Near-infrared spectral tomography integrated with digital breast tomosynthesis: Effects of tissue scattering on optical data acquisition design

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Purpose: Design optimization and phantom validation of an integrated digital breast tomosynthesis (DBT) and near-infrared spectral tomography (NIRST) system targeting improvement in sensitivity and specificity of breast cancer detection is presented. Factors affecting instrumentation design include minimization of cost, complexity, and examination time while maintaining high fidelity NIRST measurements with sufficient information to recover accurate optical property maps.

Methods: Reconstructed DBT slices from eight patients with abnormal mammograms provided anatomical information for the NIRST simulations. A limited frequency domain (FD) and extensive continuous wave (CW) NIRST system was modeled. The FD components provided tissue scattering estimations used in the reconstruction of the CW data. Scattering estimates were perturbed to study the effects on hemoglobin recovery. Breast mimicking agar phantoms with inclusions were imaged using the combined DBT/NIRST system for comparison with simulation results.

Results: Patient simulations derived from DBT images show successful reconstruction of both normal and malignant lesions in the breast. They also demonstrate the importance of accurately quantifying tissue scattering. Specifically, 20% errors in optical scattering resulted in 22.6% or 35.1% error in quantification of total hemoglobin concentrations, depending on whether scattering was over- or underestimated, respectively. Limited frequency-domain optical signal sampling provided two regions scattering estimates (for fat and fibroglandular tissues) that led to hemoglobin concentrations that reduced the error in the tumor region by 31% relative to when a single estimate of optical scattering was used throughout the breast volume of interest. Acquiring frequency-domain data with six wavelengths instead of three did not significantly improve the hemoglobin concentration estimates. Simulation results were confirmed through experiments in two-region breast mimicking gelatin phantoms.

Conclusions: Accurate characterization of scattering is necessary for quantification of hemoglobin. Based on this study, a system design is described to optimally combine breast tomosynthesis with NIRST. © 2012 American Association of Physicists in Medicine. [<http://dx.doi.org/10.1118/1.4728228>]

Key words: biomedical optics, breast tomosynthesis, spectroscopy, tomography

I. INTRODUCTION

Near-infrared spectral tomography (NIRST) is a noninvasive imaging technique that can be integrated with digital breast tomosynthesis (DBT) to produce functional images of the breast to enhance diagnostic specificity. The clinical standard for breast screening is mammography, which is effective at early detection of cancer, and has been shown to lower breast cancer mortality.^{1–4} However, it is hampered by a significant false-positive rate,⁵ which is especially high for women with dense breast tissue.⁶ The dense breast population is a particularly important subset of women because they experience higher incidence and mortality from the disease.⁷ DBT was FDA-approved in February 2011 as part of a com-

bined DBT—FFDM exam utilizing a limited angle x-ray tomography approach, because it demonstrated potential to decrease screening recall rate while maintaining or perhaps improving cancer detection, most significantly in women with denser breasts.^{8,9} It minimizes tissue overlap that may obscure breast cancer or that may falsely emulate breast abnormalities. In this study, a multimodality platform to enhance the specificity of DBT through the addition of NIRST is studied through simulations and preliminary preclinical phantom experiments to determine the minimum NIRST data required to quantify total hemoglobin (HbT) concentration with an accuracy sufficient to be of diagnostic utility. Prior studies using both optical and pathologic correlates have shown significant differences in hemoglobin levels in benign versus malignant

lesions.^{10–12} Hence, the addition of optical data may improve the sensitivity and specificity of DBT imaging alone.

While DBT provides highly resolved three-dimensional (3D) anatomical detail in the breast, NIRST produces complementary metabolic information including hemoglobin concentration, oxygen saturation, water content, lipid fraction, and scattering properties. Stand-alone NIRST has low spatial resolution due to pervasive optical scattering of the measured light. Image guidance from spatial information can improve both the resolution and accuracy of optical properties recovered with NIRST.^{13,14} Optical spectroscopy has previously been combined with other conventional imaging techniques including MRI,^{15,16} ultrasound,¹⁷ and x-ray mammography.^{12,18} Expanding clinical implementation of integrated CT and PET systems offers further evidence of the potential of multimodal functional and anatomic imaging techniques.¹⁹

A combined DBT/NIRST system has already been developed at Massachusetts General Hospital and used to image over 200 patients, as described in Zhang *et al.* and Fang *et al.*^{18,20} Early results are promising, a 2011 study showed significant differences in the optical properties of malignant and benign lesions. Different contrasts for HbT and scattering properties were obtained in each case, indicating that a multimodal imaging system of this type may improve detection sensitivity and specificity over DBT alone.¹² In this study, a different design for an integrated DBT/NIRST is investigated with the aim of improving tissue characterization with more spectral information. Four of the eight lasers emit light at over 830 nm, critical for accurate quantification of water and lipids. Additionally, the system has a flexible number and arrangement of sources and a greater number of detectors for more complete tissue analysis.

Developing an imaging modality for screening presents unique challenges. In order to be clinically successful, it must be simple to operate and interpret, have low-cost per exam, and pose minimal risks to the individual. In an effort to keep cost and complexity low, we have pursued a NIRST system which projects light onto the breast surface at discrete locations with a motor-driven mirror and measures the resulting light signals with a fixed rectangular array of silicon photodiodes integrated into a detection panel placed on the opposite side of the breast. The design relies extensively on continuous wave (CW) measurements for rapid, low-cost quantification of tissue absorption. Measuring optical scattering in tissue is more difficult and requires additional time- or frequency-domain (FD) elements that add to system cost, complexity, and examination time. Minimizing exam time is important both to limit the time, the breast is subjected to compression and to maintain efficiency of workflow in the mammography clinic. Estimation of optical scattering properties is necessary in breast imaging because of the wide variation in these values, which depends on breast composition and parenchymal density. Incorrect estimation of scattering also alters estimates of optical absorption, especially hemoglobin concentration; hence, accurate scattering values are needed to characterize and quantify optical absorption properties of the breast.

Through simulations and experimentation, we investigated whether a NIRST system with a limited number of FD channels can quantify hemoglobin and other chromophores in the presence and absence of tumor. This design is not the first to combine CW and FD information. Indeed, promising breast imaging results have been achieved with existing systems using a similar approach.^{20,21} The analysis presented here is based on simulated patient data from actual DBT breast exams and preliminary experimental results from contrast phantoms, and suggests that accurate ($\sim 10\%$ error) estimates of tissue scattering are important to the success of NIRST when combined with DBT, but can be achieved with a relatively modest number of wavelengths (~ 3) and signal channels (~ 6).

II. MATERIALS AND METHODS

II.A. DBT-NIRST simulations

Reconstructed DBT slices from eight patients with abnormal mammograms acquired during a previous study⁸ provided anatomical information for the NIRST simulations. A radiologist specializing in breast imaging identified the lesions (SPP). DBT slices were segmented into three tissue types—adipose, fibroglandular, and malignant—based on grayscale intensity, location, and radiologist interpretation using the MIMICS[®] software package.

The anatomic information from the DBT segmentation was incorporated in the finite element meshes used for NIRST image reconstruction through simple region classification. Specifically, nodes within the mesh were tagged as belonging to adipose, fibroglandular or malignant regions depending on their correspondence with the coregistered DBT segmentation. Overall breast volume from the DBT image data also defined the mesh size and shape. Two 3D volumetric meshes were created for each patient image stack: a fine mesh with about 80 000 nodes for FD simulations and a course mesh with about 30 000 nodes for the CW case. Greater nodal density in the FD simulations was required to obtain accurate phase data. Fewer nodes in the CW problem simplified the simulations and minimized reconstruction time. In both cases, nodal density was increased in the tumor region to about 5% of the total nodes in the mesh.

Oxy- and deoxyhemoglobin, water, lipid, and scattering values were assigned to each region for each patient based on prior near-infrared measurements in normal and diseased breasts.^{10,15,22–24} Within each tissue region, values for a given chromophore were kept constant. Using these optical properties, both FD and CW data were simulated and then reconstructed as described in Fig. 1.

Simulations were performed with the NIRFAST software package.²⁵ For the FD data, wavelengths were selected from 660 to 850 nm and intensity modulated at 100 MHz. In the CW case, ten wavelengths were used between 660 and 980 nm. They were selected based on the availability of laser diodes and detectors with sufficient sensitivities over this spectral band. Additionally, the absorption spectra of

FIG. 1. Software procedures used in simulation. Lower left shows source and detector configurations for the FD (left) and CW (right) data for a given patient.

oxygenated and deoxygenated hemoglobin as well as water and lipids were considered and wavelengths near absorption peaks were preferentially selected whenever possible.

The source-detector configurations were different for the simulated FD and CW measurements. The FD data resulted from six sources above the breast (cranial side) and six detectors below (caudal side). This geometry minimized the number of channels while providing sufficient sensitivity to most of the breast tissue volume.²⁶ It also accommodated a wide range of breast sizes, all eight of the simulated DBT cases studied here. Preliminary results (not shown) from a four source and four detector geometry yielded errors as high as 35% in scattering estimation compared to 8% for the six source and six detector case investigated in detail in this study. The CW acquisition consisted of a two-dimensional array of sources and detectors each spaced 13 mm apart. The number of sources and detectors varied across patients depending on breast size. Source and detector positions that did not come in direct contact with the breast were not included. All measurements were recorded in transmission geometry. In the FD case, amplitude data five orders of magnitude below the highest intensity recorded for a given wavelength were not used in order to simulate the expected noise floor for measurements from a photomultiplier tube. In the CW case, amplitude measurements three orders of magnitude below the highest recorded value for a given wavelength were not used in order to represent the uncorrupted data due to shot noise and the limited signal dynamic range from a photodiode. Three percent Gaussian noise was also added to each simulated data set. Coupling errors at tissue surfaces due to skin texture and color were not included in the simulations, in part because the CW data probes the entire breast volume from multiple surface locations, reducing these effects in the data from any single source-detector pair. The DBT-guided NIRST image reconstruction process for a given patient is illustrated in Fig. 2.

FIG. 2. Region-guided reconstruction of NIRST data involved segmentation of (a) DBT slice (arrow highlights the region of interest), creating (b) a bitmap from which (c) a volume mesh was generated. The data were simulated and reconstructed on the mesh creating (d) a coregistered image of the optical properties of the breast.

II.B. Image formation

NIRFAST software utilizes the diffusion approximation to the Boltzmann transport equation for light propagation in tissue. This approach has been studied extensively and is accurate when photon scattering events (μ_s') are much more likely than absorption (μ_a), and occurs at distances greater than one scattering path length from the sources.^{27–29} Simulated data are calculated over a finite element mesh according to [Eq. (1)],

$$\frac{1}{c} \frac{\delta \Phi(\mathbf{r}, t)}{\delta t} - \nabla \cdot D \nabla \Phi(\mathbf{r}, t) = -\mu_a \Phi(\mathbf{r}, t) + S(\mathbf{r}, t) \quad (1)$$

which describes the fluence of light, Φ , at a time, t , at a certain position, $\mathbf{r}$, in tissue due to a source, S . The four terms represent changes in flux, diffusion, loss due to absorption and gain due to a light source.²⁸ NIRFAST software employs nonlinear Gauss-Newton type minimization of the difference between measured and modeled data^{25,30} during image reconstruction. Tikhonov regularization is performed using a Levenberg-Marquardt parameter to reduce the ill-conditioning of the problem. Chromophore concentration is updated iteratively to reduce model-data misfit though [Eq. (2)],

$$\Delta c = (J^T J + \lambda I)^{-1} J^T \delta. \quad (2)$$

Here, tissue chromophore concentration estimate, c , is updated by Δc via Eq. (2) until a stopping criteria of less than 2% change between iterations is achieved. J is the Jacobian matrix, I is the identity matrix, δ is the model-data misfit, and λ is the regularization parameter. The same initial value ($\lambda = 0.01$) was reduced (by 10^{-25}) at each iteration for all simulation and phantom reconstructions in this study.

Chromophore concentration estimates are subjected to prior information defined in terms of homogenous subregions segmented from the DBT image volume where all nodes within a given region are constrained to the same value during the iterative updating process. This approach decreases the number of unknowns to be updated and converts the inversion from being underdetermined to being overdetermined, while also decreasing its size and associated computation time. It imposes tissue homogeneity within segmented zones, but when used appropriately, improves lesion detectability assessed by receiver operating characteristic (ROC) analysis

compared to no prior information.³¹ Homogenous subregion constraints can cause inaccurate reconstructions if region localization is not accurate.³² Coregistration of tomosynthesis images and near-infrared data mitigates the problem in the present case.

II.C. Instrumentation

The DBT-NIRST system used in this study incorporated eight laser diodes emitting source light with wavelengths from 660 nm to 940 nm. A mirror attached to the DBT gantry arm controlled the light source positioning on the breast surface and created a 1 cm spot size that was raster scanned to 66 positions in an 11×6 grid pattern with 2 cm spacing between the centers of adjacent locations. The detector panel consisted of 75 silicon photodiodes (Hamamatsu, S9270) each with an active area of 1 cm $\times$ 1 cm. The detector panel is removable and was placed underneath the breast after completion of DBT imaging allowing physical coregistration of the two modalities. The NIRST imaging sequence was completed in ~ 40 s. More details on the DBT-NIRST instrument can be found in another publication.³³

II.D. Phantom imaging

Agarose-based phantoms were created using water, type 1 Agarose, dilutions of 20% intralipid, and whole porcine blood. Two phantoms were created both with 15 μM blood concentration mixed with 1% intralipid solution to mimic typical breast optical properties.^{34,35} Each phantom was 6 cm in height, comparable to average compressed breast thickness during mammography.³⁶ The phantoms were composed of two sections—the first being a 5 cm lower slab, and the second being a 1 cm thick upper slab (placed on top of the lower section). The two-section design facilitated the addition of internal inclusions with different contrasts created by mixing intralipid with varying amounts of blood. System calibration was performed with a homogeneous phantom (i.e.,

upper and lower slabs with the same concentrations of blood and intralipid and no inclusions). Contrast detection was evaluated by embedding a localized region of heterogeneity in the lower section through the filling of a cylindrical hole of 3 cm in diameter and 2 cm in height with solutions of 15, 30, and 45 μM blood mixed with 2% intralipid. A 1 cm thick homogeneous slab was placed on top of this lower section to complete the internal inclusion structure.

III. RESULTS

III.A. Sample patient simulations

Simulations of the DBT-NIRST design using patient-specific tomographic images were performed and representative images are shown in Figs. 3 and 4. In both cases, six wavelengths of FD data were generated and scattering amplitude and power were recovered for two regions, one for adipose and one for both fibroglandular and malignant tissue. These scattering values were then used in the reconstruction of the other chromophores based on the CW measurements.

The difference between Figs. 3 and 4 is the chromophore values assigned to the tumor region. In Fig. 3, a malignancy was simulated with higher oxy- and deoxyhemoglobin concentrations, water fraction, scattering amplitude, and power as well as lower adipose content than in the surrounding fat and fibroglandular regions. Within the tumor, hemoglobin and deoxyhemoglobin were recovered at 18.8 and 7.1 μM compared with 12.0 and 4.1 μM in the fibroglandular region. In Fig. 4, a benign mass was simulated. Here, the chromophore values were the same as those in the fibroglandular region. No enhancement occurred in the tumor region in the image formed from the synthetic system data.

III.B. System simulations

Studies were undertaken to examine system performance based on different designs. Specifically, to explore the effects

FIG. 3. Illustrative example of a patient simulation with a malignant lesion: (a) scattering amplitude, (b) oxyhemoglobin (μM), (c) water fraction (percent), (d) scattering power, (e) deoxyhemoglobin (μM), and (f) lipid content (percent). Exact (simulated) distribution is shown on the left while the corresponding recovered image is shown on the right for each quantity.

FIG. 4. Illustrative example of a patient simulation with a benign lesion: (a) scattering amplitude, (b) oxyhemoglobin (μm), (c) water fraction (percent), (d) scattering power, (e) deoxyhemoglobin (μm), and (f) lipids content (percent). Exact (simulated) distribution is shown on the left while the corresponding recovered image is shown on the right for each quantity.

of reducing the number of wavelengths available in the FD instrumentation, we compared results for three versus six wavelengths across the same spectral range from 661 to 849 nm. For the three-wavelength case, values of 661, 761, and 849 nm were used. For the six-wavelength case, light sources of 661, 735, 761, 785, 808, and 849 nm were considered. The resulting scattering reconstructions were compared for all eight patients and the composite results appear in Figs. 5(a) and 5(b). The error in scattering power was higher, 13.1%, in the fibroglandular region for the three-wavelength case compared to 7.4% when six wavelengths were used. However, errors in HbT concentration differed by less than 1% in the tumor region as depicted in Fig. 5(c).

We also studied the effects of assuming a single bulk tissue estimate of scattering compared to using separate val-

ues for adipose tissue, and fibroglandular and tumor regions. Figure 5(d) depicts the aggregate errors in HbT concentration for each tissue type in all eight patients using a single breast scattering estimate compared with two-region estimation. It shows that the bulk value produced greater error in absolute hemoglobin recovery when compared to two-region estimations of scattering for all three tissue types. The effect was most pronounced in the tumor, in which case using two regions instead of a single bulk estimate led to a 30.6% improvement in the accuracy of its HbT concentration.

The effect of scattering mischaracterization on calculated hemoglobin values was examined as well. In this case, scattering values were assigned for the CW reconstruction instead of using FD data to estimate the scattering values. Two scattering estimates were assigned in each patient case, one for

FIG. 5. Relative error in the adipose and fibroglandular region for 3 and 6 wavelength reconstructions for all eight subject simulations in (a) scattering amplitude and (b) scattering power. (c) Error in HbT relative to the actual concentration for 3 and 6 wavelengths in adipose, fibroglandular, and tumor regions. (d) Error in HbT relative to actual concentration for single bulk and two-region scatter estimations in adipose, fibroglandular, and tumor regions.

FIG. 6. Solid line shows the mean and standard deviation of the average HbT recovered in the image volume from all patient cases as a function of error in optical scattering. Data points show the same analysis from the phantom experiments.

fat and one for the fibroglandular and malignant tissue. Fixed percentages of error were introduced into these scattering values. Figure 7 depicts how errors in scattering propagate into inaccuracies in the reconstructed images of HbT concentration. Data for all tissue types for all patients are included in the plot and indicate certain trends. For example, underestimating scattering by 20% leads to an increase in the reconstructed HbT by 35.1%, while overestimating scatter by 20% leads to a reduction in the reconstructed HbT by 22.6%

III.C. Phantom experiments

Phantoms with three different contrast levels (3:1, 2:1, and 1:1) for absorption and 2:1 for scattering were imaged with the DBT-NIRST system. The inclusions were liquid, while the phantom background was gelatinous. A homogeneous phantom was also created and imaged for data calibration. True scattering values were extrapolated from prior optical property characterization studies³⁴ and were used in the CW reconstruction algorithm. A 3D finite element mesh containing 43 971 nodes (908 nodes in the inclusion) was created with the NIRFAST software package.

As Fig. 6 shows, Hemoglobin recovery in the background was 70% of the actual 15 μM blood concentration. This level is consistent with prior measurements of a resin optical phantom from INO (data not shown) and previously conducted research.³⁷ Background values were similar across the three cases and had a standard deviation of 4.8% of the actual value. Recovered HbT values from the inclusion showed a linear relationship ($R^2 = 0.973$) with the actual hemoglobin concentration incorporated into the phantom. Average recovery in these cases was 87% of the true blood concentration. More information on system performance can be found in concurrent work.³³

An analysis of the effects of scattering error on HbT concentration recovered from the phantom data showed similar

FIG. 7. (a) Detector panel used for phantom measurements. (b) Agar phantom with a liquid inclusion used for instrumentation and simulation validation. (c) DBT slice of the agar phantom. (d) Actual (top) and reconstructed (bottom) phantom image for oxygenated hemoglobin concentration. (e) Recovered hemoglobin concentration compared to the actual value in the inclusion and background. Inclusion hemoglobin values are the three higher data points with actual values depicted in the positively sloping line. Background hemoglobin levels were kept constant and are the three lower data points with actual values depicted in the horizontal line.

results to the patient simulations in Fig. 7. Here, a two-region scatter estimate was used for the CW reconstruction and was perturbed by as much as 25% from the value extrapolated from Ref. 34. For these phantom experiments, underestimating scattering by 20% led to an increase in the recovered HbT by 40.5% while overestimating the scattering by 20% led to a reduction in HbT by 25.4%.

IV. DISCUSSION

IV.A. Patient simulations

The simulations presented here with subject-specific data from actual tomosynthesis breast exams provide insight into

some of the requirements for NIRST system design. For the eight cases simulated, HbT levels were elevated in the tumor region compared with surrounding fibroglandular and adipose tissue as expected. Additionally, simulations of benign lesions as having lower levels of hemoglobin than tumor indicate sufficient sensitivity to suggest that the DBT-NIRST approach may be able to discriminate different types of breast abnormalities based on hemoglobin concentration levels.

Software procedures for reconstructing NIRST data from DBT images were developed and will be applied during subject exams in the future. Given 75 detectors and a configurable number of source positions (66 of which were used in the phantom experiments reported here) that result in illuminations at eight wavelengths, the DBT/NIRST system generates a significant amount of data. Additionally, breast and source-detector geometry dictate that NIRST reconstructions be performed in 3D. Lesions encountered during screening are often small, most being under 2 cm,³⁸ which necessitates the use of fine meshes with high resolution, especially within regions of suspicion identified in the DBT image volume. These factors combine to make NIRST image formation a challenge. To reduce computational size in the patient simulations, the number of optical parameters was reduced by assuming property homogeneity in regions segmented in the DBT image volume. Conjugate gradient reconstruction has also been implemented to reduce memory requirements, although it did not decrease image reconstruction time.

Small differences in wavelengths and geometry exist between the physical system and the simulations (slightly larger CW detector spacing and fewer wavelengths were implemented). Also, simulations and reconstructions assumed point sources and detectors that are not representative of the actual system components which have localized, but spatially distributed footprints. Simulations based on distributed sources and detectors show similar trends to those with point source and detectors; however, these reconstructions are currently impractical computationally, and need to be optimized before a full parameter study such as the one reported here can be completed. Despite the idealization of the sources and detectors in the simulations, the phantom results are similar (Fig. 7). DBT generates limited angular sampling leading to anisotropic spatial resolution that induces image artifacts which complicate the segmentation process, leading to mischaracterization of tissue regions. Inaccurate segmentation adversely affects reconstruction results.³¹ Filtering algorithms and auto-segmentation methods have been created to address the problem.³⁹ Breast tissue has variable composition; hence, simulating it as three homogeneous regions for each chromophore is incomplete. Nonetheless, given that light propagation in the breast is diffusive, the effect of heterogeneity will be diminished from partial volume averaging; thus, representing the breast as broad regions of three tissue types is likely to be sufficient.

IV.B. System simulations

Designing new multimodal imaging systems typically presents tradeoffs and prototype simulations can guide hard-

ware selection and implementation. Minimizing the number of wavelengths, as well as the number of sources and detectors, in the FD imaging module decreases costs, complexity, and examination time in a multimodality DBT-NIRST breast imaging platform. Simulations of NIRST data for eight subject-specific breast volumes based on DBT images highlighted differences in results from each system change.

Interestingly, no significant differences were found in HbT recovery between FD simulations performed with 6 versus 3 wavelengths of light. The source light spanned the same wavelength range (661–849) in both cases. Given the wavelength dependence of scattering, if all lasers are equally stable, these results suggest that 3 wavelengths of FD data may be adequate.

Comparing two-region with single bulk tissue estimates of scattering had a large impact on the recovered HbT concentration. Mischaracterization of scattering led to errors in quantification of HbT. Significant differences in scattering are known to exist between adipose and fibroglandular tissue^{22,23} and both contribute to a large fraction of breast composition by volume. Taking a single bulk estimate of these two tissues averages their scattering effects leading to underestimation of hemoglobin concentration in the adipose region and overestimation in the fibroglandular and tumor regions. While bulk estimates of scattering could even be obtained from a single measurement, quantitative recovery of chromophore levels in the different regions will not be as accurate as in the two-region scattering case. Nonetheless, single region scattering estimates could be used for examining hemoglobin contrast between two regions. Overall, errors in tumor HbT are much larger in the bulk scatter estimate case relative to its two-region counterpart. The fixed six source and detector geometry considered in these simulations can accurately estimate scattering for two regions across a range of breast sizes.

Although limiting the FD information obtained during a scan even further decreases system cost, complexity, and examination time, it adversely affects the quantitative results. Overestimation of scattering leads to underestimation of absorption and vice versa. Malignant lesions tend to have greater scattering values than fibroglandular tissue,^{22,40,41} hence, a two-region scattering estimate is likely to underestimate tumor scattering and lead to an overestimation of HbT. Recent studies of a combined DBT-NIRST system have detected significantly higher scattering coefficients in malignant lesions when compared to benign abnormalities and cysts;^{12,42} thus, we anticipate that scattering errors will lead to a greater enhancement of hemoglobin recovery in cancers as opposed to benign lesions.

Although the inaccurate estimates in scattering may appear to be a serious flaw in system design, their impact can be mitigated. The errors in hemoglobin recovery are plotted in Fig. 7. Relative changes in scattering do not significantly depend on region size or shape or actual hemoglobin concentration. Hence, if scattering estimates are not correct, but are consistently inaccurate in different regions, quantitative recovery of hemoglobin concentration will also be inaccurate, but contrast between regions should be maintained. NIRST algorithms are known to have difficulty fully recovering

absolute HbT,¹³ yet, analyzing relative contrast has proved to be a productive alternative.¹¹ Once the FD components of the DBT/NIRST system are developed, characterization of scattering can be evaluated more completely through additional phantom measurements.

Another approach to improving scattering estimates utilizes the extensive CW measurements. By modifying the reconstruction algorithm and taking advantage of the multispectral nature of the data, CW information can be used to estimate tissue scattering properties,^{43,44} which would be possible with a higher bandwidth source such as a super-continuum laser with a tuning filter.

These patient simulations have confirmed the importance of accurate scattering estimation for quantitative hemoglobin recovery. A frequency-domain system consisting of six sources with only three wavelengths and six corresponding detectors could provide excellent two-region estimations of scattering. Thus, successful DBT/NIRST imaging is possible with a limited FD and robust CW data set.

IV.C. Phantom experiments

Phantom measurements were used to validate the DBT-NIRST recovery of hemoglobin values. Although not a complete representation of tissue, these agar phantoms do mimic breast tissue optical absorbers, such as HbT, and have known values of absorption and scattering coefficients. The NIRST system design was able to recover 70% of the background HbT and exhibited linearity when estimating blood concentration variations within a subsurface inclusion.

The phantom data also confirms the simulation results on sensitivity to scattering. Deliberately altering the scattering parameters in both the background and the inclusion led to errors in HbT recovery similar to those found in the patient simulations. Overall, a 5.4% greater error occurred in HbT in the phantoms with 20% underestimation of scattering and a 1.8% greater error in the phantoms with 20% overestimation of scattering. The phantom experiments show that the DBT-NIRST system is able to quantify inclusions as well.

V. CONCLUSIONS

NIRST and DBT is a synergistic combination that may be able to decrease the rate of false positive breast screening examinations and enhance sensitivity of breast cancer detection. Development of a combined system requires careful consideration of cost, complexity, and examination time. Here, we used simulations of actual DBT subject exams to guide hardware development and demonstrate the potential of coregistered DBT-NIRST breast imaging. Individual simulations of benign and malignant lesions suggest that coregistered DBT-NIRST may be able to distinguish between these two types of breast abnormalities, assuming they contain different levels of HbT concentration.

Scattering estimation has an important but predictable effect on HbT quantification. In terms of developing the simplest frequency-domain adjunct, measuring scattering with three wavelengths (instead of six) does not appear to affect

accuracy significantly. A hardware design limited to 6 FD sources and detectors can predict scattering in two regions. Phantom experiments validate the CW components of the system and demonstrate linearity in image reconstruction of HbT across different concentrations in inclusions of the size and contrast expected in a typical breast. In addition, the experimental data confirms the patient simulation results on the effects of scattering. Future work will focus on development of the FD components of the system design and the imaging of normal subjects.

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