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Multimode optical dermoscopy (SkinSpect™) analysis for skin with melanocytic nevus

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ABSTRACT

We have developed a multimode dermoscope (SkinSpect™) capable of illuminating human skin samples in-vivo with spectrally-programmable linearly-polarized light at 33 wavelengths between 468nm and 857 nm. Diffusely reflected photons are separated into collinear and cross-polarized image paths and images captured for each illumination wavelength. In vivo human skin nevi (N = 20) were evaluated with the multimode dermoscope and melanin and hemoglobin concentrations were compared with Spatially Modulated Quantitative Spectroscopy (SMoQS) measurements. Both systems show low correlation between their melanin and hemoglobin concentrations, demonstrating the ability of the SkinSpect™ to separate these molecular signatures and thus act as a biologically plausible device capable of early onset melanoma detection.

Keywords: Hyperspectral imaging, polarization, tissue-mimicking phantoms, and quantitative analysis

1. INTRODUCTION

The incidence of skin cancer has reached epidemic levels, and melanoma is of particular concern. In 2015, more than 73,870 new melanoma cases will be diagnosed and 9,940 people are expected to die from this cancer in the United States [1]. Recent study demonstrates that the health and economic burden of skin cancer treatment is substantial and, in the United States, increased from $3.6 billion in 2002−2006 to $8.1 billion in 2007−2011 [2]. Non-invasive detection of melanoma, especially early in the evolution of this deadly disease, is extremely important for outcomes: most lesions caught early and removed surgically yield a likelihood of cancer eradication of at least 86% (10-year survival rate). In contrast to this, late detection leads to very high (>90%) mortality rates (10-year survival rate between 10% and 15%) [3]. Immunotherapies are becoming the standard of care for metastatic melanoma. They are quite effective but extremely costly (estimates from an ASCO 2015 talk [4]).

Non-invasive optical imaging offers an important opportunity for early detection of skin cancer. Spectroscopic methods can be used to quantify tissue specific variables such as oxygenation and melanin distribution at the molecular level and aid non-invasive diagnosis. However, current commercial and research systems mapping hemoglobin and melanin in skin do not provide accurate information in pigmented lesions and darker skin types. Prior studies have demonstrated difficulty distinguishing melanin from hemoglobin [5][6].

SMI Inc. recently introduced a new dermoscope (SkinSpect) that combines polarization and hyperspectral imaging in order to accurately map the distribution of skin melanin and hemoglobin. Initial studies were limited by the small number of patients, and lack of comparative analysis to other widely accepted spectroscopy imaging devices to validate the mapping accuracy of SkinSpect. If this accuracy can be validated, it may represent a breakthrough in non-invasive clinical imaging technology for clinic and bedside use.

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In this study, we compare spectroscopic data from normal skin (types I-II) and melanocytic nevi obtained using SkinSpect to spatially modulated quantitative spectroscopy (SMoQS), a high-resolution depth-resolved spectroscopy device developed at the Beckman Laser Institute, for quantitative in-vivo measurement of tissue constituents including melanin concentration, oxy- and deoxy-hemoglobin, total hemoglobin and oxygen saturation.

2. METHODS AND MATERIALS

2.1 SkinSpect system

An in-vivo hyperspectral imaging system (SkinSpect) illuminates human skin under study with spectrally-programmable linearly-polarized light at 33 wavelengths equally spaced between 468 nm and 857 nm. Diffusely reflected photons are separated into collinear and cross-polarized image paths and images captured for each illumination wavelength (see Figure 2-1). We have developed a method which combines two depth sensitive techniques: polarization, and hyperspectral imaging, to accurately determine the spatial distribution of melanin and hemoglobin oxygenation in a skin lesion. More details about the system, skin analysis algorithm, and our method of correcting for melanin mis-estimation are described in our previous publications [5][6].

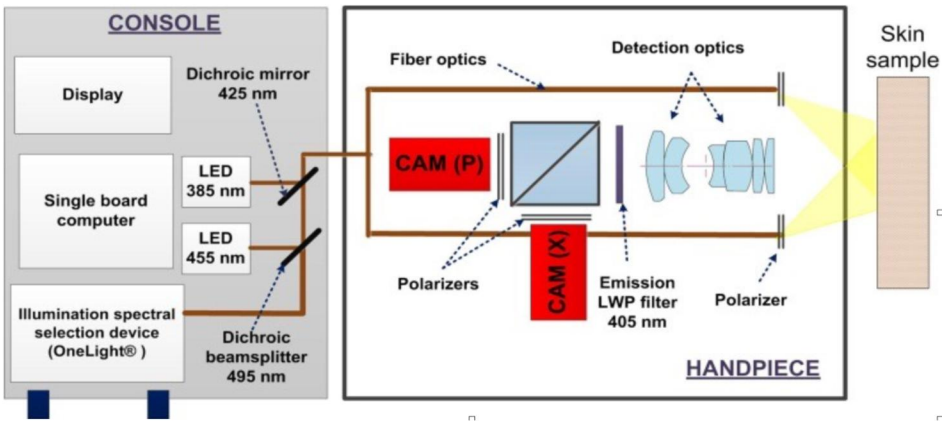


Figure 2-1. SkinSpect system diagram with dual camera hand-piece configuration

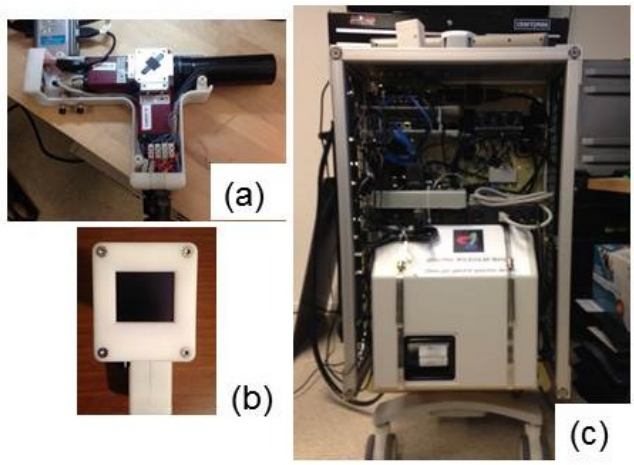


Figure 2-2. SkinSpect (Research version II) employed in the phantom and clinical trial measurements

As shown in Figure 2-2(a-c), modifications to the hand-held probe include a re-dimensioning and subsequent remanufacture of the case for better internal electrical and fiber optic cable clearance, and to accommodate an OLED viewfinder on the back of the console. The viewfinder was added to the probe so the operator can precisely position the

device over the targeted lesion. This improved very significantly both the speed and the certainty with which a skin-scan could be taken in a clinical setting. Other modifications to the research prototype probe included repositioning the switches to increase operator accuracy, and remanufacture of the electrical and fiber optic bundle to include additional signal paths to support the extended capacity. External modifications to the console cart included the addition of a NEMA 12 standard enclosure to protect both the human test population and the operators alike; an ergonomically improved probe holder for safe storage of the probe between tests; structural lashing points to permit rapid and secure tie-down during transit; and improved electrical cable management to eliminate trip hazards, and make movement of the instrument effortless and safe.

2.2 Spatially Modulated Quantitative Spectroscopy (SMoQS) system

The SMoQS system has been described previously in detail [7][8]. SMoQS collects depth-resolved high resolution reflectance spectroscopy information by projecting sinusoidal intensity patterns of a broadband source onto turbid samples or tissue under interrogation (schematically shown in Figure 2-3). The implementation of SMoQS, in this particular study, uses a 100W Quartz-Tungsten Halogen (QTH) light source (Moritex, D100LR) for the broadband illumination source and a digital micro-mirror device (DMD) (DLP developers kit, Texas Instruments) to spatially modulate the light intensity. The DMD is imaged onto the target tissue or sample, resulting in programmable spatial frequency patterns that are projected over a 22×17 mm^2 field of view.

Collection optics image a 1-mm diameter spot from the center of the field of view onto the distal end of a 1000 μm core fiber. The diffusely reflected light collected by this detector fiber is delivered to the entrance slit of a tunable grating Oriel spectrograph (model no. 77480). This spectrograph is tuned to cover a range of 430 to 1050 nm, with ~1 nm spectral resolution. A 16-bit, TEC controlled CCD (Instaspec IV, Oriel) was used to detect the chromatically dispersed light. Additionally, a crossed, 2 in., wire grid polarizer/analyzer pair are placed in the instrument to reject any specularly reflected light from reaching the spectrometer. In this system, the polarizer is positioned between the DMD and the projection optics, whereas the analyzer is positioned between the collection optics and the detector fiber.

Both DMD and CCD were computer controlled through a LABVIEW platform, allowing for automated data acquisition over a specified number of spatial frequencies. An auto-exposure subroutine was developed to optimize the dynamic range of the CCD specific to the amount of diffusely reflected light collected from sample of interest. Through this approach, acquisition times of this particular instrument ranged from 0.1 to 0.6 s per pattern projected, depending on the optical properties of the sample of interest. In terms of skin tissue, this brackets the range of acquisition times needed to collect light with acceptable signal-to-noise ratio from relatively highly reflecting fair skin to highly absorbing pigment nevi.

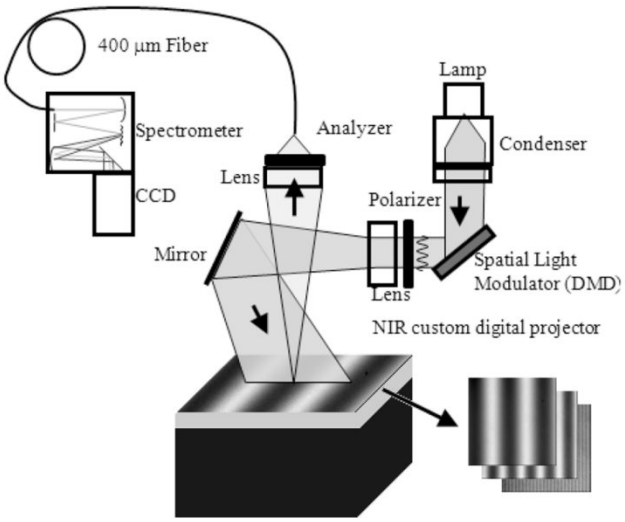


Figure 2-3. SMoQS system diagram [7]

Currently, 7 spatial frequencies are acquired, ranging from 0 to 0.35 mm^{-1}. This range was chosen to encompass the range of absorption sensitivity as a function of spatial frequency. Calibration measurements were also collected from a turbid reflectance standard to correct the demodulated spectra for instrumentation artifacts. Spatial frequency dependent tissue reflectance at individual wavelengths is then fit to homogeneous Monte Carlo models to produce unique pairs of absorption and reduced scattering. It is important to note that this method for determining optical properties is still dependent on a

homogeneous model, yet these results can still be exploited in such a way as to yield 2-layer results, as the depth sensitivity of the changes across the broad range of wavelengths employed in this system [7]. Initial results from computational simulation and experiment have demonstrated that the empirical layered approach to modeling SMoQS data is capable of determining top layer thickness within tens of microns across a physiological range for skin. Layer specific chromophore concentration can be determined to <±10% the actual values, on average.

More recently Saager *et al* have compared SMoQS *in-vivo* skin data to data obtained from multi-photon microscopy using selective two-photon excited fluorescence of melanin [8]. Subjects ranged in pigmentation from very light skin to dark skin (Fitzpatrick types I – VI) (1). Using the depth-sectioning capabilities of MPM, we were able to demonstrate, in the context of skin tissue, a layered model interpretation of SMoQS data is capable of linearly correlating *in vivo* average concentration and distribution of melanin to within ~15% and tens of microns respectively.

2.3 Human data

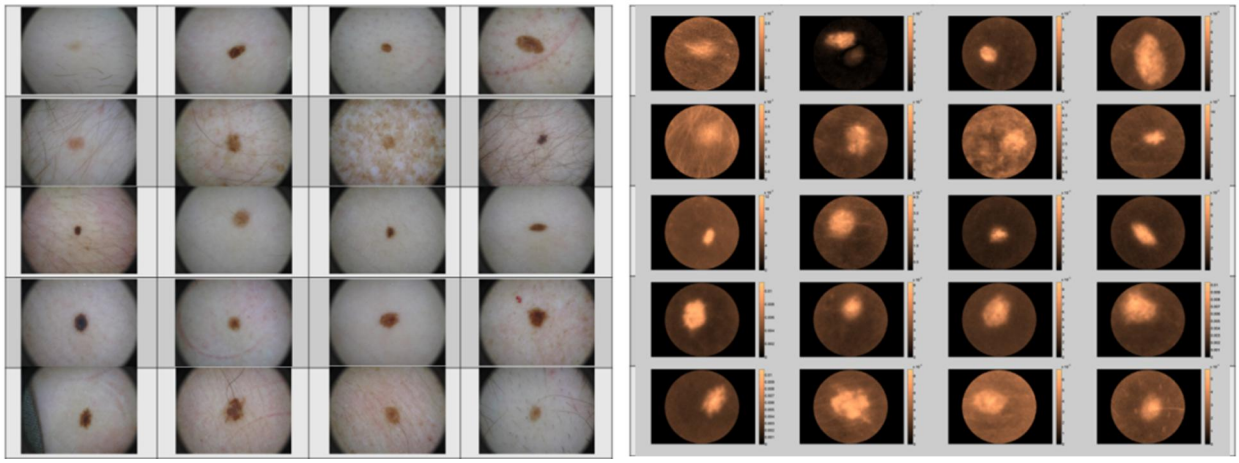
Twenty subjects with nevi on their skin and skin type I or II participated in this study. Melanin and hemoglobin concentrations of nevi and surrounding normal skin for 20 subjects were measured by SkinSpect, and SMoQS and digital images were captured using a conventional DermLite FOTO dermatoscopes (3Gen Inc.) and camera, (Canon Powershot). SkinSpect results were validated by comparing melanin and hemoglobin concentrations with the Spatially Modulated Quantitative Spectroscopy (SMoQS) measurements.

3. RESULTS AND DISCUSSION

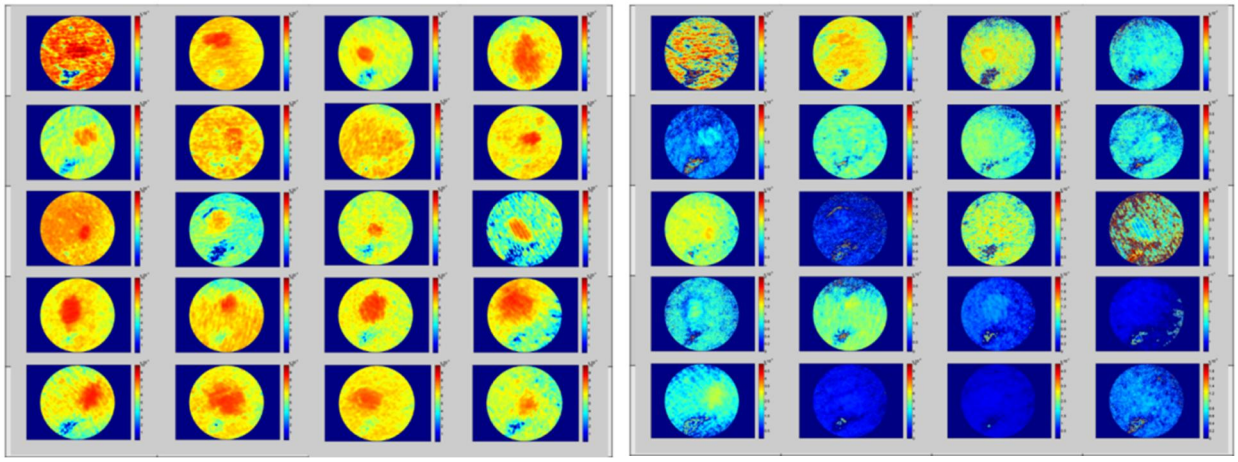
Figure 3-1a shows the RGB color images of 20 subjects with a nevus to be assessed. These pictures were taken using the DermLite dermoscope. For this study, we intentionally took nevus images from different locations on the body and from subjects with different sex and ethnicity, but with skin type I and II. Figure 3-1b shows the relative melanin concentration map estimated by measuring the attenuation spectra slope from the crossed polarization spectral image data cube.

Figure 3-1c and Figure 3-1d compare concentration maps of the relative total hemoglobin created without using our melanin attenuation correction and then using our melanin correction method. In Figure 3-1c (no melanin attenuation correction), we used a three-chromophore linear regression algorithm for spectral decomposition of A_{POL} spectra in skin in and around a melanocytic nevus. The estimated total hemoglobin maps manifest mis-estimation of oHb and Hb (strong correlation with melanin) in the highly pigmented region as expected.

The three-chromophore model uses a linear least square curve-fitting algorithm with extinction coefficients of melanin, oHb and Hb as primary vectors in the 500 - 577 nm spectral range (7 wavebands). Total hemoglobin was calculated by the summation of oxy-hemoglobin and deoxy-hemoglobin. The oxygenation saturation parameter (OSP) was calculated as the ratio of oxy-hemoglobin to total hemoglobin (as a percentage). Figure 3-2(a) and (b) shows the correlation analysis of melanin and total hemoglobin estimation before and after melanin absorption correction. After the melanin correction step the correlation value decreased significantly from R = 0.84 to R = 0.07. This low correlation between melanin and total Hb shown in all 20 subjects (both nevus and normal regions) validates the SkinSpect algorithm. In normal skin a change in hemoglobin due to the presence of normal pigmented nevi would be considered biologically implausible and so no correlation should exist.

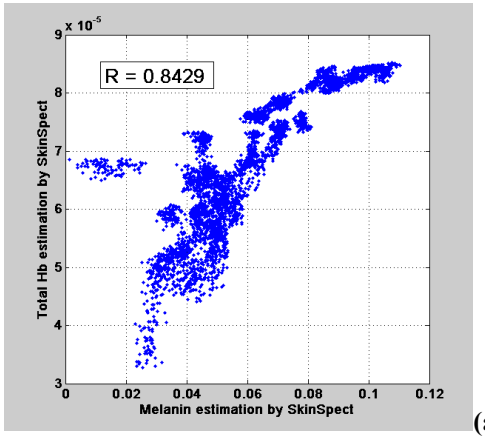


(a) (b)

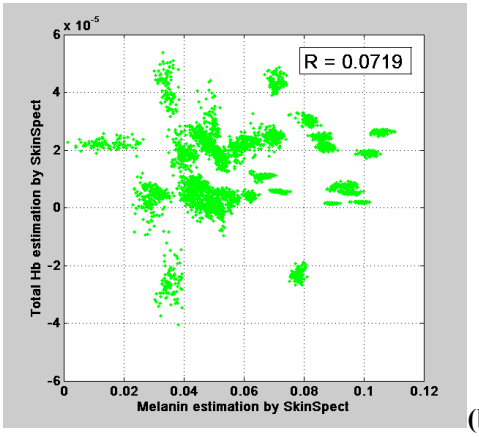


(c) (d)

Figure 3-1. Skin lesion analysis by (a) RGB by the conventional dermoscope (DermLite),(b) melanin concentration map by SkinSpect, (c) total Hb before melanin correction, (d) total Hb after melanin correction



(a)

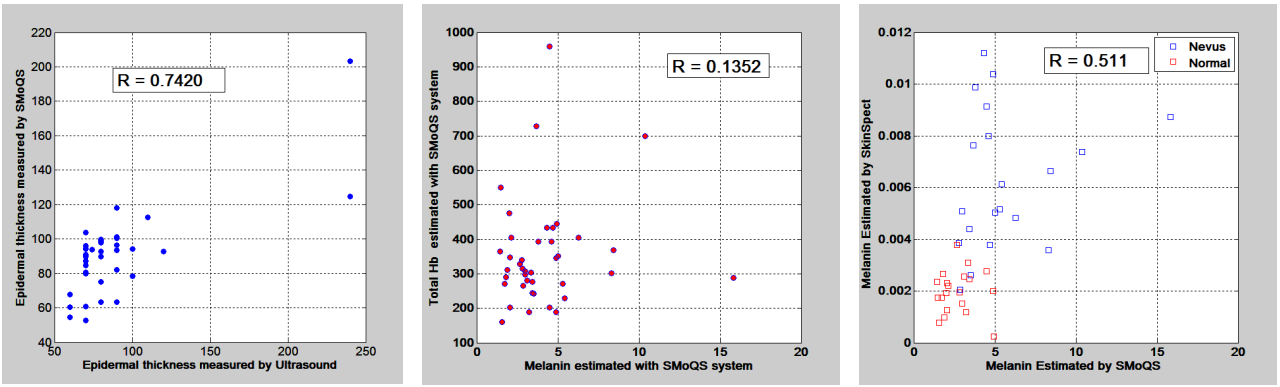


(b)

Figure 3-2. Melanin and total Hb correlation (a) before correcting melanin-Hb cross-talk (b) cross-talk corrected.

Figure 3-3 (a) shows the correlation analysis between epidermal thicknesses measured by high frequency ultrasound (40 MHz, Episcan, Longport Inc) and SMoQS. The R = 0.7420 shows correlation between SMOQS and Ultrasound measurement results. Figure 3-3 (b) shows the correlation analysis between melanin and total hemoglobin concentration estimated by SMoQS. The low correlation number shows that SMoQS measurements are not affected by the melanin and hemoglobin absorption crosstalk.

Figure 3-3 (c) shows the melanin concentration correlation analysis estimated by SMoQS and SkinSpect system. The melanin concentration map is derived from the slope of the $OD_{\perp}$ spectra between 600 nm – 700 nm. The melanin correlation for nevus seems to be lower than normal tissue. This is likely due to differences between region of interest (ROI) selection in the two methods. In SkinSpect, the ROI is defined as a 100 × 100 pixel square (each pixel is 27 µm) at the center of the nevus. However, the ROI for the SMoQS system is fixed by the collection geometry to be between 1-2 mm^2. While the smaller ROI should allow SMoQS system to more accurately sample the center of the nevus, the system was designed for measuring larger area of skin and lacks a viewfinder for positioning (to be incorporated in the newer version). This means that while the ROI for SkinSpect can always be positioned within the nevus, positioning was less certain with ROI for SMoQS (small nevi) and may include information from both the nevus and some surrounding skin.



(a) (b) (c)

Figure 3-3. (a) Epidermal thickness correlation analysis estimated by Ultrasound and SMoQS system; (b) Melanin and total Hb correlation analysis estimated by SMoQS system; (c) Melanin estimation correlation analysis between SMoQS and SkinSpect, where blue circles indicate ROIs for nevi and red circles indicate ROIs for normal skin.

4. CONCLUSION

We built and tested a polarization sensitive hyperspectral imager, SkinSpect, for in vivo skin imaging. After melanin correction, the correlation values for melanin and total Hb decreased significantly from R = 0.84 to R = 0.07 indicating very little cross-talk. The low correlation between melanin and total Hb shown in all 20 subjects (both nevi and normal regions) validates the SkinSpect algorithm with melanin-hemoglobin absorption crosstalk reduced to those that are biologically plausible for the tissue examined. Melanin concentrations determined using the SMoQS system also show lack of correlation with hemoglobin estimation as one would expect to be biologically plausible for this tissue.

5. ACKNOWLEDGEMENTS

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REFERENCES

[1] SEER database, http://seer.cancer.gov/statfacts/html/melan.html (accessed on March 09, 2016)

[2] Guy, G.P., Machlin, S.R., Ekwueme, D.U. and Yabroff, K.R., "Prevalence and Costs of Skin Cancer Treatment in the US, 2002− 2006 and 2007− 2011." American Journal of Preventive Medicine, 48(2), pp.183-187 (2015).

[3] Balch, C.M., Mihm, M.C., Gersenwald, J.E. and Soong, S.J., "The revised melanoma staging system and the impact of mitotic rate," The Melanoma Letter, 28(3) (2010).

[4] http://www.medscape.com/viewarticle/845707 (accessed on March 09, 2016)

[5] Vasefi, F., MacKinnon, N., Saager, R.B., Durkin, A.J., Chave, R., Lindsley, E.H. and Farkas, D.L., "Polarization-sensitive hyperspectral imaging in vivo: a multimode dermoscope for skin analysis," Scientific Reports, 4: 4924, 1-10 (2014).

[6] Vasefi, F., MacKinnon, N. B., Farkas, D. L., "Toward in-vivo diagnosis of skin cancer using multimode imaging dermoscopy: (II) Molecular mapping of highly pigmented lesions," Proc. SPIE, 8947-18 (2014).

[7] Saager RB, Truong A, Cuccia DJ, Durkin AJ. "Method for depth-resolved quantitation of optical properties in layered media using spatially modulated quantitative spectroscopy," Journal of biomedical optics 16(7):077002-(2011).

[8] Saager RB, Balu M, Crosignani V, Sharif A, Durkin AJ, Kelly KM, Tromberg BJ. "In vivo measurements of cutaneous melanin across spatial scales: using multiphoton microscopy and spatial frequency domain spectroscopy," Journal of biomedical optics. Jun 1;20(6):066005-(2015).