Photon phase shift imaging research on frequency domain diffuse optic tomography

H. O. Kazanci

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Abstract
Diffuse optic imaging is an important biomedical optic research tool. Diffuse optic tomography (DOT) modality needs progressive philosophical approaches for scientific contribution. Technological developments and philosophical approaches should both go forward. Phase-shift based frequency domain diffuse optical tomography (FDDOT) method was well established in the literature. The instruments were tested for brain neurofunctional imaging. A mixture of AC laser intensity and phase data were used at these works. According to those works, deep tissue resolution was improved by only using phase data. Because phase data is only related to the photon mean free path in imaging tissue media. Besides this advantage, laser intensity data is also affected by noisy background light and electrical artifacts. Another most important advantage of only using phase data can be explained as time-resolved temporal change which can be directly related to the phase shift of modulated frequency source. In this work, the FDDOT imaging method which uses phase shift data were tested for simulation. Laser source-driven forward model problem weight matrix simulation data was given to the simple pseudo-inverse-based inverse problem solution algorithm for one inclusion example. The inclusion image was reconstructed and demonstrated successfully. Forward model problem weight functions inside the tissue simulation media were calculated and used based on the phase shifts at the same core modulation frequency. 100 MHz modulation frequency was selected due to its FDDOT standard. 13 sources and 13 detectors were placed on the back-reflected imaging surface. 40 x, y, z cartesian coordinate grid elements were used in the image reconstruction algorithm. Photon absorption coefficient: $\mu_a = 0.1 \text{ cm}^{-1}$, and scattering coefficient: $\mu_s = 100 \text{ cm}^{-1}$ values were set for simulation background. One inclusion object was embedded inside the background imaging tissue simulation environment. x, y, z cartesian coordinate grid sizes were selected for 1 $\mu$m for each direction. Photon phase shift fluencies were added to the forward model problem. The forward model problem was built according to the frequency domain photon migration diffusion equation (DE) approximation. The pseudoinverse mathematical inverse problem solution function was applied to test the results. The embedded inclusion object was reconstructed successfully with the high-resolution image quality. The philosophical approach has future promising DOT imaging capability. The phase shift version of the FDDOT modality has an important advantage for future purposes.

Extended author information available on the last page of the article
Keywords Frequency domain (FD) diffuse optic tomography (DOT) · Photon phase shift imaging (PPSI) · Laser tomography · Bbiomedical optic imaging · Inverse problem solution

1 Introduction

Practical diagnostic techniques are essential to test and evaluate blood contents quickly. For this purpose, in this work, the existing frequency domain (FD) diffuse optical tomography (FDDOT) imaging technique was invoked to build a philosophical method by using biomedical photonic tools. In general terms, DOT techniques suffer from low spatial resolution and background noise. But in the past 2 years, researchers associated successful FDDOT techniques which gets benefit from phase shift only data. At the beginning of the diffuse optic imaging (DOI) era 3 decades ago, phase-shift-based FDDOT works were well established (Sevick et al. 1991). The successful biomedical optic imaging (BOI) devices were developed and tested (Toronov et al. 2004; Sassaroli et al. 2004). Finally, the researchers showed better deep tissue spatial resolution results (Doulgerakis et al. 2018, 2019) by using FDDOT. They improved the image quality by using a mixture of phase and AC intensity data of the FDDOT imaging system. Phase data is independent of the intensity data, it can only be related to the photon mean free paths. On the contrary, AC laser intensity data is affected by noisy light background and electrical artifacts. More importantly, time-resolved (TR) temporal change can be directly correlated to the phase shift of modulation frequency. FDDOT works were completed by the researchers for different clinics with various imagers such as by placing source and detectors on the back-reflected, transmission, or ring geometry. The review of these works was compiled in the literature (Althobaiti and Al-Naib 2020). FDDOT techniques for functional brain imaging were also presented comprehensively (Fantini and Sassaroli 2020). Basic instrumentational perspective and device developing methodology were also mentioned and tested for breast imaging at frequency domain (Pogue et al. 1997). Recent developments and progressive efforts were also summarized (Applegate et al. 2020). Frequency domain research was evaluated (Hou and Fang 2014). For ring imaging geometry, physical formula extraction from radiative transfer equation (RTE) and its usage in the FDDOT system was given (Pogue et al. 1995).

In this work, FDDOT imaging methodology with the help of phase shift laser source driven forward model problem weight matrix simulation data was given to the pseudo-inverse based inverse problem solution algorithm for a simple inclusion investigation example. The wavelength of the laser source was chosen according to the literature search (Hales et al. 2019). 500 nm laser wavelength was chosen for a possible microbial investigation case. Different phase shifts related to the microbial particle diameter size were applied and reconstructed images were compared and presented to the readers. Forward model problem photon weight functions inside the imaging tissue simulation media were calculated and used with the phase shifts at the same modulation core frequency. 100 MHz modulation frequency was selected. 13 sources and 13 detectors were placed on the back-reflected imaging surface. 40 x, y, z grid elements were used for image reconstruction purposes. Photon absorption coefficient: $\mu_a = 0.1 \text{ cm}^{-1}$, and scattering coefficient: $\mu_s = 100 \text{ cm}^{-1}$. One inclusion object was embedded inside the background imaging tissue simulation environment. Cartesian x, y, z grid coordinate sizes were selected as 1 μm for each direction. Over the traditional image reconstruction algorithms, extra photon phase shift fluencies were added to the forward model problem. The forward model problem was built according to
the frequency domain photon migration diffusion equation (DE) approach. Photon fluencies were calculated in the forward model. The simple pseudoinverse mathematical inverse problem solution algorithm was applied for the solution. The image of the embedded inclusion object was reconstructed successfully with the high-resolution quality.

2 Methods

In general, a 500 nm laser wavelength source is used to detect microbial instances. For this purpose, it is assumed to use 500 nm laser wavelength, and pre-calculations were done based on the center laser wavelength. The specific microbial instance has a 100–120 nm diameter size. It could be presumed the size of microbial instance is around 100 nm. One complete laser wave overlaps 5 microbial instances. 500 / 100 = 5 phase-shift steps would be thought for minimum full interaction. Let us assume tissue refraction index \( n = 1.37 \). According to the \( c = \lambda \times f = \frac{c}{\lambda} \), \( f = 3 \times 10^8 \) m / 1.37 / (500 \times 10^{-9}) m = 4.37 \times 10^{14} \) Hz. We need to have \( t = \frac{1}{(4.37 \times 10^{14})} = 2.28 \) femtoseconds (fs) full-wave photonic resolution. In one full wave, we need 5 phase-shift steps, we have 2.28 fs / 5 = 0.456 femtoseconds (fs) resolution steps. If we have frequency modulated continuous waves (FMCW) step up and down by 5 Hz steps, then time differences between 2 FMCW waves become \( 1 / (100 \times 10^6) - 1 / (100,000,005) = 0.5 \) femtoseconds (fs). 100 sequential phases were sent from source positions with a 5 Hz phase shift which corresponds to the 5-fs time delay at 100 MHz core frequency.

\( N_s = 13 \) sources and \( N_d = 13 \) detectors were placed based on the back-reflected imaging geometry structure which was demonstrated in Fig. 1. Sources are magenta, and detectors are red. Figure 1 has a top-view appearance for sources and detectors. Forward model problem weight matrix functions were calculated according to the frequency domain extraction of diffusion equation (DE) approximation of radiative transport equation (Dehghani et al. 2009). From all source and detector positions to the voxel positions forward model problem transfer functions were calculated according to the following statements based on the literature reference (Dehghani et al. 2009). Frequency domain forward model problem weight functions were parted into AC and DC components. The DE is transformed to the Helmholtz wave equation which was illustrated previously (Dehghani et al. 2009). Finally, photon density wave

![Fig. 1 Source and detector placements. Sources are magenta, and detectors are red](image-url)
or forward model problem transfer weight functions are calculated. The same procedure which was introduced in literature (Dehghani et al. 2009) was brought and used herein Eq. 1 for this work.

\[
(\nabla^2 + k^2)\Phi(d) = -\frac{\delta(d)}{cD}
\]

\[
k^2 = \frac{-c\mu_a + j(w + \theta)}{cD}
\]

\[
\Phi(d) = \frac{e^{jkd}}{4\pi cDd}
\]  (1)

According to the Eq. 1, \(\Phi(d)\) is the forward model problem transfer functions between source to voxels and voxels to the detector positions for each separate tissue voxel position. \(D\) is the photon density wave diffusion coefficient for homogeneous tissue background, \(c\) is the light speed inside the media, \(\mu_a\) is the homogeneous medium tissue background light absorption coefficient for specific laser wavelength which in our work is 500 nm, \(w\) is the radian frequency, \(d\) is the distances where from source to voxel positions and voxel to detector positions, respectively. For this work, the photon phase was added by \(\theta\) factor in Eq. 1. By adding the \(\theta\) angle, the photon phase shift was obtained. In the inverse problem solution algorithm, \(\Phi(d)\) weight functions will be used as forward model problem transfer functions as \(A\) matrix which is illustrated in Eq. 2. Tissue background absorption coefficients \(\mu_a\) is representing the \(x\) unknown vector which should be solved by using a simple pseudoinverse problem–solution method. In the phantom simulation model, a homogeneous background tissue model was built, and inclusion was embedded by adding an extra absorption coefficient for specifically related voxels. In the simulation phantom model, \(y\) vector was calculated at first, by simply doing matrix multiplication according to Eq. 2. \(X\) unknowns were calculated by simply multiplying both sides of Eq. 2 with pseudoinverse of \(A\) weight matrix which was shown in Eq. 3.

\[
y = A \cdot x
\]  (2)

\[
x = A^\dagger \cdot y
\]  (3)

First source-detector (SD) match, 5th phase frequency-domain photon fluence weight functions distribution was demonstrated at the top-view in Fig. 2. Source and detector positions have hotspots where their positions can be realized as yellow colors. Forward model problem was generated between all SD couplings with all sequential phase shifts. Figure 2 shows only one SD match, 5th phase photon fluencies which can be seen from the top view. Forward model problem weight matrix has \(16,900 \times 64,000\) dimensions. The total SD match is \(13 \times 13 = 169\). Each SD match has 100 sequential phase shift data. The total SD match and phase shift data together are \(169 \times 100 = 16,900\). Voxel dimension is \(40 \times 40 \times 40 = 64,000\). The weight matrix represents the forward model problem weight functions distribution.
3 Results

In Fig. 3a, b, the original embedded inclusion object can be seen. In Fig. 3c, d reconstructed image can be seen clearly. A simple pseudo-inverse problem solution algorithm was applied to reconstruct the inclusion object image. The original inclusion object has 100 nm size on x, y, and z directions. Position error (PE) was obtained by doing PE calculation. Depth resolution error was evaluated from the view of Fig. 3c, by comparing it with Fig. 3a. The top view can be seen from Fig. 3d. Original inclusion was embedded in 500 nm depth with the 100 nm each x, y, and z cartesian coordinate grid.
sizes which is shown in Fig. 3a. On the contrary, the inclusion image was reconstructed at approximately 300 nm depth which is shown in Fig. 3c. from the bottom of imaging media at almost 700 nm (From tissue surface it is in 1000 nm − 700 nm = 300 nm). With the rough calculation, it has 500 nm − 300 nm = 200 nm z-axis error factor over 1000 nm full scale. The error percent is 200 nm/1000 nm = % 20. In addition the rough observation PE approach, mathematical PE was calculated for three x, y, z cartesian coordinate dimensions by using Eq. 4.

\[ PE = \sqrt{\left( x_{\text{inclusion}} - x_{\text{reconst.}} \right)^2 + \left( y_{\text{inclusion}} - y_{\text{reconst.}} \right)^2 + \left( z_{\text{inclusion}} - z_{\text{reconst.}} \right)^2} \]

Quantitative PE analysis was done based on Eq. 4. Since x, and y coordinate grid elements error factor is minimum to total PE value, x, and y errors did not affect the overall PE. On the other hand, the depth z coordinate grid element affected much of PE. Based on the program calculation, the highest concentration point of z was calculated as \( z_{\text{reconstructed}} = 654 \) nm from the bottom which is at the 1000 nm − 654 nm = 346 nm from the tissue surface. \( X_{\text{reconstructed}} = 10 \) nm, and \( y_{\text{reconstructed}} = -10 \) nm. \( x_{\text{inclusion}} = 0, y_{\text{inclusion}} = 0, z_{\text{inclusion}} = 500 \) nm, \( l_{\text{ROI}} \) is the length of the ROI, \( l_{\text{ROI}} = 1000 \) nm. PE was calculated according to Eq. 4 as follows:

\[ PE = \frac{\sqrt{(0 - 10)^2 + (0 + 10)^2 + (500 - 346)^2}}{1000} = \% 15.664 \]

Generally, the DOT devices have a low spatial resolution. \% 15.664 spatial PE error condition is comparatively acceptable for DOT imaging modality. Since the photon fluencies are superficial for imaging media in DOT modality, photon hotspots affect the localization of reconstructed images negatively. Photon hotspots occur near the tissue surface under surface. Since the weight matrix functions are important in the forward model problem, it is directly affecting the localization of reconstructed images. In this work, inclusions were reconstructed with almost 15% depth localization PE error which is comparatively fine. To find the concentration contrast to noise ratio (CNR) error in the region of interest, Eq. 5 was used.

\[ \text{CNR}_{\text{error}} = \frac{\left| \mu_{\text{inclusion}} - \bar{\mu}_{\text{ROI}} \right|}{\mu_{\text{inclusion}}} \]

In Eq. 5, \( \mu_{\text{inclusion}} \) is the real embedded inclusion absorption coefficient, \( \bar{\mu}_{\text{ROI}} \) is the average reconstructed absorption coefficient of the region of interest (ROI) volume. The absorption coefficient of the real embedded inclusion was selected as \( \mu_{\text{inclusion}} = 0.7 \) cm\(^{-1}\). Homogeneous tissue background absorption coefficient is \( \mu_{\text{inclusion}} = 0.1 \) cm\(^{-1}\). In the volume of the ROI, the average reconstructed absorption coefficient of the ROI, \( \bar{\mu}_{\text{ROI}} \) was calculated as \( \bar{\mu}_{\text{ROI}} = 0.63897 \) cm\(^{-1}\). ROI volume was selected based on the higher concentration of the reconstructed inclusion image. Then concentration contrast to noise ratio error (CNR\(_{\text{error}}\)) was calculated as \% 6.1. CNR\(_{\text{error}}\) was calculated also in a comparatively acceptable scale.
4 Discussion

In this work, a well-known FDDOT imaging modality with only phase-shift simulation data was studied to reconstruct the inclusion image object. According to this method, using only the modulation signal phase is the key factor. Since the DOT methodologies easily suffer from background light and electrical artifacts, AC and DC magnitude investigations were ignored, and only phase data was used and tested for better time-resolved (TR) temporal image quality and depth resolution. 100 sequential phases were used for 100 MHz core modulation frequency. It was seen that phase shift methodology would be easily applied to future FDDOT devices. Technological developments are necessary to design and implement the micrometric frequency domain back-reflected laser tomography devices. In the possible future work scenario, photonic integrated circuits (PIC) design would be gathered with the traditional analog electronic VLSI design for high-resolution temporal TR phase shifts. TR imaging approach is equivalent to the frequency domain (FD) phase-shift method. New easy-to-apply TR imaging methodologies are necessary for DOT imaging methodology. For this reason, the TR equivalency of the DOT modality was presented to the authors for high image resolution for future works. Based on the literary works and studies, the FDDOT imaging modality uses both AC and phase data for image reconstruction. In this work, only phase shift data for simulation phantom was used since the AC data could not be applied to the image reconstruction schema. AC data would be applied if the experimental setup were constructed, and AC data were extracted from experiments.

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Declarations

Competing interest The author declares he has no competing interest.

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Authors and Affiliations

H. O. Kazanci

H. O. Kazanci

ozgurkazanci@akdeniz.edu.tr; ozgurkazanci@gmail.com

1 Department of Biomedical Engineering, Faculty of Engineering, Akdeniz University, 07058 Antalya, Turkey