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REVIEWS

Near-Infrared Hand-Held Optical Imaging Technology

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Abstract | Diffuse optical imaging is an emerging technology in the field of non-invasive breast cancer imaging and functional brain mapping. A review of the various imagers developed to date for breast cancer is described. These imagers can be broadly classified into bed-based, parallel plate, and hand-held. With hand-held optical imagers, work to date has been focused on 2D reflectance-based spectroscopic imaging of breast tumors. A hand-held optical imager capable of reflectance and transillumination imaging has been developed at the Optical Imaging Laboratory to allow deep target detection. Experiments have been performed on tissue phantoms that demonstrated detection of 5 cm deep targets via transillumination imaging, compared to 2.5 cm deep targets via reflectance imaging. Multiple targets were resolved from 2D experimental studies, when placed 1.5 cm apart even at target depths of 2 cm. Preliminary in vivo studies on breast tissues demonstrated that pressure placed a significant role in detecting the target regions during 2D reflectance imaging studies. The ongoing research efforts focus on demonstrating the 3D tomographic imaging capability of the hand-held imager for volumetric tumor localization in any breast volume and curvature.

Keywords: *diffuse optical imaging, hand-held probe, breast cancer, near-infrared imaging, resolution, reflectance, transillumination, in vivo imaging.*

1 Background of Diffuse Optical Imaging

Wavelengths in the electromagnetic spectrum from 300–1300 nm are classified as optical wavelengths. The energy found in these wavelengths is <10 electron volts (eV) making optical wavelengths non-ionizing. Within this optical range is the *therapeutic window* (within the near infrared region) which is found from around 700–900 nm.[1] Wavelengths of light from 700–900 nm are minimally absorbed and preferentially scattered upon interaction with tissue allowing for deeper light penetration than possible at other optical wavelengths (Figure 1). The technology that uses light in this near-infrared wavelength region to non-invasively image deep tissues is called as near-infrared optical imaging (or diffuse optical imaging). The low absorption occurs due to the main absorbers in physiological tissue i.e. water, oxy- and deoxy-hemoglobin, which absorb less light than at other optical wavelengths.[2]

Deeper tissue penetration allows optical imaging to be implemented as an imaging technology for breast cancer diagnosis and prognosis. Table 1 compares optical with respect to other clinical imaging modalities in terms of the physics of the imaging approach, their resolution, radiation exposure, contrast, and portability. The table displays that some imaging modalities with the exception of MRI, optical and ultrasound expose the subject to ionizing radiation in order to generate an image. The resolution of the modalities displayed in the table range from poor (e.g. nuclear, ultrasound) to excellent (e.g. MRI) while providing different types of information. Nuclear, MRI (contrast aided) and optical can provide functional (metabolism and blood flow) information while the rest of the modalities provide structural

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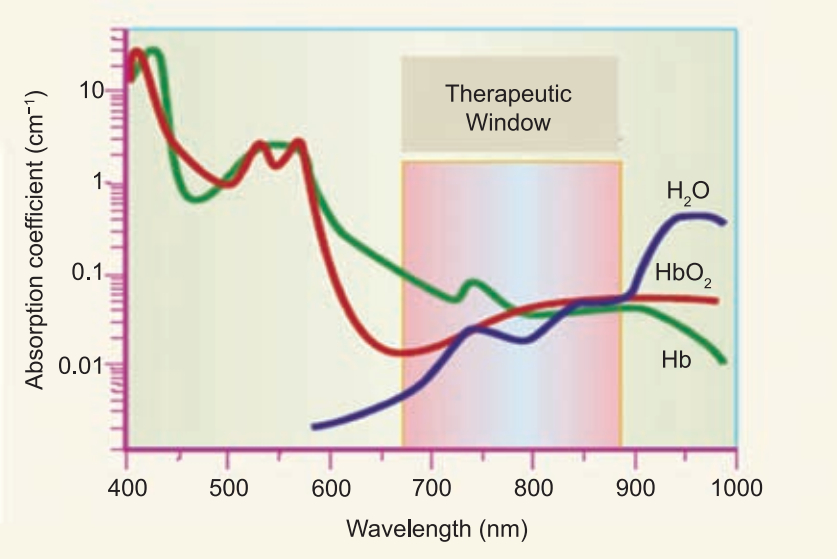

Figure 1: Spectrum of absorption from 200–5000 nm. The biological optical Imaging window allows deeper penetration of light from the wavelengths of around 700–900 nm due to minimal absorption by the tissue components, HbO, Hb and H_2O in this wavelength range. Adapted from[3]

Table 1: Advantages and disadvantages of various imaging modalities commonly used for diagnostic imaging applications.[4–6]

Feature	X-Ray	CT	Ultrasound	MRI	Nuclear	Optical
Radiation	Ionizing	Ionizing	Non-Ionizing	Non-Ionizing	Ionizing	Non-Ionizing
Resolution	Good ~ mm	Good ~ mm	Poor ~ cm	Excellent < mm	Poor ~ cm	< mm – cm depending on depth
Contrast	Poor	Poor	Poor	Good	Good	Good
Portability	Portable	Not Portable	Portable	Not Portable	Not Portable	Portable
Expense	~>$10,000	~>$100,000	~>$15,000	~>$1,000,000	~>$1,000,000	Investigational device ~>$30,000
Information	Structural	Structural	Structural	Structural	Functional	Functional
Imaging time	Fast (~less than 1 min)	Fast (~less than 1 min)	Fast (~less than 1 min)	Slow (~over 20 min)	Slow (~over 20 min)	Fast (~less than 1 min)
Physics	High energy x-rays travel in a straight path and are attenuated by interaction with tissue	3D arrays of x-rays travel in a straight path and are attenuated by interaction with tissue	Acoustic waves (mechanical) are introduced into the body and are reflected back towards a receiver	RF signal is used to align water molecules to a changing magnetic field where the resultant RF signal is collected	High energy radioactive isotopes create gamma rays that travel in a straight line towards detectors	Optical light is introduced into a tissue and is reflectance and absorbed by tissue interactions

information (location of hard and soft tissue). The time to acquire one image is also different across the different modalities, with optical, ultrasound and standard x-ray/CT requiring substantially less time than the MRI or nuclear. The imaging devices' price ranges are quite wide with optical and ultrasound generally being less expensive than MRI, and nuclear.

Optical imaging provides a functional imaging approach with decent spatial resolution and contrast. Optical imaging also requires less imaging time compared to MRI, and is also less expensive. The combination of benefits offered by optical imaging in terms of imaging time, spatial and temporal resolution, contrast, and cost suggest that optical imaging is potentially an emerging

technology for future clinical applications in the areas of cancer imaging, brain mapping, and any non-invasive body tissue imaging. Additionally, the source powers employed during optical imaging are within the safe limits (typically <50 mW).

1.1 *Contrast-enhanced vs. no contrast diffuse optical imaging*

Optical imaging can be performed with or without contrast enhancement. Non-contrast enhanced optical imaging (or diffuse optical imaging) depends on the endogenous optical contrast originating from increased protein (mainly hemoglobin), water or lipid concentration of diseased tissue during angiogenesis. Hence its application is limited in detecting small target or early-stage breast cancer as the inherent absorption contrast between normal and diseases tissues is not significant in deep or small tumors. Exogenous contrast can be introduced into biological tissue for fluorescence enhanced optical imaging. In fluorescence-enhanced optical imaging, a fluorescence contrast agent is injected, and may accumulate at the tumor site (based on its specificity). Upon launching NIR light onto the tissue surface, the light propagates through the tissue and encounters the fluorescence molecules. The fluorescence molecules excite and emit higher wavelength fluorescence signals that are unique signatures from the accumulated site; thus allowing enhanced optical contrast in deep as well as small tumor regions.

1.2 *Reflectance vs. transillumination imaging*

Optical imaging requires a light source to be launched onto the tissue surface. As the light propagates, it undergoes interactions (either with exogenous or endogenous contrast) until it is collected at the same or opposite tissue surface using appropriate detectors. The three most commonly employed imaging methods are (a) projection-shadow, (b) circular imaging geometry and (c) sub-surface imaging as seen on Figure 2.[7] Projection-shadow acquires transilluminated optical signals, whereas sub-surface imaging acquires reflected optical signals during imaging. On the contrary, the circular imaging geometry acquires both reflectance and transillumination optical signals during imaging.

Reflectance imaging (Figure 3) captures photons that have been scattered into the plane that the light was initially launched. Reflectance imaging allows for a single imaging surface in which both the source and detector are on the same imaging plane. Since the NIR light propagates through the entire depth of the tissue before it is detected, these signals bring in greater information from deep tissues, thus allowing deep target detections (as demonstrated in Section 3.1).

Transillumination imaging is when light is launched and propagates through the entire depth of the tissue, and is collected on the opposite side from where it was launched (Figure 4); that is, source and detector are on the opposite sides of the imaging geometry.

1.3 *Optical imagers*

Optical imagers developed to date (for breast imaging) can be broadly classified into three categories hand-held, bed-based and parallel plate (as shown in Figure 5). The classification is based on the implementation of these imagers on human subjects. The hand-held imagers[8–48] are capable of only reflectance imaging, while parallel plate[49–55] and bed-based imagers[56–66] are capable of transillumination and reflectance imaging (see Table 2).

Hand-held imagers are generally smaller, less expensive, portable devices which have the benefit of being placed easily by a technician. The small device ensures that all breast shapes and sizes can be imaged with minimal patient discomfort and lack

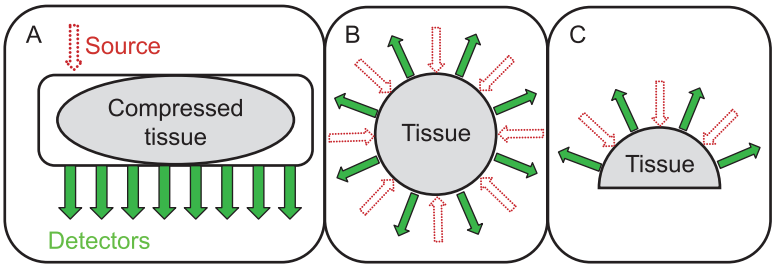

Figure 2: The three methods of applying optical imaging are (A) shadow projection (compressed transillumination), (B) circular imaging geometry (uncompressed reflectance and transillumination) and (C) sub-surface (reflectance). The red arrows represent point or area source illumination and the green arrows represent the light collected by the point or area detector after interacting with the tissue. Reproduced from[7]

of tissue compression. In addition, the hand-held imagers are typically limited to reflectance imaging, and depend on technician placement (possible source of imaging error) without additional tracking equipment. From Table 2, it can be seen that hand-held imagers are the most commonly developed optical devices in recent years. The reduced cost and enhanced placement ease has yielded a wide variety of hand-held imagers with varying source-detector configurations, wavelengths, and secondary modalities.[8,9] Most of the devices (hand-held) are used for spectroscopic measurements of tissue optical properties in order to detect the presence of abnormal tissue (2D spectroscopy). Spectroscopic devices employ multiple wavelengths (690, 830 nm used predominantly) from various illumination sources to obtain tissue properties such as the concentration of oxy and deoxy hemoglobin. Importantly spectroscopic hand-held optical imagers have been able to detect tumors (from relevant changes in optical properties) up to ~4 cm away, even though spectroscopic imagers are limited to reflectance only.[8,9]

Bed-based imagers[56–66] are a category of imagers which require a subject to lie down and suspend the breast tissue to be imaged in special imaging bins or enclosures, which facilitate data collection and 3D tomographic imaging. Sources (e.g. laser diodes) of various wavelengths are employed with higher illumination powers and quantification of oxygenation. Unfortunately the bins also cause exclusion of some patient populations such as patients whose breast may be larger than the bins (in a small percentage of overall population).

Parallel plate imagers[49–55] are similar to bed-based imagers, but instead of relying on circular bins they implement compressive plates similar to x-ray mammography systems. This reduces the exclusion of subjects by reducing their tissue thickness via compression. Similar to bed-based and hand-held imagers, these imagers can also be fitted with a wide variety of sources to quantify oxygenation and provide sufficient illumination.

A wide degree of variability exists within and across imagers even within their own respective geometry. Each optical imager variant has associated benefits and can be further optimized with source and detector choices for diagnosis, prognosis and monitoring of tissue. The most common illumination technologies are laser diodes and light emitting diodes (LED) chosen with regards to illumination power, stability and wavelength. The common detection technologies include avalanche photodiodes, charge coupled devices, and photomultiplier tubes.

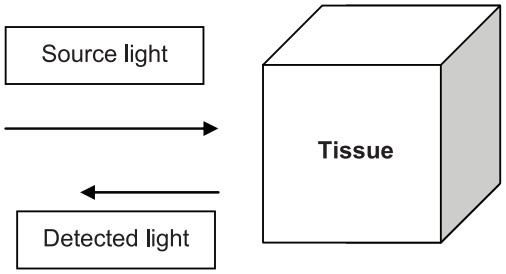

Figure 3: Reflectance imaging is when light is launched and collected from the same side.

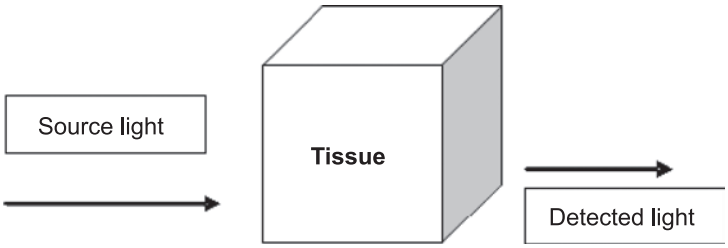

Figure 4: Transillumination is when light is launched and collected on different surface (example: opposite surface).

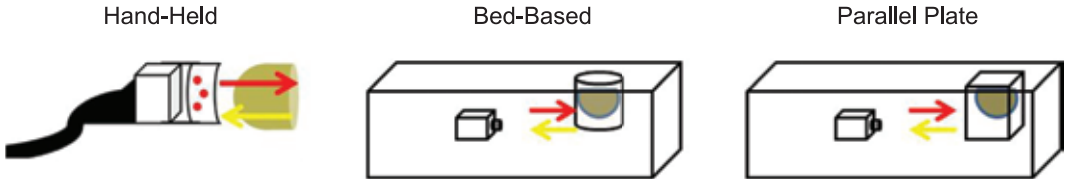

Figure 5: Different types of optical imagers developed towards breast cancer imaging.

Table 2: Condensed literature of optical imagers developed by various research groups, classified as hand-held, parallel plate, and bed-based images.[8–66]

No.	Reference	Modality	Meas. technique	Source type	Detector type	Clinical application(s)
Hand-Held						
1	Tromberg, 1997	DOI	FD (300 kHz–1 GHz)	diode lasers (10–30 mW)	APD	Compare optical properties of normal and benign lesion-containing breast tissue.
2	No, 2005	DOI	FD (10 MHz–1 GHz)	8 laser diodes (50 mW)	APD	Non-invasive breast cancer detectors based on frequency-domain photon migration.
3	Chance, 2005	DOI	CW	light emitting diodes (10–15 mA)	silicon diode detector	Determine sensitivity and specificity of detecting breast cancer in 116 human subjects.
4	Chance, 2006	DOI	FD (3 kHz)	2 light emitting diodes (20 mA)	silicon diode detector	Detection and 2D localization of brest cancer lesion in a human subject.
5	Liu, 2004	FDOI	FD (3 kHz)	4 light emitting diodes	PMT	2D phased array fluorescence wireless localizer in breast cancer detection.
6	Cheng, 2003	DOI	CW	laser diodes (0.15 W/cm^2)	PMT	Determine sensitivity and specificity of detecting breast cancer in 50 human subjects.
7	Durduran, 2005	DOI	CW	long coherence laser	APD	Measure blood flow contrast between tumor-containing and normal breast tissues.
8	Zhu, 1999	DOT & US	FD (200 MHz)	laser diodes	APD	Phantom study towards 3D tomography of breast cancer.
9	Ge, 2008	FDOT	FD (100 MHz)	laser diode (<5 mW)	CCD	Phantom towards 3D tomography of breast cancer.
10	Solomon, 2010	FDOT	CW	laser diodes (15–30 mW)	CCD	Phantom & small animal study towards sentinel lymph node mapping.
11	Xu,1 2007	DOI	CW	Laser diode	PMT	Real-time monitoring of tissue physiologic changes in response to dynamic compression stimuli.
Parallel Plate						
1	Culver, 2003	DOI	FD	Laser diodes	CCD	Compare optical properties of normal and cancerous lesions on breast tissue.
2	Carp, 2006	FDOI/ Pressure	FD	Laser diodes	RF spectrometer/ APD	Compression induced changes in breast tissue.
3	Fang, 2009	DOT & X-ray	FD, CW	diode lasers	APD	Combination of optical and x-ray mammographic systems.
Bed-Based						
1	Ntziachristos, 2002	DOI & MRI	FD	Laser diode	PMT	MRI guided spectroscopy of breast tissue.
2	Floery, 2005	DOT	CW/FD	Laser diode	PMT	Characterization of benign and malignant breast tissue.
3	Schmitz, 2005	DOT	FD	Laser diode	silicon diode detector	Dynamic near-infrared optical tomographic measurement instrumentation capable of simultaneous bilateral breast imaging.

(*Continued*)

Table 2: Continued.

No.	Reference	Modality	Meas. technique	Source type	Detector type	Clinical application(s)
Bed-Based						
4	Colek, 1999	DOT	CW	Laser diode	pin photo diode	Optical tomography system for breast cancer detection.
5	Pouge, 1997	DOT	FD	diode laser	PMT	Automated frequency-domain computed tomography scanner towardsbreast cancer detection
6	Godavarty, 2002	DOT	CW/FD	Laser diode	CCD	Optical imaging device for breast cancer detection.
7	Yates	DOI	Time Domain	Laser diode	PMT	A time-resolved optical tomography system has been used to generate cross-sectional images of the human breast.
8	Al Abdi, 2011	DOT	CW/FD	Laser diode	PMT	Breast imaging based on the interaction between controlled applied mechanical force and tissue hemodynamics.

2 Hand-Held Optical Imagers at Optical Imaging Laboratory (Gen-1 vs. Gen-2)

In recent years, hand-held optical imagers have been developed in an attempt to translate the technology to the clinic, with maximum patient comfort and portability (against bulky bed-based and parallel plate based imagers, see Table 2). The majority of hand-held optical imagers available to date have only flat probe heads (Table 2), which limit them from: (i) Contouring to tissue curvatures with good surface contact; and (ii) Obtaining depth information, due to lack of transillumination measurements (since they obtain only reflectance measurements). In addition, the hand-held imagers have not demonstrated 3D optical tomography (with or without fluorescence), and their application has been limited to in vivo spectroscopic measurements of physiological properties and 2D target localization (without tomographic analysis).

Recently, a (generation-1 or Gen-1) novel hand-held probe based optical imager was developed in our Optical Imaging Laboratory, which overcame most of the limitations of the hand-held imagers. The Gen-1 hand-held optical imager (as shown in Figure 6a) was designed with various enhancements (i.e. 3D tomographic imaging, imaging tissue contours) offered by bed-based and/or parallel plate systems, but not found in other hand-held imagers (Table 3).

The feasibility of Gen-1 imager for 2D surface mapping and 3D tomographic imaging has been demonstrated on cubical tissue phantoms[42] as well as in vivo on human subjects.[43] While the Gen-1 imager offered features not found in other hand-held imagers it was not only bulky and uncomfortable to patients, but was also challenging to employ for in vivo clinical applications because it was limited by non-homogenous source illumination resulting in multiple artifacts and poor target detection. Hence, a generation-2

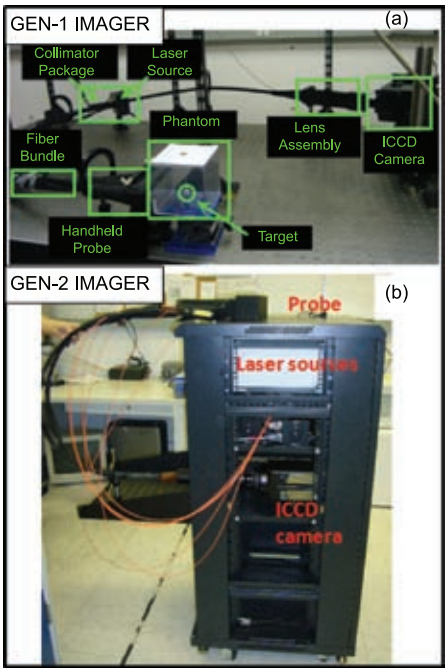

Figure 6: (a) Gen-1 bench top hand-held optical imager with a single probe head, (b) Gen-2 portable hand-held optical imager with two probe heads. First Generation hand-held optical imaging system, with the (a) flexible 3-part hand-held probe, and (b) the imaging system set-up as a bench-top unit. Reproduced from[40,44]

Table 3: Comparison of hand-held optical devices developed by other researchers to the Gen-1 imager developed at Optical Imaging Laboratory.

Other hand-held imagers	Gen-1 hand-held optical imager
Fixed probe heads, collecting only reflectance signal	Flexible probe head allowing for collection of reflectance and transillumination signal
Focused toward 2-D Spectroscopic imaging (Fewer than 20 detectors)	Focused towards 2-D and 3-D imaging (165 optical detection fibers, 3-D tomography without the need of another modality)
No collection of spacial position for the imaging performed	Paired with a 3-D spacial tracker to allow for 3-D corregistration

Table 4: Comparison of Gen-1 and Gen-2 hand-held optical imagers developed at Optical Imaging Laboratory.

Gen-1 hand-held optical imager	Gen-2 hand-held optical imager
Flexible but rigid probe face (~30% contact with a 13 inch diameter cylinder)	Multiplate, probe face design (~86% contact with a 13 inch diameter cylinder)
Single probe head (limited transillumination signal collection)	Dual probe heads (facilitates transillumination/ parallel plate imaging)
Aluminum probe face (cold when placed on subjects adding unecessary discomfort)	Plastic probe face (retains the proper fiber adhesion surface and removes unecessary discomfort)
Single laser light source split into 6 points (resulted in different intensity at each point 1.02 ± 0.937 mW)	Six independently tunable laser light sources allowing for greater homogenity in tissue surface illumination. (2.09 ± 0.06 mW)

(Gen-2) hand-held imager was developed to overcome the limitations of the Gen-1 imager.[47,48]

Table 4 shows the limitations of the Gen-1 hand-held optical imager and how they were addressed in the Gen-2 imager (shown in Figure 6b). The Gen-2 imager has dual probe heads that allows reflectance of both breast tissues simultaneously as well as transillumination imaging of a single breast tissue. The Gen-2's source system was altered from the Gen-1's source system to allow homogeneous source illumination from multiple points (either sequentially or simultaneously). This allowed better target detectability, as described in the following section:

2.1 *Target detectability using Gen-1 vs. Gen-2 optical imager*

The Gen-1 and Gen-2 imagers were compared in a phantom study employing a $10 \times 10 \times 10$ cm^3 acrylic phantom filled with a 1% liposyn solution (with absorption coefficient, μ_a = 0.1 cm^{-1} and reduced scattering coefficient, μ_s' = ~2.52 cm^{-1}, respectively).[44] A 0.45 cc spherical target filled with a 0.08% by volume India ink in 1% Liposyn solution was used to provide an absorption-based optical contrast. The optical properties of India ink solution was μ_a ~ 0.07 cm^{-1}, while finding the μ_s' was reported by past researchers to range between 4–20 cm^{-1}. The experiments were performed in the continuous-wave (CW) imaging mode where 785 nm light was launched simultaenously from multiple point sources, and all the detection points (placed 0.5 cm apart over a 4×5 cm^2 area) were detected simultaneously using an intensified CCD (ICCD) camera. A subtraction-based data processing technique[42,43] was employed to the detected intensity, in order to better differentiate the target(s) from the background. Figure 7 depicts the 2D surface plots of the detected

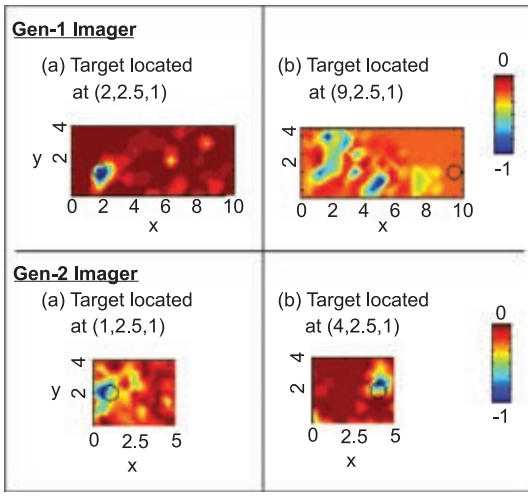

Figure 7: Two-dimensional surface contour plots of the detected NIR light intensity, using the Gen-1 and Gen-2 hand-held probes placed on tissue phantoms filled with 1% Liposyn solution and containing a single absorption-based target. The single target was located at the respective locations, as shown in each plot as black hollow circle (along with its x,y location). The blue region in each plot represents the regions of increased absorption, relating to the target location. Note that the Gen-1 and Gen-2 probe sizes are different, and hence the 2D plots are of different dimensions.

intensity (post subtraction technique) obtained using the Gen-1 and Gen-2 imagers containing targets at various [x,y] locations and similar depth (1 cm). The results indicate that the Gen-2 imager could detect targets (within 0.54 ± 0.08 cm from its true location). The Gen-1 imager was capable of detecting the targets (in one case within 0.5 cm from its true location and the other is 3.4 ± 2.8 cm away). It is also evident from Figure 7 that the Gen-2 imager was able to detect the target(s) but the Gen-1 imager was not able to detect the target placed on the right portion of the probe due to insufficient illumination intensity. Insufficient illumination in the Gen-1 hand-held optical imager results in target-like artifacts in the resultant image. The inconsistency in detecting targets using the Gen-1 imager is primarily from the non-homogeneous source illumination strengths, unlike in Gen-2 imager that has overcome this limitation.[47]

3 Tissue Phantom and In Vivo Studies Using Gen-2 Hand-Held Optical Imager

Various experimental studies were performed to assess the capabilities of the Gen-2 optical imager during actual breast imaging studies. These studies include the assessment of target depth detectability via reflectance and transillumination modes of imaging, determining the resolution of the imager from 2D imaging studies, and preliminary in vivo breast imaging capabilities.

3.1 *Experimental study 1: Reflectance and transillumination studies on tissue phantoms*

An experimental study with the Gen-2 hand-held imager was focused on demonstrating the reflectance and transillumination capability of the imager with regards to maximum localization depth of an absorption based India ink target. A cubical $10 \times 10 \times 10$ cm^3 acrylic container was filled with 3% Liposyn (with $\mu_a = 0.09$ cm^{-1} and $\mu_s' = 9.5$ cm^{-1}). Experiments were performed using 3 different target concentrations (0.008%, 0.08% and 0.8% by volume of India Ink) at four different Target:Background (T:B) ratios (1:0, 1000:1, 100:1, and 10:1). Imaging was performed on the phantoms with and without the target(s) (placed inside the phantom) and the two resulting images were subtracted and further processed via a polynomial fitting technique (described in detail in).[48] Figures 8 and 9 depict the results for these experimental studies as 2D surface contour plots of the (subtracted) detected intensity of reflectance and transmission measurements, respectively. During reflectance imaging, targets up to 2.5 cm deep were localized as observed from these 2D surface images. During transillumination

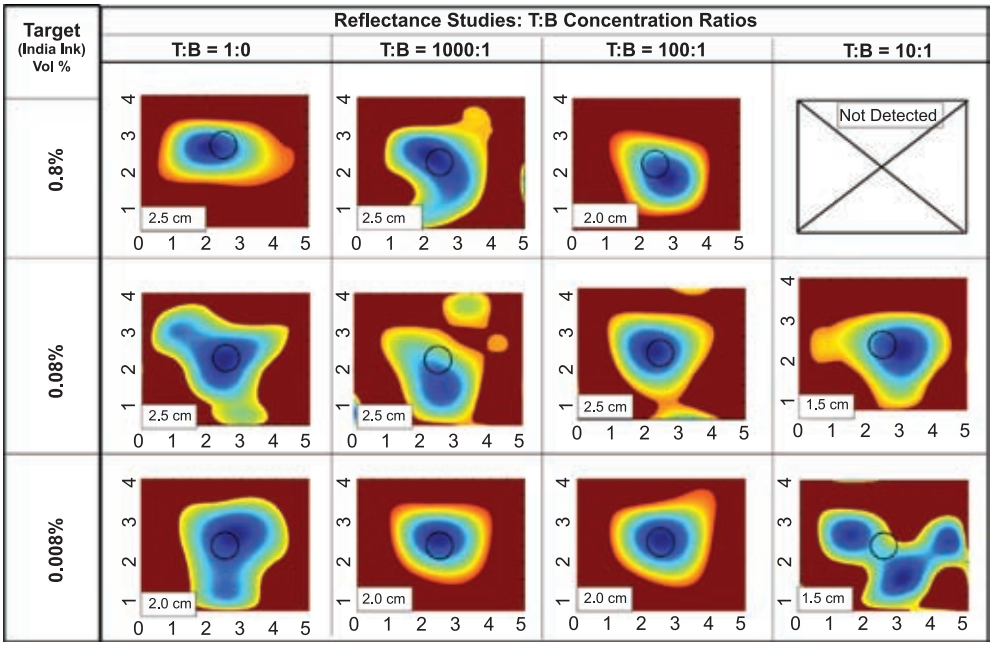

Figure 8: Two-dimensional surface contour plots of detected reflected intensity obtained using varying T:B absorption contrast ratios of 1:0, 1000:1, 100:1, and 10:1 in $10 \times 10 \times 10$ cm^3 cubical phantoms containing India Ink absorption targets (0.46 cc volume). Experiments were performed using varying India Ink concentrations in the target (e.g. 0.008%, 0.08% and 0.08%). The results shown are the maximum depths (shown in each plot) at which the target was detected for the particular experimental case. The black hollow circles represent the true target location.

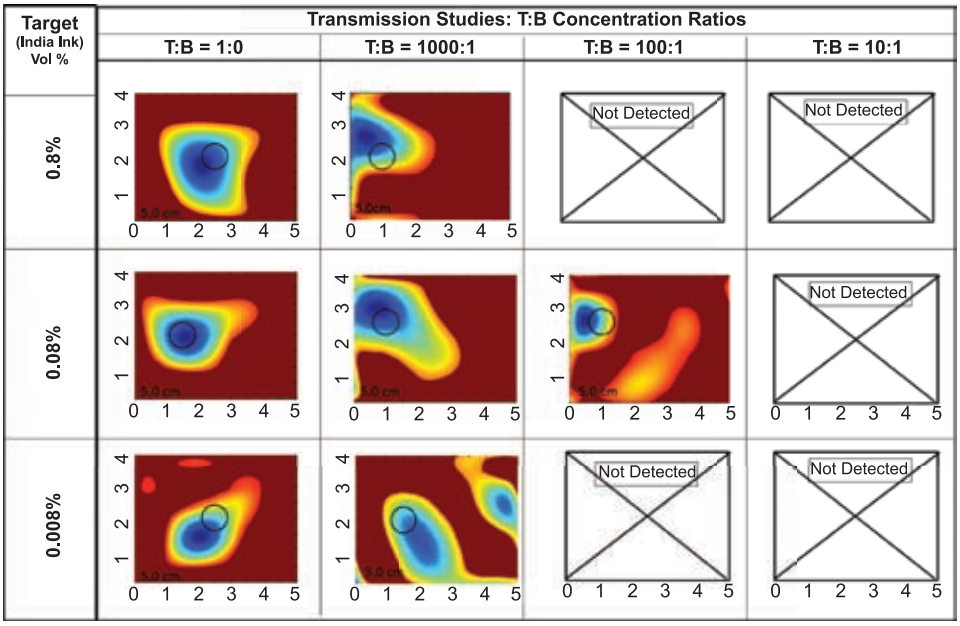

Figure 9: Two-dimensional surface contour plots of detected transmitted (or transilluminated) intensity obtained using varying T:B absorption contrast ratios of 1:0, 1000:1, 100:1, and 10:1 in 10 × 10 × 10 cm^3 cubical phantoms containing India Ink absorption targets (0.46 cc volume). Experiments were performed using varying India Ink concentrations in the target (e.g. 0.008%, 0.08% and 0.08%). The results show are the maximum depths (shown in each plot) at which the target was detected for the particular experimental case. The black hollow circles represent the true target location.

imaging, targets up to 5 cm deep were localized. It can be observed from these experimental cases that transillumination provides a greater target depth recovery than reflectance imaging. It was also observed that transilluminated signals get weaker when the target is further away from the detected surface (in other words closer to the illumination surface), especially as T:B contrast ratio reduces. The flexibility of Gen-2 hand-held optical imager to perform both reflectance and transillumination imaging is an advantage. For instance, a target closer to a surface can be detected by reflectance even at lower T:B contrast ratios, at places where transillumination can be limited by tissue volume or depth.

3.2 *Experimental study II: Resolution studies in tissue phantoms*

Resolution studies were performed in order to test the feasibility of the system to resolve two closely placed targets. The experiments were carried out using clear acrylic cubical phantoms (10 × 10 × 10 cm^3) filled with 1% Intralipid. Two spherical targets of 0.46 cc in volume (i.e. 0.96 cm diameter), filled with 1 μM Indocyanine green dye (ICG fluorescing contrast agent) in 1% Intralipid were employed. ICG targets were imaged under fluorescence conditions at different target separations (0.5 to 4 cm) and targets depth (0.5 to 2.5 cm). The images were obtained under perfect uptake T:B fluorescence contrast ratio (1:0) conditions.

Figure 10 shows the 2D contour plots of the optical intensity data obtained when placing the targets at a separation of 1.5 cm (measured as distance between centroids) at different depths. The dotted line plot (superimposed in the figure) is detected intensity distribution along the x-axis at the chosen y-axis. This y-axis point is chosen based on detection point with the maximum intensity in the imaged area. As it can be seen the line plots show two different peaks which are at a distance of approximate 1.5 cm which corresponds to the target separation. This confirms that the signals seen in red are due to the target fluorescence characteristics. These results demonstrate that the hand-held probe based imager has the capability of differentiating between two targets.

3.3 *Experimental study III: In vivo breast imaging and effect of pressure*

A single healthy human volunteer over the age of 21 was recruited (ages 20–35) in accordance with the university IRB protocol. The experimental study performed observed the optical changes in the breast tissue at 785 nm, with varying tissue pressures.

A 0.45 cc absorption target (0.8% by volume India Ink) was placed in the intra-mammary fold

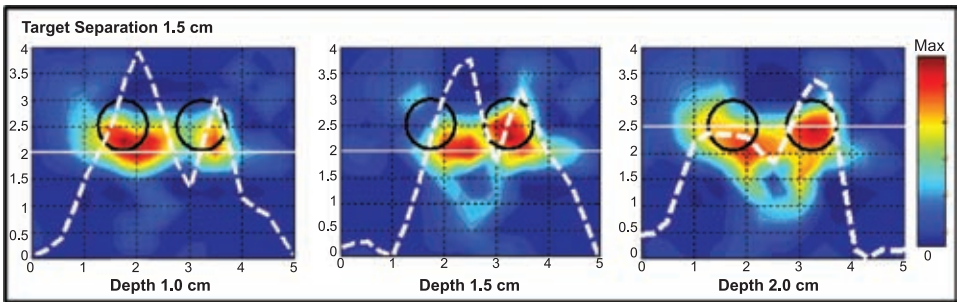

Figure 10: Two-dimensional surface contour plots of detected reflected intensity of two targets (0.46 cc volume each) placed inside 10 × 10 × 10 cm^3 cubical phantoms with T:B = 1:0. The two targets were placed with a separation of 1.5 cm (centroid to centroid) at different depths. The black circles show the true target location. The white dashed line represents the intensity distribution along the x-axis at the maximum intensity location along y-axis.

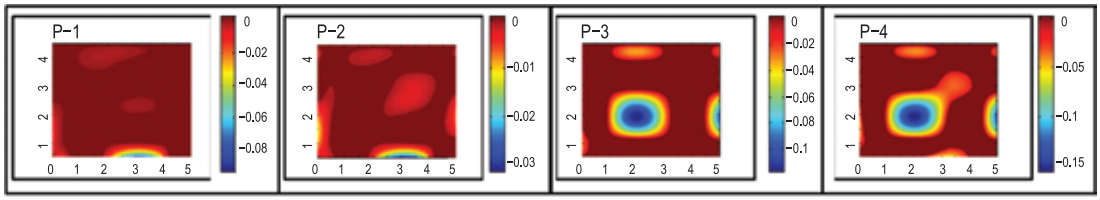

Figure 11: 2D surface contour plots of the effects of pressure on artifact generation. A single healthy human subject with a 0.45 cc absorption target (.08% by volume India Ink) placed in the infra-mammary fold of the left breast was asked to apply an incremental pressure for a series of 4 images. The pressure ranged from comfortable (P-1), slight (P-2), noticeable (P-3), and uncomfortable (P-4) which were left up to the patient's interpretation.

of the left breast (at 6'0 clock position). The subject was asked to place and hold one of the imaging probes on the left breast (target) and instructed to apply varying pressures labeled as comfortable, slight, noticeable and uncomfortable. One image was also acquired without the target and served as the background image. The images were then subtracted sequentially as P1 (Background-comfortable), P2 (comfortable-slight), P3 (slight-noticeable) and P4 (noticeable-uncomfortable) (Figure 11).

Imaging revealed a strong correlation between contact pressure and artifact generation/target detection. The effect is due to compression of the internal vasculature of the breast resulting in potential accumulation and drainage of blood between target and background images. Differential pressure between target and background images were investigated in Figure 11, which shows the 2D surface contour plots of the subtracted data after processing. The progression from P-1 to P-4 shows an increase in the difference (increase in absorption) between the target and background images (values of the color bar). An increase in absorption suggests that less light is returning to the surface, which is likely to be due to the pressure occluding the vasculature of the breast causing accumulation of blood in the tissue, thus resulting in a potentially successful localizing. In future, systematic studies would be carried out by measuring the pressure applied and the minimum/maximum pressure ranges at which target is always detectable.

4 Future Direction and Conclusion

Diffuse optical imaging has immense potential as a non-invasive and non-radiative diagnostic imaging tool in the area of breast cancer imaging. The modality can complement the x-ray and ultrasound anatomical images, with functional or physiological information that vary in the abnormal tissue regions at the early onset of the disease. With an effort to translate the technology to the clinic, many researchers have developed portable hand-held optical imagers in the past decade. While most of these devices are appropriate for 2D spectroscopic imaging and neo-adjuvant chemotherapy monitoring of breast tumors, there is also a need for 3D tomographic imaging capabilities of the device. As of date, only bed-based and parallel-plate imagers have demonstrated 3D tomographic imaging. In our Optical Imaging Laboratory, two generations of hand-held optical imagers have been developed with capabilities for

3D tomographic imaging along any breast curvature and volume. Three-dimensional tomographic imaging was made possible in Gen-1 imager, via implementing a novel approach to obtain 3D positional information of the hand-held probe during imaging. This allows coregistering of the optical measurements with respect to their imaged location, thus allowing 3D tomographic imaging using appropriate image reconstruction algorithms. In addition, the ability to track the 3D position of the hand-held probe during imaging allows for operator independent imaging (unlike in ultrasound based approach). With the development of the Gen-2 imager that has additional features of imaging in both the reflectance and transillumination modes (using the dual probe heads), there is greater potential in detecting deeper tumors in vivo. The ongoing studies at our Optical Imaging Laboratory are focused on extensive in vivo breast cancer imaging studies using the Gen-2 imager in both the reflectance and transillumination modes. In parallel, accurate coregistration (and 3D positional tracking) approaches are developed towards 3D tomographic analyses of breast tissues towards clinical translation of the technology.

From a commercialization perspective, hand-held optical imagers are preferred because of the ease with which they can image any breast tissue or volume and the surrounding chest wall regions. Upon adding multi-wavelengths to the hand-held imagers (as done by few research groups), their capabilities to map the blood oxygenation levels, water can be effective in better differentiating benign *vs.* malignant tumors. For the optical imagers to compete with the structural imaging modalities (e.g. x-ray, CT, MRI), it is essential that their resolution is in the same range (mm). However, the diffuse nature of the optical signals limits its resolution during deep tissue imaging. With improved reconstruction algorithms, improved instrument sensitivity and use of tumor-specific contrast agents, there is potential for the technology to have greater spatial resolution and eventually high specificity and sensitivity (over 90%). Improvement in reconstruction algorithms can be computational intense if 3D tomographic imaging is required. Improvement in instrument sensitivity can increase the dynamic range of the detection system, but at the expensive of the imager. Use of tumor-specific contrast agents may be appropriate for animal imaging, but would require FDA approval prior to their clinical application in vivo breast tissues. Optical imaging has an added advantage of imaging in msec range (for each image), thus making it reasonable in a clinical environment, where the entire imaging may be completed in a few minutes. The imaging time may increase if time-dependent measurements are acquired over time-independent continuous-wave measurements. With increasing network for translational research efforts performed by different research groups, the diffuse optical imaging technology has potential for clinical breast imaging in the near future.

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