Optical mammography: Diffuse optical imaging of breast cancer

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Abstract
Existing imaging modalities for breast cancer screening, diagnosis and therapy monitoring, namely X-ray mammography and magnetic resonance imaging, have been proven to have limitations. Diffuse optical imaging is a set of non-invasive imaging modalities that use near-infrared light, which can be an alternative, if not replacement, to those existing modalities. This review covers the background knowledge, recent clinical outcome, and future outlook of this newly emerging medical imaging modality.

INTRODUCTION
All women who reach a certain age are recommended to undergo annual breast cancer screening, although policies vary according to the country. The modality of choice for screening is mostly X-ray mammography. However, many clinical studies have cast doubt on its use. For women under 40 years of age, X-ray mammography is known to be ineffective because of the high radiographic density of young breasts. Also, the dose of radioactivity that the patient receives every year for screening could cause cancer, which defeats the purpose of screening. There are other imaging modalities such as ultrasound or magnetic resonance imaging (MRI) that can be used in addition to X-ray mammography, but each of them has its own drawback. Ultrasound has low sensitivity, especially before the tumor becomes hardened, whereas MRI has limited specificity and high cost of operation. Other breast-specific imaging modalities are also being developed, such as breast computed tomography (bCT) and breast positron emission tomography (bPET), but their high cost and instrumental complexity are a hindrance to general use.

Diffuse optical imaging (DOI) is being studied extensively worldwide as a possible alternative to the breast imaging modalities mentioned above. DOI uses a set of optical transmission measurements on various positions on the sample surface, by which one can reconstruct a 3D map of the inner optical properties of the sample, namely absorption and scattering coefficients. Multispectral measurement using multiple wavelengths in the 650-900-nm range makes it possible to convert the optical property maps into the concentration maps of intrinsic absorbers, such as oxy-hemoglobin (HbO₂), deoxy-hemoglobin (Hb), water, and other tissue components.
lipid. Such 3D maps of hemodynamic parameters serve as indicators of malignant tumors, as it is known that tumor position is strongly correlated with total hemoglobin concentration 	extit{a} 	extit{s} via angiogenesis.

In this review, the concept of DOI is introduced, current clinical applications are explained, and its future outlook is presented. A detailed theory of how to model the propagation of photons in highly scattering media and how to reconstruct 3D images out of a finite number of surface measurements is out of the scope of this paper, although a few basic equations and remarks are given in the next section. For a more comprehensive review on DOI with detailed theory, including diffuse correlation spectroscopy (DCS) that measures deep tissue blood flow, see the excellent earlier reviews by Choe et al\textsuperscript{[9]} (breast application only) or Durduran et al\textsuperscript{[10]} (breast, brain and other applications).

**RATIONALE**

**Background theory**

The name DOI comes from the fact that photons propagate through highly scattering media in a diffusive manner, and that we are using the diffusion model for deep tissue imaging. There are many variants in naming conventions: diffuse optical spectroscopy (DOS) or near-infrared spectroscopy (NIRS) is used for a low number of source-detector pairs, and diffuse optical tomography (DOT) is used when actual 3D imaging is attempted and final images are shown in tomographic slices. In this paper, we stick to the general term DOI to represent many variants in the literature.

The photon propagation best resembles diffusion when absorption is much smaller than scattering ($\mu_s \ll \mu_a$), and when source-detector separation is not too close. We can regard the diffusion model for photon propagation as a simplification of a more general radiative transfer equation in a limiting condition\textsuperscript{[11,12]}

The photon diffusion equation, which is the starting point of DOI, is described below:

$$V \cdot \left( D V \Phi (\bar{r}, t) \right) - \nu \mu_s \Phi (\bar{r}, t) + \nu S (\bar{r}, t) = \frac{\partial \Phi (\bar{r}, t)}{\partial t}$$

Here $D$ is the photon diffusion coefficient, $\mu_s$ is the absorption coefficient, $\Phi$ is the photon fluence rate, $\nu$ is the speed of light in the medium, and $S$ is the source term. This equation is identical to the classical diffusion equation except for the presence of an absorption term. Therefore, given the spatial distribution of $D$ and $\mu_s$, one can calculate the fluence rate at all positions with arbitrary precision, given the source and boundary condition. The diffusion coefficient $D$ is related to the reduced scattering coefficient $\mu_s'$ by $D = \nu / 3$ ($\mu_s + \mu_a$), which results in $D \approx \nu / 3 \mu_s$ when absorption is negligible compared to scattering. Note that the reduced scattering coefficient ($\mu_s'$, reciprocal of transport length) is different from the scattering coefficient ($\mu_s$, reciprocal of scattering length), but still represents the magnitude of scattering.

When absorption ($\mu_a$) and scattering ($\mu_s$) is distributed homogeneously, the above equation can be solved analytically for such simple geometries as bulk, half-space, slab, cylinder or even sphere\textsuperscript{[13,14]}. The half-space solution is especially important because many practical DOI probes are accessing the sample from one side, either by a pair of optical fibers or by free-space coupling. When half-space geometry is assumed, the sensitivity volume inside the sample can be calculated by multiplying light fluence rate distribution from the source fiber with the probability distribution of a photon's original position that reaches the detector fiber (Figure 1). The sensitivity volume has a banana-shape pattern, and we can take note of several important features of DOI from this: (1) in half-space geometry, the probing depth of a source-detector pair is roughly one half of the source-detector distance; (2) the sensitivity always peaks right beneath the source and detector fiber; (3) there is a dead volume above the banana shape to which the diffuse optical probe is not sensitive; and (4) measurement from a single source-detector pair can detect the overall change of optical property within the sensitivity volume, but it does not tell us where the change has occurred within that volume. One would need many source-detector pairs whose sensitivity volumes partially overlap within the diffuse medium, in order to attempt finer localization of the optical property change. It suggests there has to be many source-detector pairs to increase the resolving power of DOI.

**Instrumentation**

Although all diffuse optical instruments share a similar look in terms of probe geometry, there are three different categories in which an instrument works, namely continuous wave (CW), frequency domain (FD) and time domain (TD). The types of light source and detector are vastly different across the category. In terms of light source, CW uses continuous wave or low-frequency modulated laser diode or light-emitting diodes, FD uses RF-modulated laser diodes, and TD uses short-duration pulsed laser. Detectors need to be different accordingly, because FD requires either in-phase quadrature (IQ) demodulation or a frequen-
cy-lowering technique (homodyne/heterodyne) for phase-sensitive measurement, and TD requires photon-counting detectors to obtain time-point-spread-function (TPSF). The complexity of instruments increases towards the TD type, but the level of information per source-detector pair also increases accordingly. Therefore, users have to decide on which type of DOI best suits their application.

Some examples of different breast DOI instruments are given in Figure 2. The Yodh group in the University of Pennsylvania has built a series of parallel plate transmission geometry CW + FD instruments that acquire a lot of data using fast CCD[14,15]; the Pogue group from Dartmouth College has developed a three-tier, ring-type, fiber-based FD instrument[16,17], whereas the Tromberg group from University of California, Irvine has developed a hand-held scanning FD DOI device to be used with supine position breasts[18,19]. A Canadian company, ART, has also developed a time-domain transmission DOI device based on scanning fibers and photomultiplier tubes, and clinical trials are underway[20].

**Image reconstruction and artifact issues**

The way visual images are reconstructed from raw optical transmission data in DOI is very different from that of MRI or X-ray CT. As opposed to those established medical imaging modalities where an exact mathematical relationship exists, by which one can transform the measured data into images for visualization, there has been no consensus in the DOI community as to how we should reconstruct diffuse optical images. This is partly because there is no standard instrument specification shared across institutions, but mostly because of the fact that diffuse optical image reconstruction is an optimization problem solving process of an ill-posed and usually under-determined system. In more specific terms, DOI image reconstruction is equivalent to finding out a spatial distribution of variables that minimizes the discrepancy between experimental measurement and calculated fluence rates. The discrepancy can be defined as an objective function written below:

$$\chi^2 = \sum_{s,d} [\Phi_{sd} - \Phi_c(\mu_s(\vec{r}), \mu'_s(\vec{r}))]^2$$

Where subscripts $M$ and $C$ refer to measurement and calculation, respectively, and summation is done over all available source-detector pairs. Detailed forms of the objective function can vary depending on the types of regularization used, the types of weighting used, and also on whether multispectral measurement is used. In order to minimize this objective function, one normally uses iterative methods to update $\mu_s$ and $\mu'_s$ distributions towards the global minimum. Some examples of the reconstructed images are shown in Figure 3, where 3D distribution of absorption coefficients at a single wavelength is reconstructed from a breast-mimicking phantom and a real patient breast with a malignant tumor[21]. The absorption contrasts hidden in a diffuse medium is clearly seen in both cases.

Much effort has been put into developing fast, accurate, and stable optimization algorithms with given constraints from various DOI instruments[22-23], and hence resulted in a plethora of DOI image reconstruction algorithms: linear and non-linear methods, analytical and numerical methods, and line search and trust region methods. One recent development by Konecky et al[24] in linear analytical reconstruction is noteworthy, because it presents a way to solve a large data problem in a fast and memory-efficient way. When the boundary geometry of the diffuse medium has translational or rotational symmetry (infinite slab or cylinder, respectively), one can find a (spatial) Fourier domain representation of the solution of the photon diffusion equation, and linear inversion is very efficiently carried out. A high-resolution diffuse optical image is obtained using this algorithm from a large data set from consecutive transmission measurements from source-detector positions on a very fine grid, and it shows even sub-centimeter structures of complex-shaped target phantoms. Although this algorithm has limitations of being a linear reconstruction and has limited applicable boundary geometry, it provides a way to reconstruct systematically an image with relatively few arbitrary factors to tweak, and its application in actual breast cancer imaging is highly anticipated.

The lack of standard procedure in diffuse optical image reconstruction makes it challenging for the beginners to read and compare diffuse optical images correctly. No two research groups have used the same algorithm and protocol, until recent endeavor among the DOI community to standardize various algorithms into sharable packages such as NIRFAST[25,26], TOAST[27,28], and PMI toolbox[29]. To date, all the above software packages are available in Matlab, so that even beginners in programming can use them.
No matter what package you use for diffuse optical image reconstruction, there is an important issue that users of such images should bear in mind. It is about the possible image artifact that is specific to DOI, and also about the method of suppressing such artifacts. For example, the first image in Figure 4 shows many highly absorbing points that appear as a grid pattern. This happens because this reconstructed slice is very close to a plate that holds 9 × 5 source optical fibers. As explained earlier, positions right beneath the source and detector fibers have the highest sensitivity, and those volumes are updated preferentially in the iterative optimization process. When initial values in iterative reconstruction are set to a lower value than the real average absorption coefficient, all the positions in non-sensitive regions stay at the initial values, and only the points within an appreciable sensitivity volume keep increasing, which results in a grid-like pattern in Figure 4A.

Inverse problem solving generally has issues of unwanted high-frequency noise that starts to appear with many iterations, and researchers use regularization methods to suppress the image noise. One way to suppress source and detector position-specific noise, as shown in Figure 4A, is to use spatially dependent regularization in such a way that high-frequency noise close to the source and detector plane are penalized more than those points deep inside the volume. Figure 4B shows a reconstructed image of the same slice after the regularization treatment. Another way to suppress source and detector artifacts is to let the coupling coefficient values float during reconstruction, so that the algorithm finds the best source and detector coupling coefficients on its own[39]. It is usually difficult to know exactly the coupling coefficient due to optical probe contact problems (for probes in contact) and surface irregularity of in vivo samples (for non-contact probes), therefore, it makes sense to leave them as unknowns and use optimization algorithms to find them.

CLINICAL OUTCOMES

Assessing normal breast tissue properties
DOI is used in breast cancer imaging under the assumption that there is an optical property contrast between the cancerous and normal tissue. Therefore, early studies were focused on determining optical properties of normal breasts to serve as a baseline[31-38]. However, the optical properties of normal breast tissue vary significantly depending on age, body-mass index (BMI), breast size, and hormonal status. Therefore, one needs to understand the relationship between optical properties and those surrogate markers listed above, to apply DOI properly in cancer imaging. The most noticeable dependency is found between total hemoglobin concentration (THC) and BMI[31,35,39]. They are inversely related because high BMI generally means more adipose tissue, which has less blood supply than glandular tissue. It should be mentioned that we still need more systematic DOI studies on normal breast tissue, because most of the studies listed above are limited to Europe and North America, and the instrument and measurement protocols are not standardized.

Detection and characterization of breast tumors
The optical property contrast from endogenous chromophores (Hb, HbO₂, water, and lipid) has been shown to be significant enough to distinguish cancerous from normal tissue. The most prominent indicator for cancerous tissue is high THC, as reported by most of the DOI research groups[32,40-42]. The physiology behind this has to do with angiogenesis that accompanies malignant tumor growth, and some groups have actually measured microvessel den-
sities to prove it more directly\[60,63\]. Also, increase in scattering coefficient has been observed in cancerous tissue, which can be explained by rapid cell proliferation and an increase in the number of cell organelles\[43-46\].

Another important marker for cancer detection is tissue oxygenation (StO$_2$), because malignant tumor normally elevates the level of oxygen metabolic rate. However, the DOI literature has contrasting reports on StO$_2$ in cancerous tissue. A decrease of StO$_2$ has been reported by some groups\[47-49\], whereas no statistically significant changes have been reported by others\[19,20,42,45,50\]. This discrepancy could be attributable to the fact that tissue oxygenation differs depending on cancer stage and type.

Multiple physiological parameters show contrast between tumor and normal tissue, therefore, some groups have proposed the use of a customized optical index to maximize the contrast. Choe et al\[46\] have proposed an optical index defined as $r$THC × μ$_r$/StO$_2$, where $r$ stands for relative value. They have seen an average twofold increase in optical index in 41 malignant tumor cases. It is hard to apply this optical index to general DOI data, because that clinical result was based on a unique parallel-plate CW/RF hybrid DOI instrument\[51\] with a fine-tuned, non-linear image reconstruction algorithm that incorporated a spatially variant\[52\] and envelope-guided\[53\] regularization scheme. However, it was still a meaningful attempt to devise an optical index that not only increases the tumor-to-normal contrast, but also has a physiological foundation.

If patients do not mind receiving an injection, an exogenous chromophore or fluorophore can be injected to improve tumor contrast. Indocyanine green (ICG) is an FDA-approved blood-pooling agent that is popular in the DOI community, and it has been shown to enhance tumor contrast significantly via enhanced absorption\[54-56\]. The fluorescence signal from ICG can also be used to enhance the accuracy of DOI, as shown by the Sevick-Muraca group in breast phantom and canine mammary tumors\[57,58\] and by the Yodh group in human breast\[59\].

### Sensitivity, specificity, and receiver operating characteristic curve

When a new diagnostic tool is developed, one normally asks about its sensitivity and specificity. However, such quantities can only be defined in dichotomous tests where the output is either true or false (positive or negative) as shown in Table 1\[60\]. The physiological parameters that DOI provides are continuous variables (THC and StO$_2$, for example), and thus, one cannot define sensitivity or specificity until a cut-off value is determined. That is why many DOI studies have displayed their results in receiver operating characteristic (ROC) curves rather than showing a single pair of sensitivity and specificity values\[47\]. The ROC curve is a 2D plot in which the sensitivity (or true positive rate), is plotted against 1-specificity (or false positive rate). The ROC curve shows the overall behavior of sensitivity and specificity for all possible threshold values, and its area under the curve (AUC) serves as an indicator of how effective the imaging modality is, in terms of differentiating malignant from benign lesions.

| Test | Positive (disease) | Negative (no disease) |
|------|-------------------|-----------------------|
| Positive | TP | FN |
| Negative | FP | TN |

Sensitivity = TP/(TP + FN); specificity = TN/(TN + FP). TP: True-positive; FP: False-positive; FN: False-negative; TN: True-negative.

### Therapy monitoring

Neoadjuvant chemotherapy (NAC) has become an established form of breast cancer treatment\[61\]. Normally, it is prescribed for patients with locally advanced breast cancer to downstage the disease to make it operable, but now it is also used for operable cases to achieve better cosmetics. Two of the landmark trials were the National Surgical Adjuvant Breast and Bowel Project (NSABP) B-18\[62\] and European Organization for Research and Treatment of Cancer study 10902\[63\], which have demonstrated that NAC allows more patients to undergo breast-preserving surgery. NAC also allows us to acquire early information on the physiological response and mechanism of a disease. Therefore, it is crucial to develop a convenient non-invasive imaging method to monitor NAC, which will enable oncologists to optimize the treatment protocol.

Many different imaging modalities have been used to assess the tumor response during NAC, including X-ray mammography, ultrasound, MRI, and FDG-PET\[64\]. However, each modality has significant limitations to be used successfully as an NAC monitoring instrument. DOI, in contrast, is based on low-power, near-infrared light and is particularly suitable for this purpose. It is non-invasive, portable, and relatively cost-effective. DOI also allows frequent measurements with few space constraints, which enables doctors to obtain an immediate feedback that is useful for tailoring the treatment protocols to fit individual patients. Especially for such drugs as anti-angiogenic agents, frequent DOI monitoring can be a great help in strategizing the timing of treatment.

Many DOI research groups have performed NAC monitoring studies successfully. Since its first report by the Tromberg group in University of California, Irvine\[16\], the Yodh group in University of Pennsylvania\[42\] (Figure 5) and the Pogue group in Dartmouth\[44\] have used their own in-
house DOI instruments. Although most of these studies have used only a small number of patients, they have shown consistently that valuable information on treatment efficacy can be obtained by DOI within days or weeks of the onset of chemotherapy. Most recently, Soliman et al [65], by using a commercial DOI instrument (Softscan, ART Canada), have reported large decreases in Hb, HbO₂, percent water, and scatter power, from the NAC responder group. From 10 patients with aggressive diseases who received a variety of NAC regimens, they observed that the Hb concentration decreased more (67.6%, std 20.8%) for responders, than non-responders (17.7%, std 9.8%), after 4 wk of NAC. This shows that separation of pathological responders from non-responders is possible early in treatment (Figure 6).

Multimodal assessment of breast cancer

Although stand-alone DOI instruments are being successfully used in breast cancer imaging, many research groups have noticed that combining DOI with other imaging modalities can give us much more accurate reconstruction of breast lesions. When combined with structural imaging modalities such as MRI[54,66], ultrasound[67], and X-ray mammography[68], the structural information (boundary shape as well as inner structure) can be used as a priori information that constrains DOI image reconstruction. DOI alone cannot produce a crisp image due to ill-posed nature of the inverse problem, therefore, incorporation of such structural information can dramatically improve image accuracy via reducing the number of variables.

Figure 5 (Upper) Neoadjuvant chemotherapy timing diagram. Four cycles of adriamycin + cytoxan are followed by four cycles of taxotere. Time points for magnetic resonance imaging (MRI) and diffuse optical tomography (DOT) measurement are indicated. (Lower) A: Decrease in tumor volume; B: Change in total hemoglobin concentration (THC) (from Choe et al[42], copyright, 2005, American Association of Physicists in Medicine).

Figure 6 Non-responders (A) vs responders (B) to neoadjuvant chemotherapy for each of the optical parameters as measured by diffuse optical imaging in breast tumors (from Soliman et al, copyright, 2010, American Association for Cancer Research). SP: Scattering power.
Multimodal measurement can be performed concurrently (at nearly the same time in the same setting), or non-concurrently (at two different times in a different setting). Concurrent multimodal measurement may be more desirable in terms of image registration, but there are many instrument-related constraints that might render it impractical. For example, in order incorporate DOI into MRI, one needs to replace all components with non-magnetic material and also use very long optical fibers that connect to the control module located outside the MRI room. Therefore, some researchers are studying non-concurrent multimodal measurement, although it is challenging to register between two breast images with different deformation. Promising results using the non-concurrent image registration have been reported between bPET and DOI.

CONCLUSION

DOI has tremendous potential in terms of clinical application. Although this review focuses on its use in breast cancer imaging, many other applications have been reported in brain functional imaging, muscle studies, head and neck cancer therapy monitoring, and photodynamic therapy monitoring. DOI in breast, along with the emerging DCS that measures relative blood flow, will completely change our method of breast cancer screening and therapy monitoring in the future. Although X-ray mammography will remain as a method of choice for some time, the advantages of optical mammography will eventually be recognized in the clinical community. There are many challenges to overcome, such as improving spatial resolution, increasing tumor specificity, and proper artifact removal. However, the most important aspect is the standardization of instruments and software. Several big research groups are using their own custom-made instruments and reconstruction software, and the way in which they are collaborating with hospitals is also different. It is encouraging that the DOI community has realized this issue and is making efforts towards standardization via forming a multi-institutional network. In summary, DOI is a promising non-invasive, deep tissue functional imaging modality that is especially suitable for breast cancer diagnosis and treatment monitoring, and it will find increasing applications in clinics.

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