Measuring blood content, oxygen saturation, and scattering in cervical tissues using multi-spectral imaging

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Abstract

Objective: Optical detection systems have potential to address challenges in cervical cancer care. Compact, inexpensive light sources, sensors, and wireless internet connectivity are ubiquitous. It is possible to build mobile multi-spectral imaging systems that acquire data at the point of care, and perform computations in the cloud to estimate blood content, oxygen saturation, and light scattering in the cervix. Over time, this additional information would enable better triage at the point of care. **Methods**: A novel mobile multi-spectral imaging system was built around a tablet form factor, with a 13-LED illumination board and an area-scan camera. Image frames corresponding to each wavelength were recorded. Each multi-spectral cervical data set was captured in under five seconds and uploaded to the cloud for computational analyses. Pixel wise calculations of blood content, oxygen saturation, and scattering were made in the cloud and returned to the clinician. Sites of cervical biopsies were tracked in software; spectral output were compared to histopathology. The protocol was for this pilot study was approved by the institutional review board. **Results**: Images of blood content, oxygen saturation, and scattering were obtained. The estimated values were within the range expected for epithelial tissues. Abnormal measurements of blood content and scattering spatially correlated with biopsy sites. Analyses were done in near real time. **Conclusions**: Full resolution images of blood content and oxygen saturation of cervical tissues hold great potential to supplement current cervical cancer screening methods. Future upgrades will reduce the device size and analysis time.

Introduction

Need

There have been few improvements in colposcopy and treatment of cervical lesions in recent years. Taking more biopsies at colposcopy has increased the sensitivity for CIN2, CIN3, and AIS, but has not reduced cancer risk. Colposcopy in particular is limited by the absence of a specific, sensitive stain for cervical abnormalities. Currently colposcopy relies on visual methods based on acetowhitening, a process which occurs after dilute acetic acid applied to the cervix, turning abnormal areas whitish within 1-2 minutes. However, not all cervical abnormalities become visually obvious and not all acetowhite tissues represent pathology. Similarly, a better visual test could more accurately visualize the cervix prior to LEEP and ensure the entire lesion is removed (clear margins) in order to lower risk of cervical cancer.

Technology

Multi-spectral imaging has been proposed as a non-invasive method with potential to improve detection of cervical pathologies. The method involves imaging the tissue at selected wavelengths, yielding a 3D dataset that contains a discrete spectrum at each (x, y) position. By fitting this spectrum to a theoretical model, it is possible to quantify absorption and scattering in the imaged tissue, as well as their respective components. This information contains not only concentrations of ***oxy- and deoxy-hemoglobin***, but also water content and relative amounts of large and small scattering particles, all at the pixel level. Multi-spectral imaging can thus give clinicians ***non-invasive, label-free, localized oximetry measurements*** on an image, providing new physiological information which has never been so readily available.

The ***novelties*** in our system are as follows:
(1) It captures an *entire image worth of data*, whereas previous systems made only point measurements
(2) Multi-spectral hardware is *integrated into the colposcope*, to streamline data acquisition and analysis
(3) The system was *optimized for mobility and price*, with a bill of materials of $~1000

Clinical potential

Oximetry images can potentially play several roles in cervical cancer care. These include (1) triaging patients who screened positive for HPV and/or cytology tests; (2) guiding biopsies during colposcopy; or (3) assessing margins of LEEP and other excisional therapies. Clinical testing is needed to establish where the technology can best improve care.

Screening: HPV + Pap → Colposcopy → Biopsy → LEEP → Monitoring + prognosis

As a high-specificity *triage test* acquired at the point of Pap

As a tool that helps less experienced clinicians (nurses, GPs) *identify sites for biopsy*

As a tool that *defines lesion margins* in order to better assess which tissue to remove

Methods

Device

The setup consists of a multi-spectral LED board that was integrated into an optical head (functionally equivalent to a colposcope), and controlled by a tablet. The system worked in either white light mode (preview), or in multi-spectral mode (capture). Capture takes ~30 sec.

Fig. 2: (A) Optical head of multi-spectral device, with camera on right and LED board on left. (B) Entire setup, showing optical head mounted on tripod and coupled to a tablet.

Patients

Patients referred to colposcopy or LEEP per ASCCP guidelines were recruited. Prior to colposcopy/LEEP, the cervix was washed with saline and imaged using the multi-spectral device. Colposcopy/LEEP then proceeded following the standard of care. Sites of biopsies were marked in software. The data was processed offline to not affect care.

Analysis

In analyzing our data, we first reconstructed white light colposcopy-equivalent images from the multi-spectral dataset for each patient, which we used for annotation. Areas corresponding to the cervix were delineated in the images in software. Spectral data from homogeneous areas were averaged and fit to theoretical model of light transport in tissue based on diffusion theory [1] to estimate absorption and scattering. Absorption values were further broken down to oxy- and deoxy-hemoglobin, and water.

Hardware calibration

Diffuse reflectance measurements were used to compare our multi-spectral setup (LEDs + camera) to a white-light spectrometer (Ocean Optics). Measurements were made on both spectralon reflectance standards (Labsphere) and the skin of health volunteers.

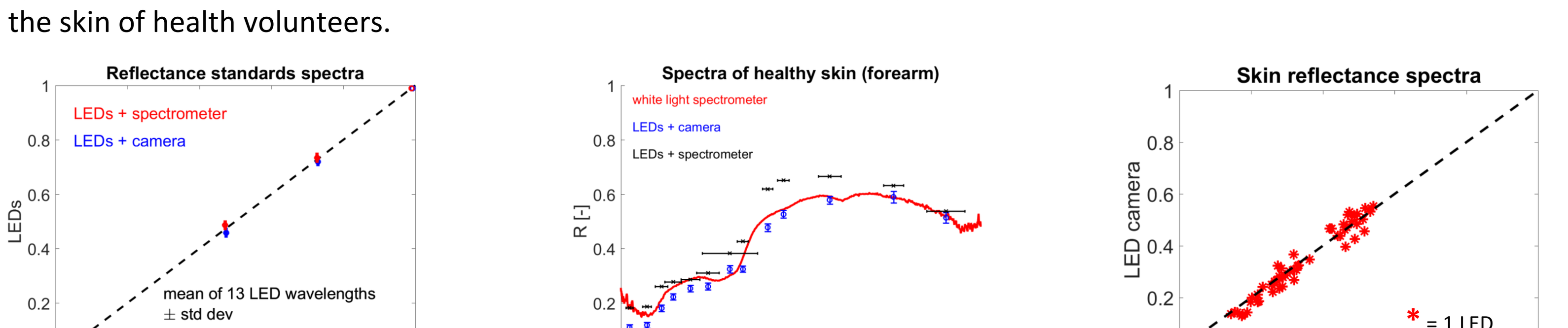

Fig. 3: (A) Comparison of multi-spectral setup (LEDs + camera) to white light spectrometer on phantoms. Data from LEDs + spectrometer served as a control. (B) Representative spectrum of skin (forearm) of a healthy volunteer from all 3 methods. (C) Comparison of skin reflectance measured by multi-spectral setup to a spectrometer for 4 volunteers.

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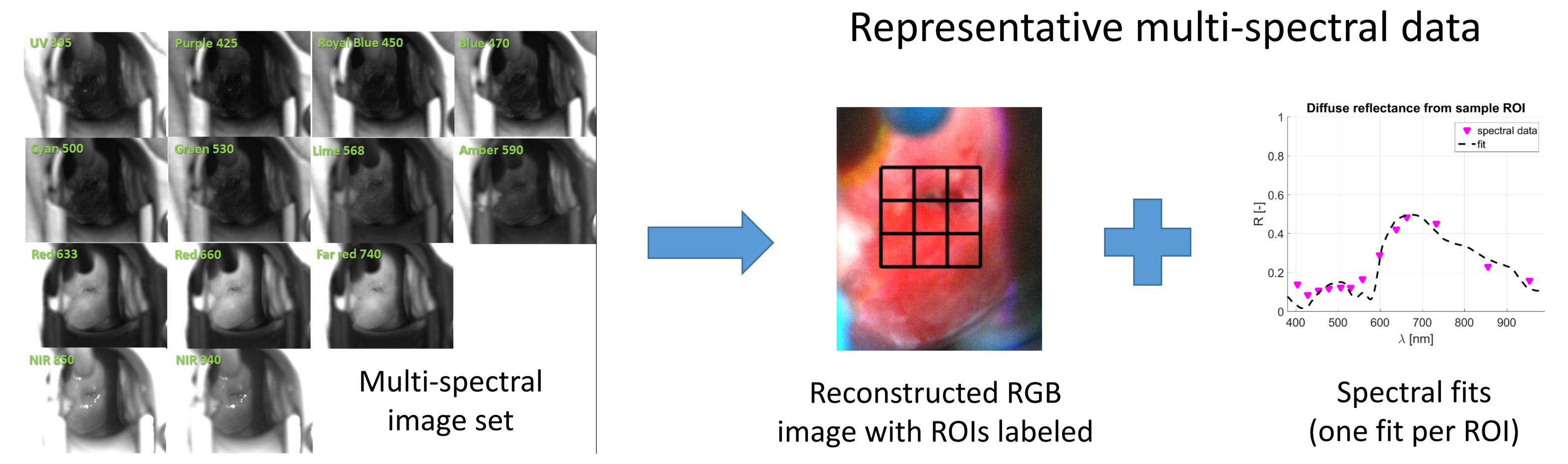
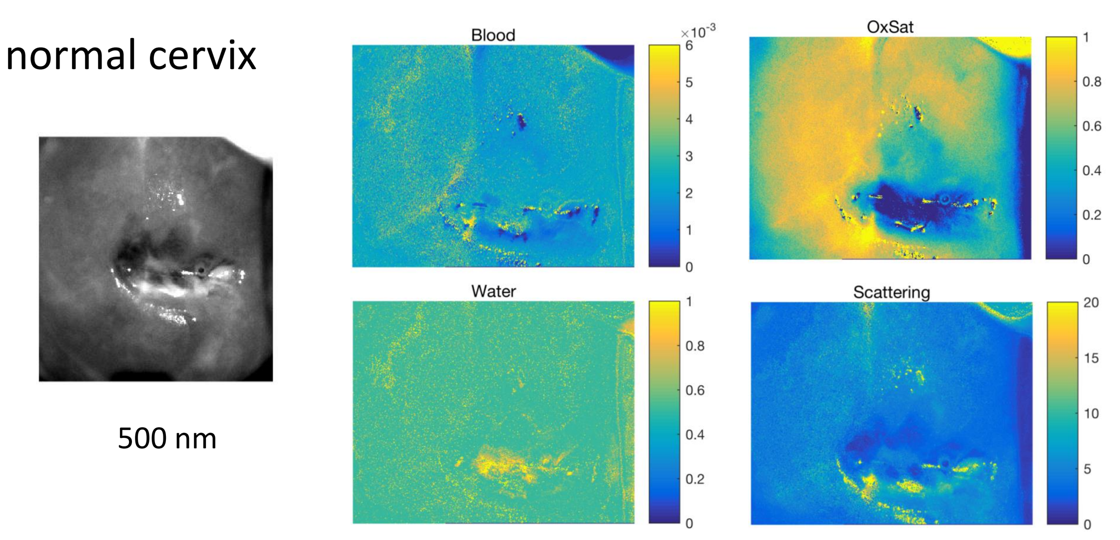
Results

Representative multi-spectral data

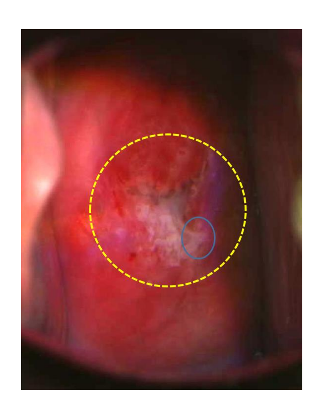


Oximetry imaging of a normal cervix

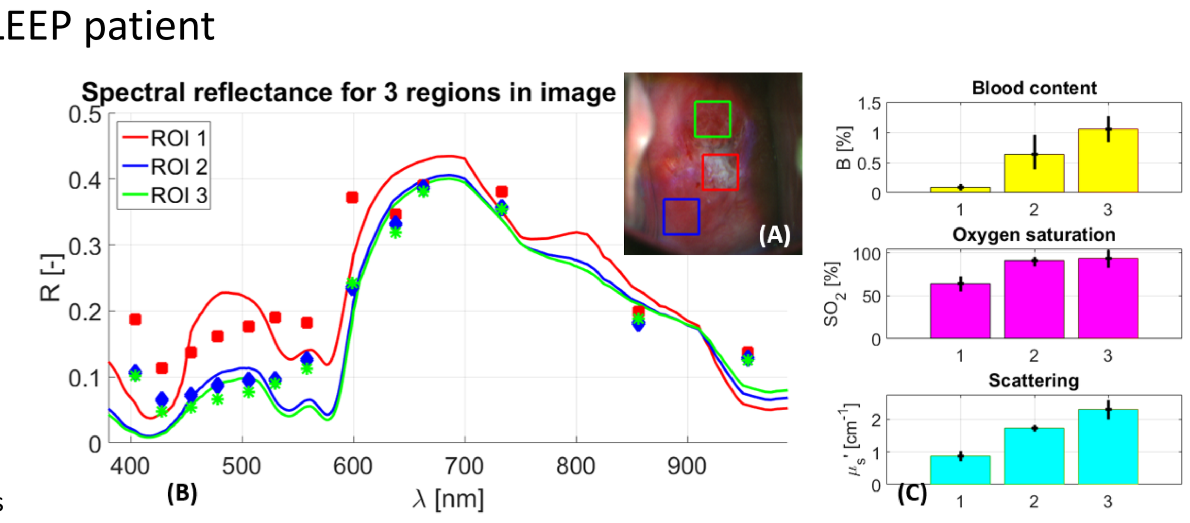
Spectral fits transform image data at the pixel level to tissue properties: blood content, oxygen saturation, water content, and scattering parameters



Analysis of cervix in LEEP patient



Biopsy-confirmed CIN3 at 4 o'clock (blue), ECC with atypical squamous metaplasia, cannot exclude dysplasia. LEEP margin in yellow dashed circle.



Discussion and Conclusion

The above results show preliminary analysis of patients imaged with our multi-spectral system characterized by our algorithm. The image data allows for comparing tissue properties from different regions in the same image, which is advantageous in procedures like colposcopy in which the sensitivity increases with the number of biopsies a provider takes. Moreover, comparing different regions from the same patient controls for effects like the menstrual cycle and local microflora that could also affect the tissue properties.

In looking at the data, it can be seen that the spectral response from normal tissue above and below the excised tissue are consistent with one another. Relative to normal tissue, the averaged spectra from the acetowhite lesion at the center shows that a much higher reflectance at blue and green wavelengths, but not as much at red and near infrared wavelengths. The increased reflectance corresponds to a higher scattering to absorption ratio there than in the normal regions [1]. All these results are consistent with theory – in normal tissue, there is less scattering so that the light can penetrate into the stroma where it is absorbed by the microvasculature, whereas in the acetowhite areas the additional scattering of green and blue light increases the amount of light that diffusely reflects from the tissue, while preventing it from reaching the deeper tissue and getting absorbed. Consequently, the increased levels of green and blue reflected light is what gives the tissue its white appearance.

The theoretical model used in the fitting in the above analyses was derived from diffusion theory. One of its key assumptions is that the tissue is a semi-infinite, homogenous medium. However, the cervix has geometrical complexity in 3 dimensions, and is organized by histological layers. Moreover, the blood supply in the tissue is not uniform, as is presumed by the model. As such, the measurements presented here can be considered a first approximation to the true tissue properties. Numerical simulations of light transport in tissue which can easily vary the geometrical properties of the tissue [2, 3] are needed in order to elucidate how different layers with different properties affect the spectral reflectance. Any refined algorithm will need to be validated through experimentation with tissue phantoms.

Further studies are needed to determine the potential of multi-spectral imaging for cervical cancer care. Specifically, there is a need to better understand the relationship between the menstrual cycle and menopause to the tissue properties, to systematically study a larger cohort of patients from different demographics, as well as better understanding the role acetowhitening has water content in the cervix, in a quantitative manner.

References

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