Media Characterization under Scattering Conditions by Nanophotonics Iterative Multiplane Spectroscopy Measurements

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ABSTRACT: Characterizing materials is preferably done by multiple wavelengths. In opaque materials, the scattering poses a challenge due to the additional complexity to the spectroscopic measurements. We have previously demonstrated an iterative multiplane method for characterizing materials using the reflection from turbid media. Initial studies were performed in the red wavelength regime (632.8 nm) which is optimal for biomedical applications. However, in order to differentiate between materials, it is better to use multiple wavelengths, as spectroscopy may detect the material fingerprint. In this paper, our iterative multiplane optical property extraction (IMOPE) technique is presented in the blue regime (473 nm). Agar-based solid phantom measurements were conducted and compared to our theoretical model. Compatibility between experiments in the red and blue wavelengths shows the robustness of our technique.

INTRODUCTION

Light–matter interactions have been studied for hundreds of years in different research areas, for example, material analysis, quantum physics, and biomedical optics. The interaction of light with different materials depends on the material optical properties, with the refractive index being a main factor. Spectroscopic methods examine the spectral dependence of the interaction, which reveals the material fingerprint. A very established spectroscopic technique is Raman spectroscopy (RS),1,2 which is based on the medium inelastic scattering. It is an important tool for determining structural information of solid and liquid media and chemical bonding changes. RS as a nondestructive technique has been applied in analytical chemistry, skin studies,3,4 food analysis,5 and detection of exogenous substances in latent fingerprints where it is important not to harm the samples. Another technique is the near-infrared spectroscopy (NIRS) that uses the NIR radiation (780–2500 nm) and the light attenuation by the sample to understand its chemical constitution and physical parameters.6,9 The use of the NIR region allows a greater penetration depth for biomedical applications, meaning it is useful for probing bulk materials; however, the tradeoff is the technique sensitivity.7 Hyperspectral imaging (HSI)10 in comparison to RS and NIRS obtains not only the sample spectral information but also the spatial information with high sensitivity to minor elements. The combination of conventional imaging and spectroscopic measurements makes HSI very appealing for various fields such as remote sensing,10,11 astronomy,12 agriculture,13 pharmaceuticals,14 and medical applications.15 Numerous spectroscopic techniques are applied in different research fields with each having its advantages and disadvantages. Nevertheless, they are all able to detect the sample atomic, molecular, or macro information by the use of spectral measurements.

We have previously presented our iterative multiplane optical property extraction (IMOPE) technique16−21 for extracting the scattering properties of different tissues. The fundamental idea of the IMOPE is the connection between the scattering properties of an irradiated medium and the re-emitted light phase. The irradiation of the medium is done by a laser source chosen to be in the red regime (λ = 632.8 nm). Our IMOPE technique was initially aimed for biomedical applications where the red wavelengths are the desired radiation source due to higher penetration depths. However, as in spectroscopy, multiple wavelengths, rather than just one, can provide more accurate information about the components within the sample. Each component has a different optical signature according to its optical properties, which determines the preferable radiation spectral region. For example, detecting different materials within an opaque aqueous environment, e.g., seawater, is better done using the blue regime. As the absorption of seawater is lower in the blue regime than in the red, the penetration depth of the blue light is higher, which enables detection of components deeper in the seawater.

In this research, the use of the IMOPE technique in the blue regime is presented. The IMOPE technique reconstructs the re-emitted light phase from an irradiated medium using the iterative Gerchberg−Saxton (GS) algorithm,22 which is known for beam shaping23 and phase retrieval24 for image reconstruction.25 The GS algorithm uses the propagation equations of the electromagnetic field and known intensity images at identified locations in order to reconstruct the light phase. Note, in contrary to the GS algorithm that uses the phase itself, the
IMOPE rather examines the phase distribution, specifically its second moment, the root mean square (RMS). Following the computation of the reconstructed phase RMS, its value is compared to our theoretical model for extracting the scattering properties of the sample. The IMOPE technique at the red regime was applied first in transmission mode for detecting organic nanoparticles within tissues and the quantitative signature of milk components (lactose and milk protein). Followed by this, reflection-based IMOPE was constructed and applied for tissues viability test and detection of gold nanorods and blood flow in the femoral vein of a mouse.

In this paper, we examine the feasibility of extracting the scattering properties by the IMOPE technique in the blue regime. The IMOPE experimental setup was duplicated, and a blue laser, rather than a red one, was used as a light source. In addition, the scattering properties of solid tissue-like phantoms had to be extrapolated and computed for the blue regime as the literature only provides liquid phantom scattering properties. To the best of our knowledge, this is the first time that solid phantom scattering properties are calculated in the blue regime. Finally, the blue regime reflection-based IMOPE was tested on solid tissue-like phantoms and produced high compatibility to theory and results of the red regime reflection-based IMOPE.

## MATERIALS AND METHODS

### Iterative Multiplane Optical Property Extraction (IMOPE)

The IMOPE technique is a combination of a theoretical model, an experimental setup, and the iterative GS algorithm (IMOPE) (as shown in Figure 1a). The theoretical model links the re-emitted light phase distribution to the reduced scattering coefficient ($\mu'_s$) of a medium. The experimental setup records the light intensity images at different distances, which are then processed by the iterative GS algorithm to reconstruct the reflected light phase. Finally, the reconstructed light phase RMS is computed and compared to the theoretical phase RMS to receive the medium $\mu'_s$.

The IMOPE theoretical model was described previously in the red regime where a master–slave dual-source model is taken into account. In this configuration, the physical source is represented by two virtual sources, a primary and secondary isotropic source, which their locations depend on the optical properties of the irradiated sample (as described in detail elsewhere). The dual-model theory describes the reflected intensity only; hence, we have proposed to define the phase as the product of the wavenumber and average pathlength, which depends on the differential pathlength factor (DPF). Translating the DPF to a phase accumulation, we received

$$\varphi(\rho) = \frac{2\pi n}{\lambda} \text{DPF} \rho$$

where $n$ is the medium refractive index, $\lambda$ is the light source wavelength, and $\rho$ is the distance between the source and the detector.

As can be seen in Figure 1a, the IMOPE technique starts with reconstructing the re-emitted light phase using the multiple-measurement GS algorithm with recorded light intensity images. The GS algorithm reconstructs the phase based on the electromagnetic field free space propagation (FSP) equations. In general, the algorithm uses $M$ intensity images at known distances and the propagation between them to reconstruct the reflected light phase that was lost once the image was captured. The propagation back and forth repeats until it reaches a threshold condition (the detailed protocol is described elsewhere). Following the reconstruction of the phase image, we compute its distribution and specifically its RMS by the following equation

$$\text{RMS}_{\varphi_j} = \sqrt{\frac{\sum_{x,y} [A_{M}(x, y) e^{i\varphi_M(x, y)} - A_{M}(x, y) e^{i\varphi_j(x, y)}]^2}{\sum_{x,y} |A_{M}(x, y)|^2}}$$

where $A_{M}(x, y)$ is the amplitude (the square root of the intensity) at the desired $M$th plane along $z$, $\gamma$ is the spatial region of interest, $\varphi_M(x, y)$ is the reconstructed phase accumulated at the desired plane following a propagation distance of $D$, and $\varphi_j(x, y)$ is the average phase.

At the last step of the IMOPE algorithm, the experimental phase RMS is compared to the theoretical model for extracting the reduced scattering coefficient of the medium.

**Experimental Setup.** A noninvasive reflection-based experimental setup was constructed for recording light intensity images at different $z$ locations, separated by a distance $dz$. The recorded images were then utilized by the multiple-measurement GS algorithm in order to reconstruct the reflected light phase. The experimental setup is composed of a laser source, polarizers (LPVISE100-A, Thorlabs, Japan) for optical clearing purposes (where the first polarizer positioned where the maximum intensity is received and the second polarizer is positioned 90° to it in order to clear the surface reflection), a lens (focal length of $f = 75$ mm) in order to focus the light beam, and a CMOS camera (DCC1545M, Thorlabs, Japan). Initially, the setup was designed with a Helium-Neon (He-Ne) gas laser with a wavelength of $\lambda = 632.8$ nm and power of 3.4 mW. In order to perform measurements in the blue regime, an additional experimental setup was constructed (Figure 1b) exactly as detailed above only that the laser source was now chosen to be...
diode-pumped solid-state (DPSS) laser with a wavelength of $\lambda = 473$ nm and attenuated power of 1 mW (MLL-III-473, CNI, China). The lens, polarizer, and camera were set on a micrometer stage (distanced to receive a magnitude of 1) with an angle of $14.5^\circ$ from the laser source; hence, the images were corrected accordingly. For each sample, the intensity images were recorded at multiple planes by moving the entire camera-polarizer-lens assembly. Samples were held by an adjustable holder, which was set on a three-axis micrometer stage for fine-tuning during experiments. Each phantom was tested at three different points by moving the holder along the $x$-$y$ planes (as described in Figure 1b).

**Solid Tissue-like Phantom Preparation.** For mimicking media with different optical properties, solid phantoms with different reduced scattering coefficients were prepared.\(^{30}\) The phantoms were prepared using varying concentrations of IntraLipid (IL) (IntraLipid 20% Emulsion, Sigma-Aldrich, Israel) as a scattering component\(^ {31}\) and 1% agarose powder (Agarose - low gelling temperature, Sigma-Aldrich, Israel) in order to convert the solution into a gel. Double distilled water (DDW) was heated, while the agarose was slowly added at a mixing temperature of $\sim 60^\circ$C. Once the agarose melted, the IL was added to the solution and mixed for 1 min at a mixing temperature of $\sim 40^\circ$C in order not to heat the IL. The phantoms were prepared in cell culture plates (60 mm) and cooled under vacuum conditions (to avoid bubbles). The phantoms were prepared with a thickness of 10 mm and different IL concentrations (0.4, 0.55, 0.75, 1, 1.25, 1.5, 1.75, and 2% IL). Figure 2 presents the relation between the reduced scattering coefficient and IL concentrations for solid (red line) and liquid phantoms (black line) in the blue regime. The relation of the liquid phantom was received by extrapolation from Assadi et al.\(^ {32}\) to the range of the IL concentrations we used. According to Cubeddu et al., there is a factor (smaller than 1) between liquid and solid phantoms. Here, a factor of 0.55 was used to receive the relation between $\mu'_s$ and IL concentrations for solid phantoms (red line). The equations for both liquid and solid phantoms are located on the graph with proximity to their respective curves.

Table 1. Solid Phantoms’ $\mu'_s$ in the Blue and Red Regimes

| IL (%) | $\mu'_s$ ($\lambda = 473$ nm) (mm$^{-1}$) | $\mu'_s$ ($\lambda = 632.8$ nm) (mm$^{-1}$) |
|--------|---------------------------------|---------------------------------|
| 0.4    | 0.41                            | 0.44                            |
| 0.55   | 0.55                            | 0.55                            |
| 0.75   | 0.74                            | 0.71                            |
| 1      | 0.885                           | 0.91                            |
| 1.25   | 1.21                            | 1.3                             |
| 1.5    | 1.44                            | 1.5                             |
| 1.75   | 1.68                            | 1.5                             |
| 2      | 1.915                           | 1.69                            |

Figure 2. Calculated reduced scattering coefficient for different IL concentrations in the blue regime. For liquid phantoms (black line), $\mu'_s$ was obtained by an extrapolation from Assadi et al.\(^ {32}\) to the range of the IL concentrations we used. According to Cubeddu et al.,\(^ {31}\) there is a factor (smaller than 1) between liquid and solid phantoms. Here, a factor of 0.55 was used to receive the relation between $\mu'_s$ and IL concentrations for solid phantoms (red line). The equations for both liquid and solid phantoms are located on the graph with proximity to their respective curves.

**RESULTS**

**IMOPE Theoretical Model.** In order to apply the IMOPE in the blue regime, some adjustments were made in our theoretical model. However, for the blue regime, all optical properties had to be modified accordingly. Hence, $\lambda = 473$ nm, $g = 0.85$, and the absorption coefficient of water $\mu'_a = 2 \times 10^{-5}$ mm$^{-1}$ were used.\(^ {35,36}\) As we have described previously,\(^ {19,20}\) the phase RMS is calculated from two areas, which the border between them is approximately $1/\mu'_s$: the single-scattering regime ($\rho < 1/\mu'_s$) and the multiple-scattering regime ($\rho > 1/\mu'_s$). These two areas have shown their opposite behavior in the red regime. The theoretical phase RMS for the single- and multiple-scattering regimes in the blue wavelength, presented in Figure 3 (dashed and straight line, respectively), produced the same behavior as in the red regime (data not shown). The theoretical model for the blue wavelength is approximately the same as the one received in the red wavelength.\(^ {20}\) This is reasonable, as due to the spectral shift, the main impact on the phase RMS is the changes of $\mu'_s$. ($\mu'_a$ is still very small and can be neglected compared to $\mu'_s$). Given that the phase RMS is presented with dependence on given $\mu'_s$ values, the changes due to spectral shifts are not visible.

**Scattering Computations of Solid Phantoms in the Blue Regime.** Having our theoretical model in the blue regime, the scattering properties of the prepared solid phantoms had to be calculated for $\lambda = 473$ nm. It is known from the red regime that liquid and solid phantoms with the same IL concentrations have different scattering properties.\(^ {31}\) The relation between IL and the reduced scattering coefficient for liquid phantoms experiments in the blue regime was presented\(^ {32,35}\) where Flock et al.\(^ {32}\) showed the spectral $\mu'_s$ for only 10% IL and Assadi et al.\(^ {32}\) showed the spectral $\mu'_s$ for different IL concentrations. With the

![Table 1. Solid Phantoms’ $\mu'_s$ in the Blue and Red Regimes](image)

![Figure 3. Phase RMS obtained theoretically (black) and experimentally (blue) for different $\mu'_s$ values. The phase RMS was computed from two regimes: single-scattering regime (black dashed line and blue stars correspond to theory and experiment, respectively) and multiple-scattering regime (black straight line and blue circles correspond to theory and experiment, respectively). The theoretical results were received for the theoretical adjustments of $\lambda = 473$ nm, $\mu'_a = 2 \times 10^{-5}$ mm$^{-1}$, and $g = 0.85$.\(^ {35,36}\) For both regimes, the RMS obtained from experiments produced a standard deviation <0.014.](image)
purpose of relating IL concentration to \(\mu'_s\), we have extrapolated the data presented by Assadi et al.\textsuperscript{32} to receive the reduced scattering coefficient values for the IL concentrations. The extrapolation was done based on an assumption of a linear relation between IL concentration and \(\mu'_s\) as is known in the red regime.\textsuperscript{31} Our extrapolation was validated by the Mie theory approximation where, for 10% IL, the spectral scattering coefficient \(\mu_s(\lambda)\) and the anisotropy \(g(\lambda)\) calculated by eqs 3 and 4, respectively,\textsuperscript{36} results in the spectral \(\mu'_s(\lambda)\) as shown in eq 5:

\[
\mu_s(\mu m^{-1}) = 0.016 \cdot (\lambda(\mu m))^{-2.4}\quad (3)
\]

\[
g(\lambda) = 1.1 - 0.58 \cdot g(\lambda)\quad (4)
\]

\[
\mu'_s(\lambda) = \mu_s(\lambda) \cdot (1 - g(\lambda))\quad (5)
\]

Having constructed \(\mu'_s\) dependency on IL (\%) for the liquid phantoms, the equation \(y = 1.71x + 0.06\) was received (black line, Figure 2). It is known that, in the red regime, solid and liquid phantoms both depend linearly on IL concentration where each has a different slope, \(m_{\text{liquid}}\) and \(m_{\text{solid}}\). The relation between the slopes is \(m_{\text{solid}}/m_{\text{liquid}} < 1\). Our second assumption was that, as in the red regime, the relation between the slopes remains \(m_{\text{solid}}/m_{\text{liquid}} < 1\). In the red wavelength, Cubeddu et al.\textsuperscript{31} presented a factor of 0.7. For the blue regime, we found this factor to be 0.55 based on experiment compatibility that will be presented in the next paragraph. This resulted in the red line and its equation \(y = 0.94x + 0.03\), in Figure 2, as the representative for the scattering of solid phantoms in the blue regime.

Following the translation of IL concentrations to \(\mu'_s\) for solid phantoms in the blue regime, based on Figure 2, our sample optical properties were calculated, and their values in the red and blue regimes are presented in Table 1 where the \(\mu'_s\) values in the red wavelength were taken from Cubeddu et al.\textsuperscript{32}

**IMOPE Experimental Results in the Blue Regime.** Solid phantoms were prepared as described above and measured using the experimental setup shown in Figure 1b. The reflected light phase from each measurement was reconstructed by applying the multiple-measurement GS algorithm with \(M = 7\) intensity images at a size of 3.35 mm × 3.35 mm, \(dz = 0.635\) mm, and threshold conditions, which are described elsewhere.\textsuperscript{21} The phase was reconstructed for all measurements from the same location, at a depth of \(dz(M - 1)\) from the surface, resulting in a propagation distance of 3.81 mm for all measurements. The reconstructed phase images presented two areas as was received in the red laser experiments (as shown in Figure 4a,b for \(\mu'_s = 1.21\) and 1.44 mm\(^{-1}\), respectively).\textsuperscript{19–21} The border between these two areas is marked by the white circles in Figure 4 where the areas inside and outside the circle represent the single- and multiple-scattering regimes, respectively. Hence, the phase RMS was calculated from the single- and multiple-scattering regimes (correspond to blue stars and circles in Figure 3) was compared to the theoretical ones (dashed and straight black lines in Figure 3), respectively. Note, as is known from the diffusion theory, changes in the light source translate to a constant.\textsuperscript{37} Hence, as the used blue laser is far from being a point source (\(\omega_0 \sim 1\) mm), we add a constant of 0.75 to the experimental phase RMS values. By comparing the theoretical and experimental phase RMS for both scattering regimes, we could validate the accurateness of our IL translation to \(\mu'_s\) for solid phantoms in the blue wavelength. The compatibility between experiments and theory produced a factor of 0.55 that was used to calculate the \(\mu'_s\) values of the solid tissue-like phantoms as shown in Figure 2.

**Spectral Comparison of Solid Phantom Phase RMS.** Having the phase RMS theoretically and experimentally in the blue regime, we compared how the wavelength change affects our measurements. For that, the solid phantoms were measured in the experimental setup with the red laser as well. The comparison between the obtained phase RMS in the blue and red laser experiments for the multiple-scattering regime is presented in Figure 5 by the blue and red circles, respectively.

![Figure 4. Reconstructed phase images obtained following the multiple-measurement GS algorithm for solid phantoms in the blue wavelength with (a) \(\mu'_s = 1.21\) mm\(^{-1}\) and (b) \(\mu'_s = 1.44\) mm\(^{-1}\). The border between the single- and multiple-scattering regimes is marked with the white circles. The phase was reconstructed using a distance between images of \(dz = 0.635\) mm, a total propagation distance of 3.81 mm, and an image size of 3.35 mm × 3.35 mm.](image)

The theoretical phase RMS of the multiple-scattering regime is also shown in Figure 5 by the black straight line. The results show high compatibility between the two wavelengths and theory.

**DISCUSSION**

The theoretical model of the reflection-based IMOPE for the blue regime has been presented. Following the required adjustments, the theoretical model, which describes the phase RMS dependency on \(\mu'_s\), has shown the same behavior we have presented in previous studies in the red wavelength.\textsuperscript{19–21} This lays in the fact that the spectral changes in \(\mu'_s\) are the dominant changes in comparison to \(\lambda_s\), \(g_s\), and \(\mu_s\). The phase RMS is described for given \(\mu'_s\) values; hence, it is not expected to detect the impact of the spectral changes through its values. However, for the solid phantoms, which constitute our calibration experiments, the spectral change impacts their scattering values greatly. As the search for scattering properties of solid phantoms...
in the blue regime provided spectral information for liquid phantoms only, it had to be translated to solid phantoms. Reasonable assumptions were made to receive \( \mu'_s \) for solid phantoms in the blue regime: (1) the \( \mu'_s \) linear dependency on the IL concentration and (2) the relation between liquid and solid phantoms expressed by a factor smaller than 1. Both assumptions are based on phantom studies from the red regime.\(^{31}\) To the best of our knowledge, this paper presents for the first time the relation between \( \mu'_s \) and IL concentration in the blue regime. Notwithstanding, we recommend performing a thorough study regarding this relation between liquid and solid phantoms.

The solid phantom experiments produced a similar curve to the theoretical model (Figure 3). The additional bias value of 0.75, which was added to the experimental phase RMS, is a result of the change of the light source. In the diffusion reflection theory, the change in the source size is taken into account by a constant that depends on the source size and intensity.\(^{39,37−39}\) It is known that sources with wider beam waist, that incident a medium experience smaller beam expansion than narrow beam sources. Furthermore, the beam expansion occurs deeper in the medium. Hence, wider beams start with a lower phase RMS that should be compensated by a constant bias. The source size effect on the reflected phase and its RMS will have to be quantified in the future studies for constructing a precise analytical model. Nonetheless, the blue regime reflection-based IMOPE for extracting scattering properties is presented in this paper.

\section*{CONCLUSIONS}

This paper introduces the spectral reflection-based IMOPE technique for extracting the reduced scattering coefficient of a medium in the blue regime. The reflection-based IMOPE, which estimates medium scattering properties, combines a theoretical model with an experimental setup and the multiple-measurement GS algorithm. The experimental setup is used for capturing light intensity images at different locations along the \( z \) axis, which are then being processed by the multiple-measurement GS algorithm to reconstruct the light phase. The phase distribution, that is, its RMS, is then computed and compared to theory for \( \mu'_s \) estimation.

This paper contains, first, the theoretical model for the blue regime. Then, as the literature provides only the \( \mu'_s \) values of liquid tissue-like phantoms, a computation of \( \mu'_s \) for solid phantoms is suggested. Finally, the experimental results of solid tissue-like phantoms in the blue regime reflection-based IMOPE are presented with high compatibility to theory and results of the red regime reflection-based IMOPE. The compatibility of the experimental results between the red and blue lasers and the theoretical model indicates the applicability of the IMOPE as a spectral tool for material detection and analysis.

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\textbf{Author Contributions}

This research conceptualization was formed by D.F. as well as the project administration and funding acquisition. In addition, D.F. together with H.D. were responsible for the research supervision methodology. The software, investigation, and formal analysis were done by I.Y. The experiments were performed by C.S. and I.Y., and final validation was conducted by I.Y. and H.D. The writing of the original draft preparation was performed by I.Y. and H.D. D.F. was responsible for the review and editing for improving the paper.

\section*{Notes}

The authors declare no competing financial interest.

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