. However, since the 1990’s optical mammography has been substantially revisited, enhanced, expanded, and refined both in its instrumental and theoretical aspects, opening new avenues toward its development into a valuable clinical diagnostic tool. This article has touched on a number of these innovative aspects, with a special emphasis on the key and unique role that spatial and spectral information play in optical mammography.

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**References**

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