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Broadband frequency-domain near-infrared spectral tomography using a mode-locked Ti:sapphire laser

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Abstract

Frequency-domain near-infrared (NIR) diffuse spectral tomography with a mode-locked Ti:sapphire laser is presented, providing tunable multiwavelength quantitative spectroscopy with maximal power for thick tissue imaging. The system was developed to show that intrinsically high stability can be achieved with many wavelengths in the NIR range, using a mode-locked signal of 80 MHz with heterodyned lock-in detection. The effect of cumulative noise from multiple wavelengths of data on the reconstruction process was studied, and it was shown that inclusion of more wavelengths can reduce skew in the noise distribution. This normalization of the data variance then minimizes errors in estimation of chromophore concentrations. Simulations and tissue phantom experiments were used to quantify this improvement in image accuracy for recovery of tissue hemoglobin and oxygen saturation.

1. Introduction

Near-infrared (NIR) spectral tomography is a noninvasive method to obtain physiological information about tissue and has been used in imaging applications associated with breast cancer and brain function. The accuracy in estimating absorber concentrations is superior when time-resolved or frequency-domain measurements are used because these data types provide a measure of the average photon path length, which allows diffusion theory to be used to separate absorption from scattering values [1–4]. However, the ill-posed nature of NIR image reconstruction can limit the accuracy of the spectral fitting process, thereby producing substantial errors in the concentration values of absorbers. There are actually few published data available about the magnitude of these errors, but spectroscopy with as little as 2–3 wavelengths through bulk tissue is thought to be inaccurate for absolute tissue spectroscopy. Incorporating spectral constraints into the image formation problem can enhance the accuracy of NIR tomographic spectroscopy [5–9], especially when additional wavelengths are added. Most accurate systems use current-modulated diode lasers as the light source for NIR imaging because of their low cost, stability, and ease of use, but they are typically low in power, and the wavelength availability in the NIR range can be limited. Combining a small number of discrete frequency-domain wavelengths with additional broadband continuous-wave spectroscopy [10] is an effective option, but the optimal system would generate frequency-domain data across the entire usable spectrum.

In our previous work, a systematic simulation study showed that including more wavelengths of data could improve the recovery of chromophore concentrations and scattering properties [9]. Following that work, in this paper the experimental validation of

this conclusion is shown, where broadband NIR frequency-domain data are acquired, based on using a high-power, wavelength-tunable mode-locked pulsed laser as the light source. Previous studies have demonstrated the use of a Ti:sapphire pulsed laser to generate supercontinuum light for time-resolved spectral quantification of chromophore concentrations and scattering parameters [11]. Frequency-domain measurement with a pulsed laser was also reported in a human brain study with a single wavelength, where the reference optical signal was used for lock-in detection [12]. In our work, phase-sensitive detection relative to the intrinsic mode-locked frequency of a Ti:sapphire laser is accomplished with sufficient stability and concomitant measurement noise characteristics to allow high-fidelity spectral image reconstruction. The mode-lock stability of these lasers is not routinely very reliable, and so the development here of a system where the phase stability is good is a critical development in the potential use of Ti:sapphire lasers for this application. The system signal amplitude and phase noise are systematically compared with that produced with diode lasers over the full photomultiplier tube (PMT) detection band. Image reconstruction improvements with increasing numbers of wavelengths are quantified.

In addition to the instrumentation work, the reason that adding more wavelengths gives better reconstruction results is explored based on the noise behavior of the imaging system. It has been widely accepted that the advantage of spectral reconstruction lies in the *simultaneous* inversion of multiple wavelength data. Corlu *et al.* proposed an approach to select the optimal wavelength set that best quantifies tissue properties by maximizing the uniqueness of the inverse problem and equalizing the contribution of different chromophores [7]. What is examined here is that even if the criteria in [7] are satisfied, the addition of more wavelengths can still benefit the reconstruction process through reduction in unpredictable measurement errors which have bias in their origin. The total noise of the system was analyzed as a function of different numbers of wavelengths to assess the value of added wavelengths in the eventual recovered chromophore concentrations, relative to the total multiwavelength noise figures.

Phantom experiments were conducted to examine the improvement in spectral imaging accuracy, using phase-sensitive detection at the mode-locked frequency of the Ti:sapphire laser. This system was used to perform heterodyne measurement at the wavelength range from 700 to 845 nm, which covers the major spectral feature of oxygenated hemoglobin (HbO₂) and deoxygenated hemoglobin (Hb). The ability to differentiate total hemoglobin (Hbt) concentration and oxygen saturation (StO₂) has been improved. Simulations and experiments showed that more wavelengths give proportionate benefit to the reconstructed chromophore accuracy. Moreover, this approach maximizes the allowable light dose in tissue for diagnosis (established by ANSI standards), which increases measurement signal-to-noise ratio and enables imaging through thick tissues.

2. Materials and Methods

The propagation of NIR light in tissue is determined by both absorption and scattering effects, and the diffusion equation is commonly used to model the relevant transport process based on the assumption that scattering dominates absorption in tissue [13]. In the frequency domain, this radiative transport process is given by the diffusion equation

$$-\nabla \cdot D(r) \nabla \Phi(r, \omega) + \left[\mu_a(r) + \frac{i\omega}{c} \right] \Phi(r, \omega) = q_0(r, \omega), \quad (1)$$

where $q_0(r, \omega)$ is an isotropic light source at position r , $\Phi(r, \omega)$ is the isotropic fluence at angular modulation frequency $\omega = 2\pi f$, and c is the speed of light in tissue. $\mu_a(r)$ is the

absorption coefficient map, and $D(r) = 1 / \{3 [\mu_a(r) + \mu'_s(r)]\}$ is the diffusion coefficient distribution. An image reconstruction algorithm based on the finite-element method is used, and the distribution of optical properties is estimated through a Newton-type minimization of the objective function:

$$\chi^2 = \sum_{j=1}^M \|\Phi_j^m - \Phi_j^c\|, \quad (2)$$

where Φ_m is the measurement data and Φ_c is the calculated model response for M measurements. Incorporating spectral information for the chromophores of interest can effectively decrease matrix ill conditioning and the ill posedness of the inversion process [8]. To map the absorption and scattering properties to chromophore concentrations and scattering parameters, $\mu_a(r)$ is considered to be a linear combination of all chromophores in tissue based on Beer's law:

$$\mu_a(\lambda) = \sum_i \varepsilon_i(\lambda) C_i, \quad (3)$$

where C_i is the concentration of each chromophore and $\varepsilon_i(\lambda)$ is its molar absorption coefficient. With an approximation of Mie scattering theory, elastic scattering has been found to fit the empirical equation:

$$\mu'_s(\lambda) = a\lambda^{-b}, \quad (4)$$

which can be used to constrain the model by reducing the problem to two unknowns, often termed scattering amplitude a and scattering power b . The updated equation in the spectral reconstruction process becomes

$$[J^T J + \lambda I] \Delta c = J^T \Delta \Phi,$$

where J is the Jacobian matrix measuring the sensitivity of boundary data to the change of tissue properties, including chromophore concentrations and scattering amplitude and power [8]. Here Δc is the update of tissue properties and $\Delta \Phi = \Phi_j^m - \Phi_j^c$. Since $J^T J$ is ill conditioned, λI is added as a regularization term. For all simulations and experimental data in this work, a Levenberg–Marquardt algorithm for regularization was used [14], where λ starts at ten times the maximum value of the diagonal of $J^T J$ matrix and is decreased at a constant rate with successive iterations.

The existing frequency-domain spectroscopy system for NIR imaging has been developed with a set of six diode lasers that are modulated by using an external signal generator where the detected light response is electrically heterodyned with a reference signal so that the intensity and phase of transmitted light can be determined [3]. In this work, a pulsed, wavelength-tunable Ti:sapphire laser (Mai Tai HP, Spectra-Physics Inc.) was used as the light source. The system configuration is shown schematically in Fig. 1. Unlike the diode-laser-based frequency-domain instrument, which generates intensity-modulated light by

using an external frequency generator, the new approach takes advantage of the pulsed light occurring at the intrinsic mode-locked frequency (f_1), which hovers around 80 MHz and shifts slightly with different wavelengths of operation. The real-time mode-lock frequency and phase can be triggered by using the analog signal provided in the rear of the laser head. In this system, the frequency of the output electrical signal from the laser is further divided to 10 MHz by using a phase-locked loop frequency synthesizer (Analog Devices Inc, EVAL-ADF4007EB1) and is used to trigger the external clock of a signal generator (IFR Inc., PSG1000). The output of the signal generator is offset from the fundamental frequency, f_1 , by 1 kHz (δf), giving $f_2 = f_1 + \delta f$. Then the signal at f_2 is split into two paths, one of which is used to electrically heterodyne the detected light signal from the PMTs (Hamamatsu) through a mixer to a low frequency (at $\delta f = 1$ kHz) for data acquisition. The dynamic range of the PMT response is kept within the range of 0.01–0.1 V for data acquisition purposes, and this range is dynamically maintained by automatically setting the gain of the PMTs to the appropriate range at each source position. This voltage range was calibrated to real intensity and indicates that the sensitivity of the detected power is within the range from 10^{-13} to 10^{-9} W [3]. The other part of the f_2 signal is mixed with the electrical output from the laser at f_1 to obtain a phase reference at δf . The laser pulses are extremely short in time, near 100 fs, when initially exiting the laser, meaning that there is a wave packet of multiple harmonic frequency content in this pulse train, which extends well into the gigahertz range. However, these pulses pass through the lenses and fibers associated with the imaging system that blur the laser signal in time, thereby converting more amplitude into the fundamental part of the power spectrum around f_1 . The actual mode-lock frequency of the laser varies around 80 MHz, but this variation is reflected in the analog output signals and is tracked by taking the Fourier transform of the heterodyned signal and extracting the maximum value to keep the lock-in detection scheme working properly. The δf heterodyned signals are bandpass filtered and amplified by $100\times$ and then read by a multichannel analog-to-digital data acquisition board. As shown in Fig. 1, sources and detectors are arranged in a circular geometry. Controlled by an automated rotary stage, the measurement is taken at 16 source positions sequentially and 15 detectors acquire transmitted light signals simultaneously [3]. A complete measurement (16 sources $\times$ 15 detectors) requires less than 30 s at one wavelength. The output wavelength of the Ti:sapphire laser is automatically switched with a LabVIEW control program. In this work, the total time for all 11 wavelengths to be measured was about 7 min, including laser wavelength switching time and settling time.

For the experiments reported here, the average power of laser light measured at the fiber interface was attenuated to about 20 mW. This was about the same level as our present diode lasers [3]. However, the laser is capable of delivering power up to 2.9 W at its output. Output power is an important consideration because it will potentially improve the depth of tissue that can be imaged (by several centimeters) beyond what is achievable with low-power diode lasers without exceeding safety standards. The existing diode laser system has been used to image through breasts with diameters of 9–12 cm, depending on the blood content of the tissue, so that this new source should allow imaging through 11–14 cm of breast tissue. The limit on input power for diagnostic use is dictated by federal ANSI standards, which is near 1 W/cm^2 at 800 nm. Of course, use of the full power range requires careful safety assessment to eliminate the potential of overexposure. This is readily achieved in well-designed systems with redundant interlock.

The other important feature of the wavelength-tunable Ti:sapphire laser system is the superior spectral coverage compared with discrete diode lasers. The tunable wavelength can be chosen from 690 to 1020 nm with 5 nm resolution. To study the stability variation of the system across the full wavelength range of PMT signal detection, repeated measurements (100 trials) were recorded in a solid phantom every 5 nm from 695 to 845 nm. The standard deviation of the logarithm of amplitude (in percentage) and phase (in degrees) is shown in

Fig. 2(a). The amplitude and phase noise levels, assessed as the normalized standard deviation in the measurements, fluctuated at different wavelengths owing to the wavelength-dependent stability of mode-lock circuits working with the Ti:sapphire laser. This varying noise level is particularly high at the low- and high-wavelength range limits. This is primarily determined by two factors that arise from the source and detector. The instability near 690 nm was caused by the higher loss of the laser cavity near its low-wavelength limit, while the increasing instability close to 850 nm was caused by the significantly decreasing sensitivity of the PMT cathodes. It is important to clarify that the upper limit of 0.1% in amplitude and 0.5° in phase does not represent the actual noise level of the system, because the solid phantom used for measurement gave good signal-to-noise ratio levels at all wavelengths. To compare the limit of noise levels of the Ti:sapphire laser source with a diode laser system [3], a variable attenuation liquid phantom was used to decrease the signal intensity continuously. All the measurement data points for all detectors were put together to show the noise levels of amplitude and phase versus signal intensity in both systems, as shown in Figs. 2(b) and 2(c). The noise level was up to 1% in amplitude and 3° in phase, which is higher than that in Fig. 2(a). The noise level goes higher as the signal intensity decreases toward the response limit of the PMTs. Although noisier at some amplitude values, the Ti: sapphire source generally shows stability similar that of to the diode laser system at the same signal intensity levels [3].

3. Results and Discussions

As mentioned Section 1, multiwavelength data can improve the accuracy of quantification of chromophore concentration and convergence of the inverse problem in the face of experimental noise. In spectral image reconstruction, the number of unknowns is fixed as the number of chromophores multiplied by the number of nodes. Inclusion of more wavelengths of data can decrease the ill conditionedness of the inverse problem and certainly cover more spectral features across the whole spectrum of chromophores [9]. In this work, the advantage of multispectral reconstruction was analyzed from a statistical view of noise distribution in simulations and examined in experiments.

A. Simulations

Simulations were used to guide the experimental study plans, and, in particular, one of the most critical unknown factors related to these simulations was the actual experimental noise features. The NIR image reconstruction is essentially a least-squares fitting process. In a spectrally constrained reconstruction, data of multiple wavelengths are combined for estimation of chromophore concentration and scattering properties. So it is the distribution of combined noise that determines the fitting process in spectral reconstruction. Most related work assumes that the noise in the data is normally distributed [7,15–17]. However if the noise is not normally distributed, the fitting results can severely deteriorate. Although it is difficult to isolate all the sources of noise in a realistic system, what can be studied is the net effect of all the factors, and what matters to the reconstruction process is whether this net noise is close to a normal distribution. In the following simulations, two noise models were assumed for comparison. The first one was a zero-mean noise case, which assumed that (1) the noise of each measurement at one detector and one source position was proportional to the signal intensity, and (2) the sum of all the noise from all 240 measurements at one wavelength was normally distributed and had zero mean value. This noise model has been almost universally used. The second noise model also assumes that the noise of each measurement was proportional to the signal and that the noise of the data at each wavelength was normally distributed, but the mean value of the total sum noise at each wavelength varies randomly, which introduced error with different non-zero-mean values into each wavelength. When multiwavelength data are combined, the non-zero-mean noise leads to an

overall nonnormal distribution. To simplify the problem, only amplitude noise was considered, since it was the major effect in the quantification of chromophore concentrations.

The simulation example was created with contrast in Hbt, StO₂, and water. The homogeneous circular background was 86 mm in diameter, and the source–detector configuration was the same as the system setup (16 sources × 15 detectors). The inclusion was 20 mm in diameter and had 3:1 contrast in the chromophore concentration. The recovered average value of this region of interest was compared with the two noise models. A finite-element mesh with 1785 nodes was used to calculate the forward data, based on the optical properties of this example. As for the first noise model, a normally distributed zero-mean noise was generated at each wavelength as follows:

$$I_{\text{sim}}^{\lambda} = I_{\text{theory}}^{\lambda} + N\left(0, \varepsilon I_{\text{theory}}^{\lambda}\right), \quad (5)$$

where I_{sim}^{λ} and $I_{\text{theory}}^{\lambda}$ are simulated experimental data and theoretical forward data, respectively. In Eq. (5), I represents the natural logarithm of amplitude data incorporated into the inverse calculation. $N\left(0, \varepsilon I_{\text{theory}}^{\lambda}\right)$ is normally distributed noise with zero mean and standard deviation $\varepsilon I_{\text{theory}}^{\lambda}$ with ε equal to 2%. This assumed noise percentage is larger than the upper limit of noise level (1%) estimated from the standard deviation of repeated measurements, as shown in Fig. 2(b), because ε represents the overall difference between the true data and the measured data, having both bias and variance. This difference comes from (1) instrumentation sources such as variation in detector response and the instability of laser power and (2) coupling errors between the fiber interface and the breast tissue. To keep the comparison consistent, the wavelengths were chosen to be the same for simulations and experiments: a 5-wavelength set including 700, 740, 790, 830 and 845 nm and an 11-wavelength set including 700, 710, 720, 740, 755, 770, 790, 810, 830, 840 and 845 nm.

The histograms of the noise level distribution (in percentage) for the data sets with 5 and 11 wavelengths are plotted in Figs. 3(a) and 3(b), respectively. In this zero-mean case, when the data with multiple wavelengths were combined, the whole noise data set still displayed normally distributed features. Figure 4 shows the reconstructed images of the 5-wavelength and 11-wavelength cases. The true values of chromophore concentrations and scattering properties were shown in the first row. Since the 5-wavelength and 11-wavelength data sets result in similarly low condition numbers (56.4 and 62.3) according to Corlu's criteria [7], both wavelength sets provide sufficient spectral information to differentiate the chromophores. Therefore no significant differences in recovery results were found. The bar graph in Fig. 5(a) shows the recovered error in the region of interest. When noise at each wavelength has zero mean value, reconstructed chromophore error with few wavelengths was similar to that with a higher number of wavelengths. The reconstructed images of water were dominated by noise in both cases. This was because the spectrum of measurement was limited under 845 nm according to the response ability of the PMT. The major spectral peak of water above 900 nm could not be covered. To increase the accuracy of water concentration recovery, a continuous-wave approach might be incorporated with frequency-domain measurement, and this strategy is currently under investigation.

Under the second noise model, first the zero-mean normal-distribution noise was generated for data at each wavelength, and then a random shift of mean value was added on each data set, so that a normally distributed noise scenario with different center positions at each wavelength was simulated:

$$I_{\text{sim}}^{\lambda} = I_{\text{theory}}^{\lambda} + N(a(\lambda), \varepsilon I_{\text{theory}}^{\lambda}), \quad (6)$$

where $N(a(\lambda), \varepsilon I_{\text{theory}}^{\lambda})$ is the normally distributed noise with a mean value of $a(\lambda)$ and standard deviation $\varepsilon I_{\text{theory}}^{\lambda}$ with ε equal to 2%. In the simulation, $a(\lambda)$ is a random value in the range of 5% of $I_{\text{theory}}^{\lambda}$. The chromophore properties are the same as in the previous example. Data for 5 and 11 wavelengths were combined for spectral reconstruction.

In this case, the combined noise of the 5-wavelength data set showed a nonnormal distribution feature in Fig. 3(c), while the 11-wavelength set gives a nearly normal distribution in Fig. 3(d). The reconstructed images in the second row of Fig. 6 show that the deviation from a normal noise distribution leads to poor inversion results. The bar graph in Fig. 5(b) displays the recovered error in the estimated value of the inclusion. Under the noise model defined in Eq. (6), nonnormal distributions with fewer wavelengths lead to significant underestimation of chromophore concentrations with about 60% error in HbT and StO₂ as compared with less than 40% error in Fig. 5(a). However, the error using 11 wavelengths in Fig. 5(b) is decreased significantly and is about the same level as in Fig. 5(a), since the combined noise behavior was close to a normal distribution. The underestimation of parameters can be understood as a distortion of the least squares fitting process by the nonnormal deviation noise. In the maximum likelihood sense, the fitting curve was biased in the wrong direction to bring the noise into the model. Even though the five-wavelength data set was well selected spectrally [7], the reconstruction was considerably affected by noise in a non-zero-mean situation.

The comparison of these two different models provides an important guidance for the experiment. The ability to have spectral fitting results that are minimally sensitive to noise does not largely depend on the number of wavelengths if the noise distribution of each wavelength is close to the ideal zero-mean normal distribution. Yet, these simulations do indicate that including more wavelengths of data has a distinct advantage when there is a variation in the mean value of noise at each wavelength. The non-zero-mean value of noise can occur in all data sets, and this value is likely different in each wavelength data set. Combining more wavelengths in the inversion provides a sum data set that appears to be closer to a zero-mean noise set. This observation was examined with experimental data, as described below.

B. Experiment

The broadband frequency-domain system provided a unique approach to test presented noise models because the measurement wavelengths could be chosen freely across the Ti:sapphire laser tuning range. To study the resulting image accuracy of this system, gelatin phantom experiments with a heterogeneous target were constructed for hemoglobin concentration measurements. The gelatin phantom was composed of porcine gelatin (Sigma-Aldrich G2500), TiO₂ powder (Sigma-Aldrich T8141), porcine blood, and saline. The details of phantom preparation were discussed in previous papers [9,18]. The first test phantom had a blood solution inclusion and gelatin background. The Hbt concentration throughout the background of this phantom was approximately 10 μM , and the blood solution inclusion had approximately 30 μM Hbt concentration and 1% Intralipid. The diameters of the phantom and inclusion were 88 and 18 mm, respectively. This provided a hemoglobin target with 3:1 contrast and essentially no contrast in scatter. The water concentration of the inclusion was around 100%, and the gelatin background was assumed to have a lower water concentration than the blood solution inclusion [19]. To study the ability to differentiate between

oxygenated hemoglobin and deoxygenated hemoglobin, a second phantom test was designed to feature a contrast in both Hbt and StO₂ by dissolving some yeast in the blood solution inclusion to decrease the oxygen concentration. A chemical microsensor (Diamond general development corporation, Ann Arbor, Michigan) showed that the StO₂ was around 50% during measurement. Two different data sets consisting of acquisition with 5 and 11 wavelengths, respectively, were collected for spectral tomography reconstruction over the wavelength range from 700 to 845 nm. Figure 7 shows the reconstructions of the first phantom with contrast only in Hbt, and Fig. 8 shows the reconstructions of the second phantom with Hbt and StO₂ contrast. In the first row of Figs. 7 and 8 of the 5-wavelength case, the contrast in Hbt was significantly underestimated, while the 11-wavelength case in the second row shows better recovery of Hbt, and the inclusion with StO₂ contrast was better spatially resolved with more wavelengths. The bar graphs in Figs. 9(a) and 9(b) display the improvement when data sets of 11 wavelengths are used for spectral constrained reconstruction.

The experimental results have shown quite a similar trend, as was observed in the non-zero-mean noise model in Fig. 6. To explore the connection between the experiments and simulations further, an approximation noise distribution of the experiment was extracted from the multiple wavelengths of data for the first phantom experiment shown in Fig. 7, as follows:

$$\varepsilon = I_{\text{expt}} - I_{\text{theory}}, \quad (7)$$

where I_{expt} is the experimental data and I_{theory} is calculated with known phantom properties by using the theoretical diffusion model. Besides the systematic errors mentioned before, ε here also includes the uncertainty of the actual phantom properties, which largely depend on the procedure of preparation of phantoms. However, the critical factor is the combined noise distribution of all these realistic factors.

The histograms of combined noise with 5 and 11 wavelengths were plotted in percentage in Fig. 10(a) and 10(b) respectively. The five-wavelength case shows larger deviations from a normal distribution, which is consistent with the non-zero-mean noise model of Eq. (6) in the simulations. Both the noise distribution plots and measured data would support that the mean value of noise varies at different wavelengths. This nonzero unpredictable bias is a mixture of several factors with (1) the varying stability of the mode-lock performance at different wavelengths and (2) the variation of response between detectors. These wavelength-dependent factors lead to varying noise behavior across the spectrum, which in turn causes underestimation of the chromophore properties if the combined noise distribution deviates from normal distribution. This occurs even though the few sampling wavelengths are chosen to maximally differentiate the chromophores. Including more wavelengths proved to be an effective strategy that compensates for this unavoidable systematic error in two ways. First, when more wavelengths of data are combined, the collective noise behavior appears closer to a normal distribution, and, second, more wavelengths provide a more comprehensive data set of spectral information about the chromophores. From a practical point of view, adding more wavelengths leads to extra cost in the instrumentation and usually a longer acquisition time. The best strategy is to find the trade-off between the gain in quantification of tissue properties and cost in practical implementation of a multiwavelength system. In this work, adding wavelengths does not bring more instrumentation work, since the Ti:sapphire laser is inherently tunable across the NIR range. Yet measurement time is another important issue in clinical study of NIR tomography, and here the total measurement time for 11 wavelengths was about 7 min,

which has been acceptable in patient imaging studies. Moreover, the increased stability of the reconstruction could also be useful for NIR systems with less expensive diode lasers. Usually, the diode lasers are chosen at wavelengths that provide maximum sensitivity to target chromophores. The results in this work show that the seemingly redundant wavelengths could play a critical role in improving quantification of chromophore concentrations. The extra cost in diode lasers is usually low, and the time of measurement is also convenient for reduction with a laser-diode-based system using approaches such as frequency encoding in frequency-domain measurement [20] and broadband spectroscopy in a continuous-wave system [21]. Several studies have been presented to find the optimum wavelength set for better quantification in chromophores [16,22]. With a larger number of wavelengths, the similar optimized approach can still be implemented to differentiate the chromophores, while the distortion by noise is effectively lessened. Both simulations and experiments show that even with large numbers of wavelengths, there is significant underestimation on HbT, with recovery error from 40% to 55%. The difficulty in obtaining accurate quantification comes from the ill-posed nature of diffuse optical tomography reconstruction. The number of unknowns ($1785 \text{ nodes} \times 5 \text{ parameters}$) is much larger than the number of data ($240 \text{ measurement} \times 11 \text{ wavelengths}$) even though the spectral reconstruction method is used. Normally distributed noise can still bias the objective function χ^2 and leads to underestimation of parameters. The cross talk among chromophores is another reason for the recovery error, and including longer wavelengths to better quantify water concentration could improve the hemoglobin results. Incorporating spatial prior information has been shown to be a good way to improve this quantification further [9,23,24] and leads to diffuse NIR spectroscopy being used for alternative purposes, which is as an adjunct to standard imaging systems. The potential optimum imaging system that incorporates spectral constraints in this type of optical method combined with magnetic resonance imaging is currently being tested clinically.

4. Conclusions

In summary, a new frequency-domain system consisting of a tunable pulsed laser was developed for NIR spectroscopic imaging. The intrinsic signal from the laser was used for lock-in detection. This system exhibited excellent stability across the entire wavelength range of operation and resulted in noise levels that are essentially equivalent to using a diode-laser source. The ability to select more wavelengths significantly improved spectral reconstruction and generated more accurate information about chromophore and scattering properties. The effect of the noise distribution was studied with simulations and experiments. A non-zero-mean distribution of the noise at different wavelengths was found to cause underestimation of the chromophore concentrations in the spectral reconstruction. Including more wavelengths has proved to be a reliable way to compensate for this effect of systematic random shift. A high signal-to-noise ratio can potentially be achieved because of the availability of more input power at each wavelength, which is especially important for imaging through thicker breast tissues. Evaluation of this approach is under way, including its implementation with a magnetic-resonance-guided NIR imaging system for incorporating spatial priors and with combining spectral information above 850 nm through spectrometer detection. The results here demonstrate the proof in principle that the system can work, and, while expensive, it has major benefits for biomedical and scientific applications. The system can also be utilized in a parallel implementation where the spectrum is subdivided and all wavelengths are detected in parallel, as was demonstrated previously [25]. Thus, while the current version is simply the initial demonstration, the benefits of arbitrary wavelength selection makes the demonstration of this system promising in quantitatively accurate tissue spectroscopy or image-guided spectral tomography.

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Fig. 1.

System diagram of the frequency-domain NIR imaging instrument that incorporates a mode-locked Ti:sapphire laser as the broadband light source, with a 10 MHz lock to an external signal generator for a reference signal, and heterodyne mixers after the PMT detectors.

Fig. 2.

(a) Measurement noise levels (normalized standard deviation) for amplitude (Amp.) and the phase (unnormalized standard deviation) are shown as a function of the wavelength when using the Ti:sapphire-laser-based approach. (b) Amplitude noise levels and (c) and phase noise levels shown as a function of mean signal amplitude (on a logarithm scale) to compare the Ti:sapphire laser to a diode laser system, showing they have overall similar error values.

Fig. 3.

Histograms of noise distribution of two noise models with 5 and 11 wavelengths: zero-mean noise distribution (a) for the 5-wavelength data set and (b) for the 11-wavelength data set; non-zero-mean noise distribution (c) for the 5-wavelength data set and (d) for the 11-wavelength data set.

Fig. 4. (Color online) Reconstructed images using the simulated zero-mean noise data. The first row shows the true properties of chromophores (total hemoglobin, Hbt; oxygen saturation, StO₂; water) and scatter parameters (amplitude and power). The second and third rows show the reconstruction results with 5-wavelength and 11-wavelength data sets, respectively.

Fig. 5.
(Color online) Bar graphs of reconstruction errors of the region of interest are shown for (a) the results with the zero-mean noise model (b) the results with non-zero-mean noise model.

Fig. 6. Reconstructed images using the simulated non-zero-mean noise data. The first row shows the true properties of chromophores and scatter parameters. The second and third row display the reconstruction results with 5-wavelength and 11-wavelength data sets, respectively.

Fig. 7.
 (Color online) Experimental results of gelatin phantom with blood solution contrast in Hbt. The first row shows reconstructed results with the 5-wavelength data set; the second row shows reconstructed results with the 11-wavelength data set.

Fig. 8. (Color online) Experimental results of gelatin phantom with blood solution contrast in Hbt and StO₂. The first row shows reconstructed results with the 5-wavelength data set; the second row shows reconstructed results with the 11-wavelength data set.

Fig. 9. Bar graphs of reconstruction errors of inclusion in two phantom experiments with (a) contrast in HbT and (b) contrast in both HbT and StO₂.

Fig. 10.

Noise distribution of experimental data from the phantom with contrast in Hbt: histogram of noise distribution for the (a) 5-wavelength data set and (b) 11-wavelength data set.