Deep tissue imaging using spectroscopic analysis of multiply scattered light

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Scattering limits the penetration depth of most optical imaging techniques. Efforts to overcome this limitation often require complex optical or computational schemes. We have developed a new method of assessing tissue properties based on spectroscopic analysis of multiply scattered light. The technique, multispectral multiple-scattering low-coherence interferometry (ms2/LCI), uses coherence and spatial gating to produce images of tissue optical properties up to 9 mm deep, with millimeter-scale resolution. The capabilities of ms2/LCI are demonstrated using tissue phantoms composed of chicken breast. Discrimination of diseased and healthy tissues is shown through imaging and analysis of burns in ex vivo human skin samples. Our technique may provide a powerful way to assess burn depth and progression in sensitive, burned tissues where physical contact is undesirable. © 2014 Optical Society of America

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1. INTRODUCTION

Scattering is the dominant mechanism of light transport in tissue. It limits the penetration depth of most optical imaging techniques by attenuating the incident light while simultaneously burying it beneath a diffuse background signal. Techniques that image with photons that have only interacted a single time with tissue such as confocal microscopy and optical coherence tomography must have a way to separate these photons from the diffuse background. Confocal microscopy uses an aperture as a spatial filter to selectively detect light arising from a localized region and reject out-of-focus light. This approach is effective but is limited to roughly three scattering mean free paths (MFPs), defined as the average distance needed for light to experience one scattering event, typically about 150–200 μm in tissue depending on the tissue type and wavelength of illumination, in this case 800 nm [1]. Optical coherence tomography (OCT) and other low-coherence interferometry (LCI) methods use coherence gating to selectively detect photons by optical path length. OCT uses near-IR light and is effective in selecting singly scattered photons up to about 27 scattering MFPs or about 1–2 mm in tissue [2].

There have been several recent efforts to extend optical imaging beyond this few-millimeter depth. These include photoacoustic tomography, which detects ultrasonic signatures of absorptive features up to a few centimeters deep [3] but does not provide scattering contrast. Further, the need for acoustic impedance matching requires contact with the tissue, which may not be feasible in some clinical applications. Another approach is to shape the wavefront of light to focus deep within tissue using ultrasound [4] or speckle variance [5] encoding. These approaches offer great potential for deep tissue imaging but may be limited by the need for complex optical and computational schemes.

Recently, we have developed an alternative method for deep tissue optical imaging based on exploiting forward-scattered light. Multiple-scattering low-coherence interferometry (ms/LCI) uses coherence gating to restrict photon path length with spatial gating to localize photon paths to achieve imaging up to 90 scattering MFPs with millimeter resolution in tissue.
phantoms [6]. Further development of the method shifted detection from the time domain to the frequency domain [7], which greatly reduced data acquisition times while incorporating multispectral capabilities, covering a bandwidth of 60 nm centered at 633 nm. The multispectral multiple-scattering LCI (ms2/LCI) system was able to detect an absorptive feature at 90 MFPs (9.5 mm) within a tissue-like phantom.

In this article, we now present the first application of ms2/LCI to deep tissue imaging and analysis. Imaging is demonstrated by detecting a reflective target through 8.8 mm of chicken breast. Absorptive contrast is shown by detecting the spectroscopic signature of a dye-filled capillary through 6 mm of chicken breast using a purely biological feature to generate scattering contrast. Finally, the potential clinical utility of ms2/LCI is established by imaging scattering changes due to thermal damage in ex vivo human tissues at depths of several millimeters. Spectroscopic analysis of these images shows a potentially powerful way to assess burn progression.

2. EXPERIMENTAL SETUP

The tissue imaging experiments presented here use the Fourier domain scheme for ms2/LCI described previously [7]. Briefly, light from a supercontinuum source (Fianium SC-450) is filtered and split into two components, an input to the sample and a reference. The input to the sample was a 6 mm diameter beam focused using a 100 mm lens but offset from the optical axis. The result is light incident at an angle of approximately 4° relative to normal with an approximately 14 μm diameter spot at the focus. This corresponds to an effective input NA of 0.03 and a Rayleigh range of 0.9 mm. The schematic in Fig. 1 shows this arrangement along with a projected detection path also offset from the optical axis by the same distance that intersects the illumination beam within a focal zone several millimeters beneath the sample surface. The arrangement of separate illumination and detection apertures allows selective detection of light that has passed through the focal zone. Light that has been forward scattered en route to the focal zone or on the return path retains useful information about the sample. Diffusely scattered light is not efficiently collected by this geometry, and thus it is suppressed in the detected signal.

The ms2/LCI scheme uses a custom-built spectrometer with a spectral resolution of 0.014 nm, corresponding to a maximum detection range of \( z_{\text{max}} = 5.6 \) mm. An enhanced depth imaging approach was used [8] where the zero path delay point (\( z = 0 \)), which offers the highest response for spectral detection, was set at the deepest sample feature. The coherence length that can be achieved with this scheme is 2.4 μm, but the effective axial resolution achieved with the ms/LCI geometry is typically 100 μm.

In the previous time-domain implementation of ms/LCI, long integration times were used to enable a high dynamic range. With the Fourier domain implementation, short sensor integration times must be used to avoid phase washout. The maximum A-scan rate allowed by the sensor in this scheme is 40 kHz. However, to enable a high enough SNR to obtain deep tissue imaging, multiple A-scans are averaged at a slightly lower rate. For each 3 s acquisition, approximately 75,000 A-scans are averaged to produce a 144 dB SNR. A digital lock-in scheme was also employed to correct for any baseline drift during this acquisition time [7].

Spectroscopic data were obtained from the A-scans using short-time Fourier transforms (STFTs), which can degrade depth resolution. By using the dual-window method [9], where spectra are processed individually using two windows...
of 1.25 and 40 nm, this effect is mitigated. The corresponding depth resolution is defined by the wide window to be 5 μm, and the effective spectral resolution is defined by the narrow window. The STFTs are implemented in real time using GPU processing, significantly reducing the amount of time needed for signal analysis.

3. TISSUE IMAGING

To demonstrate the penetration depth of the technique, images of a technical target, in this case a mirrored surface, were acquired through various thicknesses of chicken breast by mechanically scanning the sample between A-scans. Figure 2 shows the geometry of the imaging sample. Chicken breast has a mean free scattering path of 43 μm [10]. Thus, the imaging data, acquired through tissue up to 8.8 mm thick, illustrate a penetration depth of greater than 200 MFPs (Fig. 3). Because light scattering in chicken breast is highly anisotropic, the transport MFP of the tissue (i.e., the length over which the direction of photon propagation is randomized) is one to two orders of magnitude larger than the scattering MFP and varies between approximately 1.25 and 2.5 mm [10,11].

Given that the total depth range of a single ms2/LCI acquisition is 6.8 mm, two frames were acquired at different depths to create the image in Fig. 3. Each frame required approximately 5 min to acquire. The first image at the top half of Fig. 3 shows the chicken breast surface and extends up to 5 mm deep across a range of 13 mm in the lateral direction. The second image at the bottom half was obtained by adjusting the selected depth range using the delay stage shown in Fig. 1 to access a deeper penetration depth of up to 8.8 mm. As the chicken breast section gets thicker from left to right, the signal from the mirror (top panel in Fig. 3) is seen to broaden in depth profile. The bottom panel shows the depth profiles at 0, 6, and 13 mm, illustrating how the depth profile broadens from 0.125 to 0.6 to >1 mm. A couple of interesting features warrant discussion. First, the spectral domain method exhibits artifacts due to aliasing, often termed the “complex conjugate.” That is, because each depth is encoded by a spectral oscillation frequency, the approach cannot distinguish between positive and negative frequencies. Since the reflection from the mirror is a strong signal, the complex conjugate artifact is apparent in the top half of Fig. 3 but is not a significant confounding influence in subsequent tissue images below. We point out that several methods have been developed for eliminating this artifact that could be employed if this were found to limit imaging utility. Second, since the chicken breast has a higher refractive index than the surrounding medium (air), the apparent depth of the surface appears to increase as the thickness of the chicken breast increases. Thus on the left (0 mm lateral position), the mirror appears at a depth position of 7 mm, yet on the right (13 mm lateral position), the mirror appears at a depth of 9 mm, even though the mirror is oriented perpendicular to the optical axis. The total optical depth is equal to the physical thickness times the refractive index such that for the largest physical thickness of 8.8 mm, the optical thickness appears to be >13 mm. This effect could be corrected using knowledge of the thickness and refractive index of tissue layers. However, when imaging tissue properties of substantially planar layers, it may not be strictly necessary to identify the physical depth of a particular feature for diagnostic utility.

The inclusion of spectroscopic information greatly increases the utility of the ms2/LCI technique for tissue diagnostics. Figure 4 shows an image of a tissue phantom as an example of the ability to distinguish tissue types using spectral
information. A schematic of the phantom, consisting of a piece of chicken breast atop a segment of tendon with a dye-filled capillary inserted in between is shown beneath in the bottom left panel. The dye used here is undiluted green food coloring (Kroger Private Label Product) contained within a glass capillary (200 μm i.d., 500 μm o.d.). In order to easily present the spectroscopic information, we created a false color image based on spectral subband coding of the spectral information, as used previously in spectroscopic OCT [12]. The intensity at each wavelength contributed to the weight of the RGB channels as shown by the spectral windows in the lower right panel of Fig. 4, with the bandwidth from 620 to 660 nm shown as blue (dashed line), 640–680 nm as green (solid line), and 660–700 nm as red (dotted line). The underlying coloring in this figure shows the expected coloring for a given spectral composition. As in Fig. 3, this image consists of two panels, the topmost panel, which shows the surface of the chicken breast, and the bottom panel, which shows the tendon and the dye capillary. The horizontal line at 4 mm depth indicates the point where the two panels were joined. A second horizontal line, visible at 2.2 mm depth, is due to incomplete subtraction of a common path artifact, i.e., fixed pattern noise from correlations in the spectral data. The signal from the chicken breast decreases with increasing depth until a sharp contrast is seen where the tendon is visible from the increased scattering contrast. The presence of the dye capillary can be detected by the spectroscopic features. The spectroscopic shadow of the capillary is colored red, since the shorter wavelengths have been absorbed.

Figure 5 shows the recovered spectrum for the light returned from beneath the dye-filled capillary as compared to that from the tendon alone. By normalizing to the source spectrum, the absorption of the dye can be obtained [Fig. 5(a)]. Compared to a reference measurement of the dye absorption, good agreement is seen ($R^2 = 0.8219$). Another interesting feature in Fig. 4 is the presence of red spots, which are visible near the tissue surface. The absorption spectrum for this region was computed [Fig. 5(b)] but does not show good agreement with oxyhemoglobin, producing a negative $R^2$ value, indicating that the data would be fit better by a horizontal line than the oxyhemoglobin spectrum. Instead, the spectrum shows better agreement with that of methemoglobin ($R^2 = 0.6839$), the variant of hemoglobin usually found in blood stains and consistent with the red-brown spots sometimes observed on the surface of chicken breast samples.

To illustrate the applicability of ms2/LCI imaging for assessing tissue health status, several samples of ex vivo burned human skin were examined. In the first example (Fig. 6), the amplitude of the ms2/LCI signal is presented in a false color scale, with red representing the most intense and deep blue the least intense. This simulated burn was created by heating a brass rod and then applying it to the ex vivo skin sample for a fixed duration [13,14]. Figure 6(a) simulates a deep, second-degree burn where the rod was heated to 100°C and
applied for 30 s. The ms2/LCI image shows differences in the signal from the epidermis at the topmost 1 mm of the tissue, with a greater signal seen for the unburned tissue. The altered collagen architecture associated with the burn is also visible in this image. It appears as a decrease in signal in the dermis for deeper portions of the burned tissue. The decreased signal seen for the collagen is consistent with previous examples of in vitro collagen samples also exposed to a heated metal rod (data unpublished). Figure 6(b) shows an example of less severely burned sample. In this case, the rod was heated to 80°C and applied for only 20 s. The result was a shallow dermal second-degree burn. Here the signal from the epidermis again shows differences between unburned and burned, but the contrast is not as distinct as in the deep second-degree burn. Likewise, the collagen signal shows some difference between burned and unburned, yet it is not as apparent as in the case of the deep second-degree burn. Further clinical study is needed to assess if this amplitude-only image can be used as a clinical diagnostic method. However, the ability to visually discern the effects of thermal damage that correlate with burn stage is a promising indication of the utility of ms2/LCI.

Figure 7 shows another example of ms2/LCI imaging of ex vivo burned human skin at a higher resolution. While Fig. 6 presented B-scan images composed by sampling three A-scans per millimeter in the lateral direction, Fig. 7(a) uses the highest resolution of the ms2/LCI system to sample eight A-scans per millimeter. As with the previous example, the ex vivo human tissue samples were prepared by applying a brass rod heated to 80°C for 30 s. This protocol produced a deep second-degree burn, with the corresponding histology shown in Fig. 7(c). Evidence of the burn is apparent by the vacuolization in the epidermis, pyknosis of the cell nuclei, and alteration of the collagen structure. The image in Fig. 7(c) is at 10× magnification and thus only represents a small portion of the tissue region presented in Fig. 7(a), which extends for over 20 mm in the lateral direction. The intensity-only image in black and white shows some distinction between the unburned (left) and burned (right) tissue segments based on only the signal intensity, similar to the results in Fig. 6. In this representation, the largest difference is the lack of a distinct high-intensity layer in the epidermal surface of the burned region (right). Additionally, a decrease in the signal from collagen in the dermis can also be seen, similar to the other burned tissue images.

Upon incorporating spectroscopic information, the distinctions in tissue health become more apparent. Figure 7(b) shows a false colored ms2/LCI image created by the same coloring scheme as shown in Fig. 4, where the spectral content
is segmented into three bands and a red–green–blue (RGB) color scheme is used to indicate the spectral content between 620 and 700 nm. Figure 7(d) shows the detailed spectra for the burned and unburned sections for a depth of 3–4 mm at the base of the dermal layer. At this depth, there is significantly more short-wavelength spectral content for the burned tissue than the unburned tissue, which appears as regions of blue coloring, alternating with the reddish pink seen mostly for the unburned tissue. We investigated the spectral differences by dividing the spectral data by the source spectrum and then fit the result to a power law of the form $A \lambda^b$, where $\lambda$ is the wavelength. The exponent $b$ is seen to provide distinction between the burned and unburned tissue, with the exponent increasing from $b = 14.7 \pm 2.5$ (unburned) to $b = 30.7 \pm 2.4$ (burned), a significant change. We note that the power law exponents are significantly larger than those found in the literature [15]. This departure suggests that the changes may not be entirely due to scattering and that absorption may also play a role here. While further investigation is needed to separate the interplay of these two factors in the ms2/LCI signal, the sharp difference may provide a simple, empirical method of discrimination.

For comparison, Fig. 8(a) shows a false colored ms2/LCI scan of a superficial first-degree burn, achieved by applying a brass rod heated to 80°C for 3 s. In this image both the left and right sides show similar spectral content. As expected for this shallow burn, the false coloring at the transition from the dermis to the adipose tissue beneath does not show the blue coloring. The spectra for burned and unburned regions show little to no difference [Fig. 8(c)]. There is no apparent change in the signal intensity of the bright epidermis between regions. Histology also shows little change in the tissue with only a small amount of inflammation and minor alterations to collagen architecture seen at the dermal–epidermal junction. However, the superficial dermis is not damaged.

4. DISCUSSION

The data presented here demonstrate that ms2/LCI offers truly unique capabilities in tissue imaging. While existing optical imaging techniques cannot penetrate more than a millimeter or two with high resolution, the ms2/LCI technique shows a several-millimeter penetration depth. Approaches such as laminar optical tomography (LOT) have sought to image dermal lesions with a penetration of 1–2 mm [16], and like ms2/LCI, LOT can obtain multispectral measurements with a single acquisition [17]. Newer optical techniques that are in development [3–5] offer potential for even deeper tissue imaging, but they have their own limitations. In particular, none of these can image scattering-based contrast and instead must rely on fluorescence or absorption. For scenarios where there is a large scattering homogeneity to provide strong contrast, such as the chicken breast examples shown here, the potential exists to image as far as 9 mm deep with ms2/LCI. Many potential applications can be envisioned where scattering contrast in tissue is useful to this depth. The demonstration that endogenous sources such as bone or tendon can likewise provide the scattering contrast needed for achieving such depths points to further targeted applications.

Inclusion of spectroscopic information further extends the utility of ms2/LCI for tissue diagnostics. The ability to spectroscopically assess changes in scattering and absorption is an essential component of optical diagnostics. While spectroscopic contrast in OCT is not necessarily a new development, with the first experiments presented years ago [18,19], most spectroscopic OCT studies have focused on absorption signatures [20–24] often generated by exogenous contrast agents such as gold nanoparticles [25–27] and near-IR dyes [28,29]. Our group has used scattering contrast previously but sought to obtain single particle signatures [30,31] in an effort to assess early cancerous changes in superficial epithelium [32]. Thus, the work here is among the first to detect spectroscopic scattering changes to discriminate tissue types.

The data for detecting burns here are preliminary but demonstrate that the ms2/LCI technique has the potential to be used to distinguish between burned and unburned human tissues. The spectroscopic information, obtained from up to several millimeters deep, provides unique characterization of tissues and could address an unmet clinical need. In the United States, there are over 2 million burns reported each year, and in the military ~5%–20% of injuries are thermal related [33]. Burn injuries are estimated to cost ~$7.5 billion/year [34]. Currently, clinical judgment of burn depth is only ~70% accurate [35]. The ms2/LCI imaging technique has the potential to overcome existing hurdles in burn assessment, since it can image skin properties up to several millimeters deep in a noncontact modality. In contrast, photoacoustic imaging typically requires acoustic impedance matching through physical contact, an arrangement that may not lend itself to imaging of sensitive, burned tissues.

Fig. 8. ms/LCI imaging of burned ex vivo human tissues. (a) False colored ms2/LCI image of a superficial first-degree burn (right) compared to unburned tissue (left), with the same color scheme as in Fig. 4. Little change is seen in signal intensity or spectral content. (b) Histological image of the same burned tissue at 10x magnification; (c) the raw spectra from the base of the dermis [dotted lines in (a)] show no changes between burned and unburned tissue.
5. CONCLUSION
We have presented a new application of ms2/LCI for deep tissue imaging. Imaging depths up to nearly 1 cm were demonstrated in technical tissue samples. Significantly, the approach can incorporate spectroscopic contrast of absorptive and scattering features, although further work is needed to separate the influences of these two mechanisms. Potential application in assessing burn depth has been demonstrated with spectroscopic contrast from deep tissues (3–4 mm), offering a potential solution to an unmet clinical need.

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