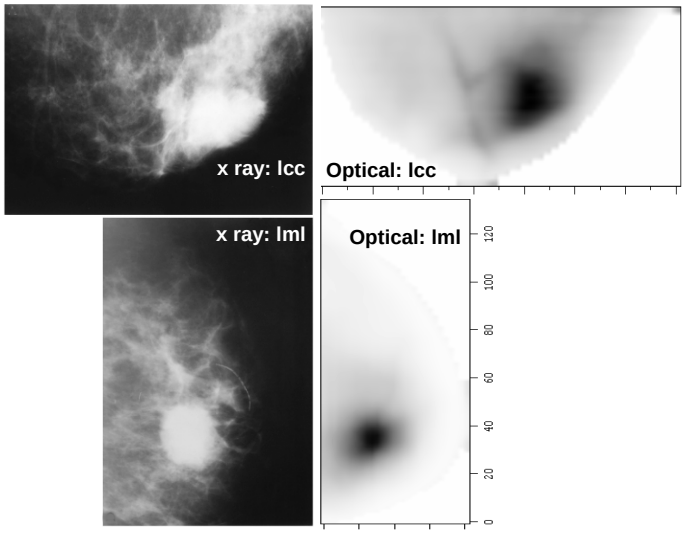

Optical Mammography

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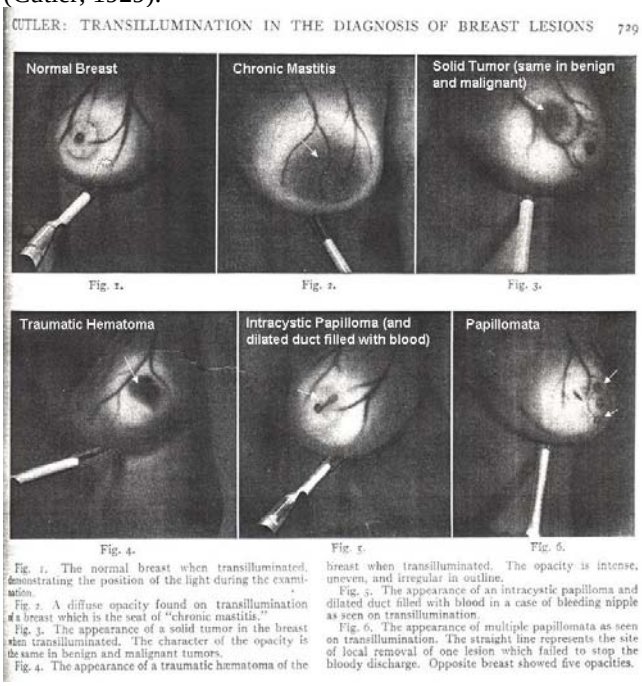
Brief history

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. The figure below shows optical transillumination images of the breast as reported in the 1929 pioneering article of Max Cutler (Cutler, 1929).



Breast transillumination as reported by M. Cutler in 1929 [adapted from Cutler, 1929 (now J. Am. Coll. Surg. (1994))].

Refinements of the methods in the 1970's and early 1980's (Gros *et al.*, 1972; Watmough *et al.*, 1982; Jarry *et al.*, 1984; Ertefai *et al.*, 1985) led to the development of commercially available equipment for diaphanography or lightscanning (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 lightscanning (Ohlsson *et al.*, 1980; Carlsen, 1982; Bartrum *et al.*, 1984; Marshall *et al.*, 1984; Wallberg *et al.*, 1985; Greene *et al.*, 1985), while others were critical and raised questions about its clinical viability (Ängquist *et al.*, 1981; Sickles, 1984; Kopans, 1984; Geslien *et al.*, 1985; Drexler *et al.*, 1985; Gisvold *et al.*, 1986). In the late 1980's, a multi-center clinical study on a population of 2,568 women concluded that "lightscanning in its current form is inferior to standard mammography" (Alveryd *et al.*, 1990), 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 (Navarro *et al.*, 1988; Patterson *et al.*, 1989), together with the development of time-resolved experimental techniques, either in the time-domain (Patterson *et al.*, 1989; Delpy *et al.*, 1988; Wang *et al.*, 1991; Alfano *et al.*, 1994) or frequency-domain (Gratton *et al.*, 1990; Chance *et al.*, 1990; Lakowicz *et al.*, 1990), led to new developments, in the 1990's, in the areas of continuous-wave (Yamashita *et al.*, 1993; Hoogenraad *et al.*, 1998; Barbour *et al.*, 2001), time-domain (Wells *et al.*, 1997; Grosenick *et al.*, 1999;

Cubeddu *et al.*, 1999), and frequency-domain (Kaschke *et al.*, 1994; Franceschini *et al.*, 1997; Zhou *et al.*, 1997; Pogue *et al.*, 1997; Tromberg *et al.*, 1997; Götz *et al.*, 1998; Fantini *et al.*, 2000) optical mammography.

Contrast and resolution

Optical mammography features a limited spatial resolution as a result of the diffusive nature of light propagation in tissue, but can take advantage of the exceptionally high optical contrast featured by blood vessels and blood-rich areas in the breast. Previously proposed methods to enhance spatial resolution include using time-gating techniques in the time domain (Hebden *et al.*, 1991; Wang *et al.*, 1991), using high frequencies of intensity modulation (Fishkin *et al.*, 1993) or two-element phased-arrays (Chance *et al.*, 1993) in the frequency-domain, or identifying optimal wavelengths in continuous-wave approaches (Contini *et al.*, 1996). We developed a method to correct for edge effects (Fantini *et al.*, 1996), a spatial second-derivative algorithm (Pera *et al.*, 2003), and a two-dimensional phased-array approach (Liu *et al.*, 2005; Liu *et al.*, 2005) to maximize the image contrast, enhance the spatial resolution, and achieve depth discrimination in optical mammograms.

Instrumentation

The frequency-domain breast imagers that collected clinical data which were analyzed by us were developed independently by Carl Zeiss, Oberkochen, Germany (Kaschke *et al.*, 1994; Franceschini *et al.*, 1997), and by Siemens AG, Medical Solutions, Erlangen, Germany (Götz *et al.*, 1998; Fantini *et al.*, 2000). The Zeiss instrument (operating at a modulation frequency of 110 MHz and at wavelengths of 690 and 810 nm) is shown in Fig. 1(a), whereas the Siemens instrument (operating at a modulation frequency of 70 MHz and at wavelengths of 690, 750, 788, and 856 nm) is shown in Fig. 1(b). Both imagers acquire a 2-dimensional projection image of the slightly-compressed breast by tandem-scanning the illumination and collection optical fibers.

Edge correction

In this approach to optical mammography, the frequency-domain optical data (amplitude and phase) collected closer to the breast edge are significantly affected by a reduced tissue thickness and by the particular shape of the slightly compressed breast. Because these geometrical factors are important in areas close to the edge of the breast, they are referred to as edge effects. 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 (Fantini *et al.*, 1996). 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. Figure 2 shows the raw-data images (amplitude and phase) and the edge-corrected image (N) of a representative case (the right breast of a 74-year-old patient (reference number: 184)). The arrows in the optical mammograms indicate the position of a 2.5 cm invasive ductal carcinoma.

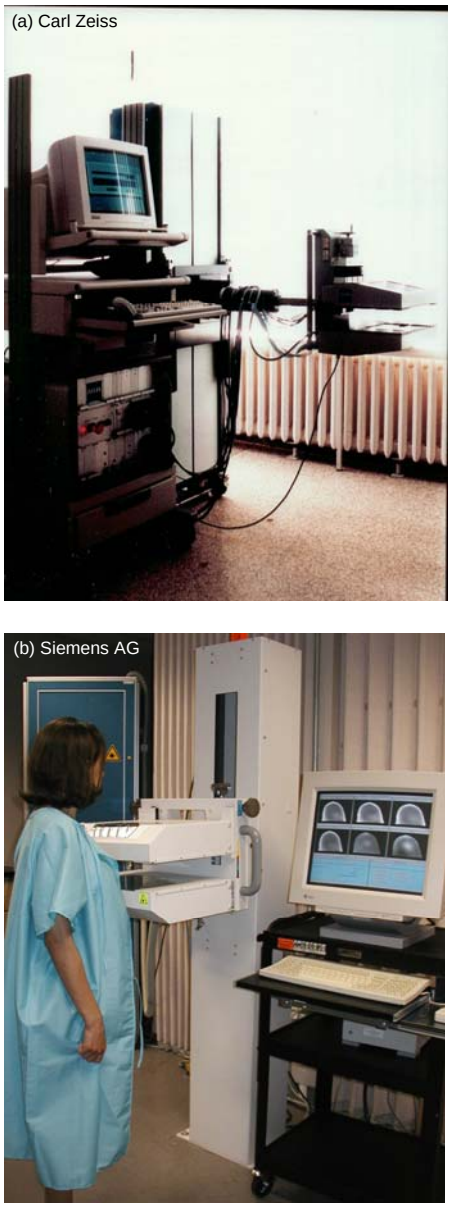


Figure 1. Research prototypes for frequency-domain optical mammography developed in the 1990's by (a) Carl Zeiss, Oberkocken, Germany, and (b) Siemens AG, Medical Solutions, Erlangen, Germany.

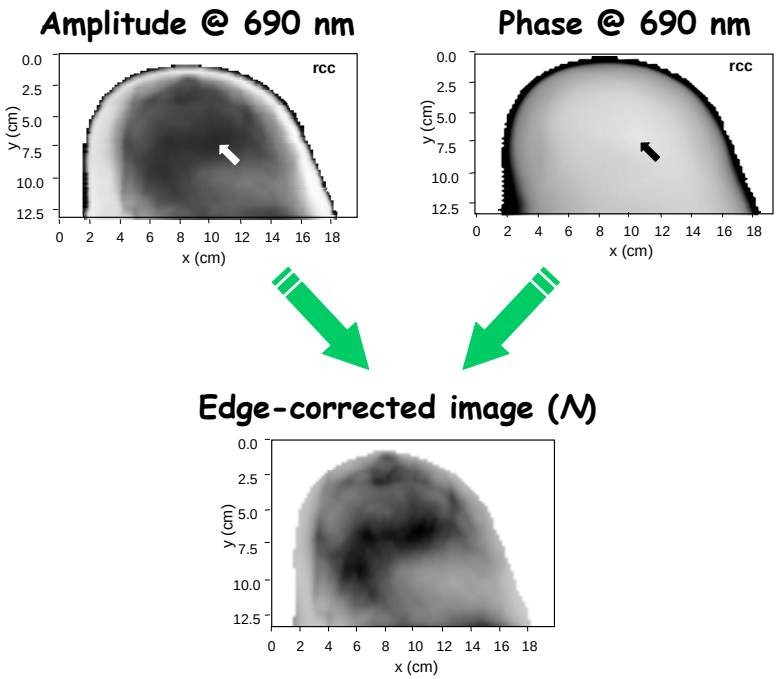


Fig.2. Using frequency-domain data to correct for edge effects: the N-parameter. (Patient number 184, 74 years old, 2.5-cm-diam invasive ductal carcinoma in the right breast, cranio-caudal (rcc) view. The arrow indicates the location of the cancer.)

Optical mammograms based on a spatial second-derivative

To improve the visibility of the vasculature and breast lesions, we have introduced an algorithm based on a spatial second-derivative operator (Pera *et al.*, 2003). This algorithm is formally similar to commonly employed edge-detection algorithms, and has the potential to play a unique role in diffuse optical imaging. 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 ($\hat{\mathbf{x}}$, $\hat{\mathbf{y}}$, $\hat{\mathbf{x}}+\hat{\mathbf{y}}$, $\hat{\mathbf{x}}-\hat{\mathbf{y}}$) and we take the minimum of these second derivatives to enhance the visibility of directional structures such as blood vessels. These image processing steps are illustrated in Fig. 3.

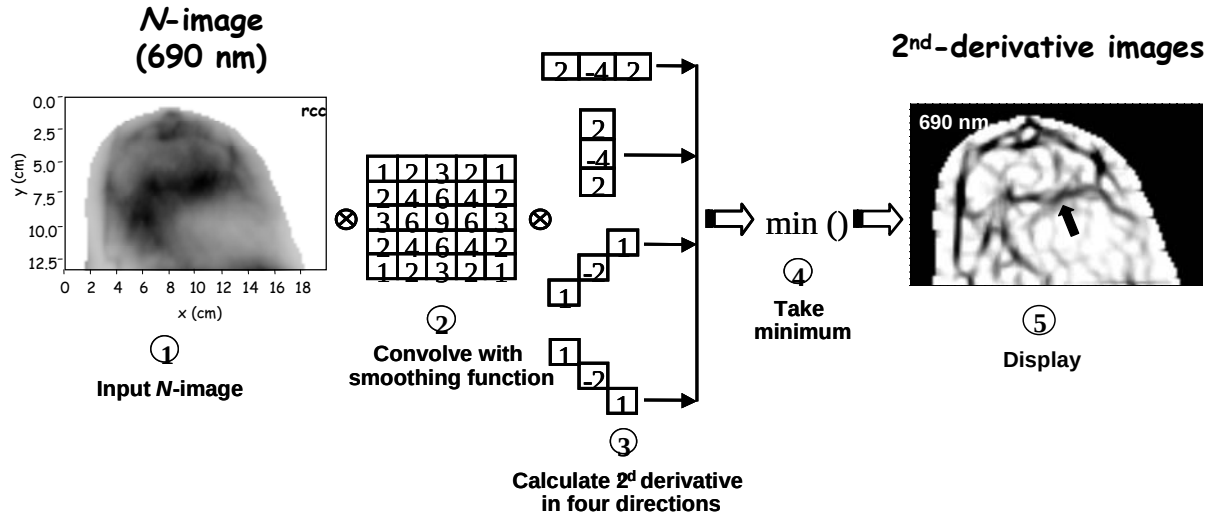


Fig.3. The spatial second-derivative algorithm. (Patient number 184, 74 years old, 2.5-cm-diam invasive ductal carcinoma in the right breast, cranio-caudal (rcc) view. The arrow indicates the location of the cancer.)

Optical oximetry based on multi-wavelength data

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. The differentiation of cancer and benign lesions or normal tissue may 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. We devised an approximate method that takes advantage of the spectral sensitivity of the transmitted intensity to hemoglobin saturation. 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 (Heffer *et al.*, 2004). This fit provides a relative measurement of hemoglobin oxygenation on an arbitrary scale. The combination of second-derivative images at four wavelengths to generate an oxygenation-index image is shown in Fig. 4.

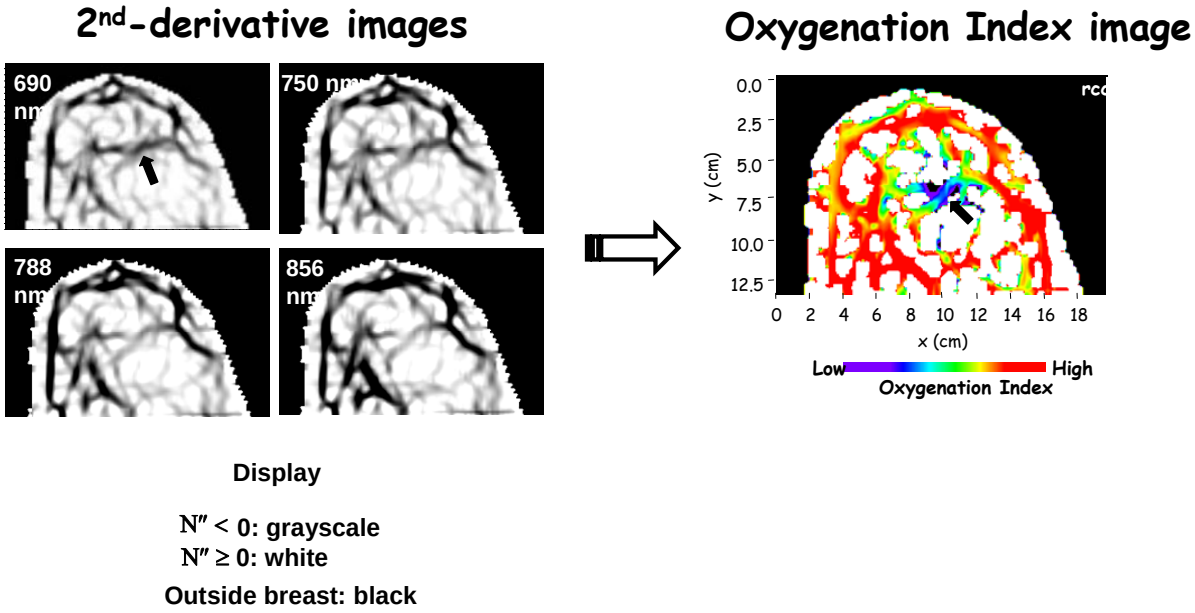


Fig.4. Second-derivative and oxygenation-index images of the right breast of a 74-year old patient. The arrow indicates the position of a 2.5cm invasive ductal carcinoma. (Patient number 184, cranio-caudal (rcc) view.)

Optical oximetry based on continuous broadband spectroscopy

The qualitative oxygenation information shown in Fig. 4 may be enhanced by performing spectral imaging, so that each pixel is associated with a broadband continuous spectrum. The mechanical scanning platform was originally designed and built by Siemens Medical Engineering, Erlangen, Germany, as part of a prototype for frequency-domain (FD) optical mammography. We later incorporated the continuous-wave (CW) domain capability to this scanning scheme, allowing for a full 650~900 nm spectrum acquisition. The acquisition time is in the order of 1-2 min per scan, depending on breast size. The block diagram of the instrument for spectral imaging of the human breast is showm in Fig. 5. This instrument allows for breast imaging with a spatial sampling rate of one point every 2 mm along *x* and *y*, a spectral sampling rate of one point every 0.5 nm, and a temporal sampling of one point every 57 ms (Yu *et al.*, 2009). We have recently proposed a method of paired-wavelength spectral analysis to measure the oxygen saturation of tissue inhomogeneities such as tumors or blood vessels (Liu *et al.*, 2007). By applying this method, we can generate quantitative oxygenation images such as the one in Fig. 6.

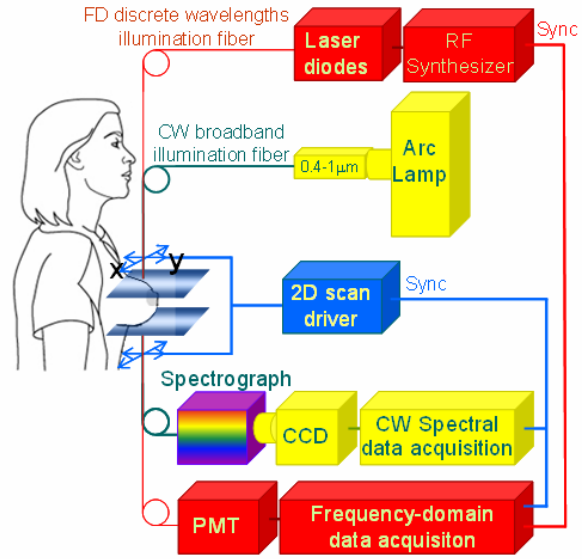


Figure 5. Instrument for hybrid frequency-domain/continuous-wave spectral imaging of the female breast.

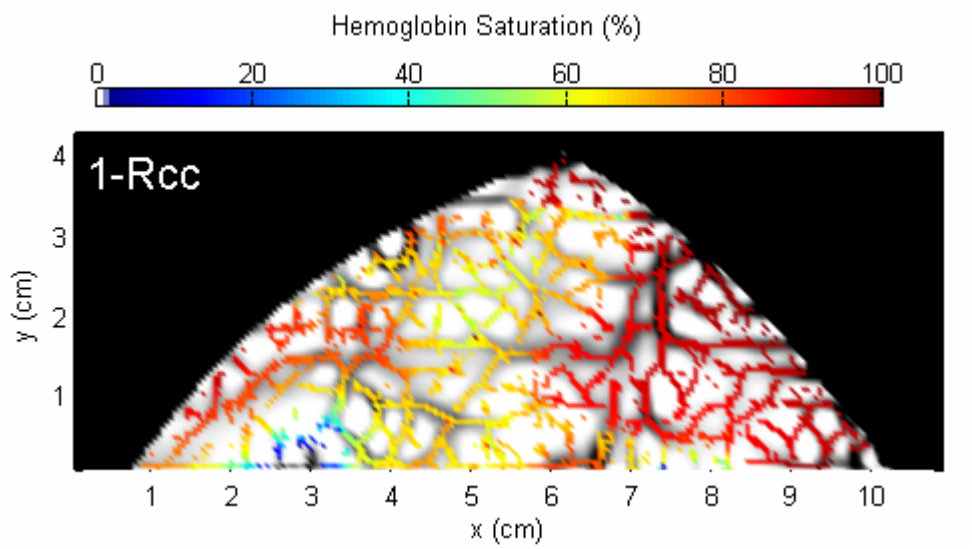


Figure 6. Quantitative oxygenation map for a healthy breast. The majority of values for hemoglobin saturation are between 60% and 95%, which are physiologically reasonable as they are within the range of venous-arterial saturation.

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