Design and Characterization of a Computational Endomicroscopy Platform for Optical Biopsy

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Abstract: We are using compressive sensing concepts to overcome the resolution limitation imposed by discrete fibers in coherent bundle-based endomicroscopy. Resolution can be improved beyond the native pixel number by integrating system-specific information within reconstruction algorithms.
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1. Introduction

Of the estimated 1.7 million new cancer cases expected in the US in 2015 [1], most will undergo some type of surgery with the goal of completely removing abnormal tissue. To minimize recurrence, accurate tumor margin identification is essential to ensure that all dysplastic or neoplastic tissue is removed and healthy tissue is preserved. For some procedures, intra-operative frozen-section histopathology is used to identify resection margins. However, this technique permits diagnosis at only a few discrete sites, while lengthening procedures and increasing costs.

The clinical need to improve these procedures has lead to the development of various techniques for "optical biopsy", aiming to provide real-time tissue assessment *in situ*. Several systems for high-resolution, *in vivo* imaging have emerged, including confocal, two-photon, and second-harmonic microscopies, which have all shown to be capable of imaging cellular and sub-cellular morphology and function with fine detail [2]. Confocal endomicroscopy techniques that that rely on single optical fibers are difficult to miniaturize as they require electrical connections to a fully packed actuator at the distal tip [3]. Other confocal endomicroscopy techniques [4] eliminate the need for distal end scanning by using a coherent fiber-optic bundle with beam scanning at the proximal end. Non-scanning endomicroscopy techniques based on wide-field fiber-bundle imaging have been developed and shown diagnostic potential for neoplastic and dysplastic lesions in various tissues [5-7]. These fiber bundle based methods are all amenable to miniaturization, but suffer from limited spatial resolution due to the finite size of discrete fibers within the bundle (Fig. 1). It is technically challenging to fabricate fiber bundles with more densely packed fibers, and it is impractical to use larger diameter bundles due to the need for minimally invasive tissue access. A new approach is needed in order to improve the resolution of fiber bundle based imaging without increasing the size of the endomicroscopy probe.

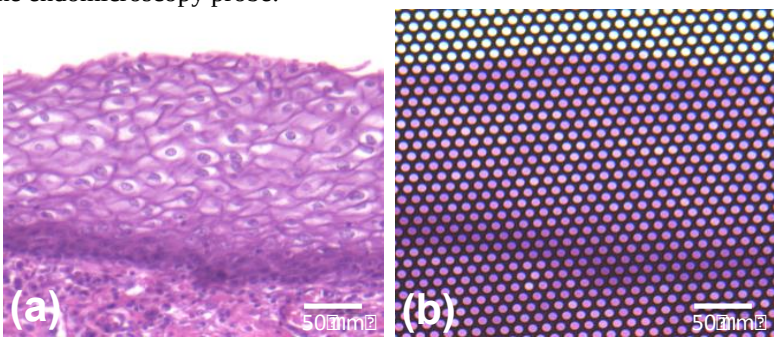

Fig. 1. (a) H&E stained pathology section of squamous tissue, imaged directly under white light. (b) Same sample imaged through a fiber-optic bundle, illustrating the loss of spatial resolution.

Our approach aims to integrate new concepts from the compressive sensing field with fiber bundle endomicroscopy. By allowing mathematical principles to guide the design of the optical hardware, and then

integrate hardware parameters within the image reconstruction algorithms, we aim to recover higher-resolution images than predicted by the hardware alone. By adapting compressive sensing techniques utilized by single pixel cameras [8] and block-based compressive imagers [9,10], we hypothesize that fiber bundle resolution can be improved without the need to manufacture smaller fibers or increase outer diameter. This presentation outlines our initial proof-of-concept results toward development of a computational endomicroscopy platform.

2. Methods

Recently, principles from the field of compressive sensing (CS) have been translated to optical imaging applications. The CS framework states that high-fidelity images can be constructed with a larger number of pixels than are physically present in the optical sensor. This is achieved by taking several sequential measurements of an object through coded masks, each corresponding to a linear projection of the object intensity onto one of the elements in a set of known functions. By selecting an *appropriate* set of functions, a high-resolution image can be recovered from a low-resolution sensor through CS reconstruction methods. Our computational endomicroscope platform is designed after a highly parallel extension of the CS-based single pixel camera. The single pixel camera architecture (Fig. 2a) has a coded mask located at a conjugate image plane, with multiple elements mapped to a single sensor. Our platform maps multiple mask elements to individual optical fibers in a bundle (Fig. 2b) essentially treating each fiber in the bundle as a single pixel camera.

Our experimental platform (Fig. 2c) uses a digital micromirror device (DMD) to generate binary mask patterns. A Texas Instruments DLP6500FYE DMD with 1920 x 1080 mirrors, each 7.56 μm in diameter, is placed at a plane conjugate to the sample, which is imaged onto the DMD via a two lens system with 1:1 magnification. Relay optics (Olympus PlanFL N, 10x/0.3) then, at a 12 degree angle, image the DMD plane onto a 14-bit CCD array with 1384 x 1036 pixels, each 6.45 μm square (Point Grey Research, GRAS-14S5M-C). The CCD array serves as a stand in for a fiber-optic bundle while we characterize the system-specific optical effects that must be integrated into the system model for accurate image reconstruction. The relay optics were adjusted to achieve a demagnification factor of 0.107 from the DMD to the CCD plane, such that a 2x2 block of DMD mirrors maps exactly to a single CCD pixel (or an "undersampling factor" of 4).

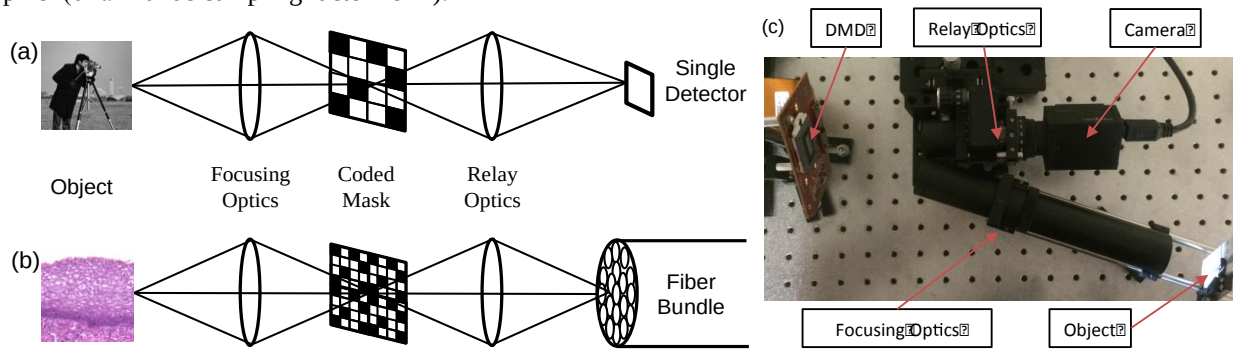

Fig. 2. (a) The single-pixel camera applies a coded mask at an optical plane that lies conjugate to both the object and detector. (b) Multiple sub-masks can be mapped to neighboring optical fibers in an imaging fiber bundle. generating a highly-parallel version of the single pixel camera. (c) Photograph showing the primary components of our experimental platform.

3. Results

We performed calibration experiments to quantify the system-specific DMD mask to CCD pixel mapping and aberrations arising between the mask and CCD sensor plane. These measurements are subsequently integrated into the CS mathematical model. We then imaged a USAF 1951 resolution target and selected an 80 x 80 pixel region from the CCD for analysis, equivalent to a 55 μm square region of the target. An optimization-based CS reconstruction technique based on Nesterov's proximal gradient (NPG) method [11] was used for image reconstruction. When imaged directly onto the CCD with no intermediate mask, the resolution target features beyond group 2 were not well resolved (Fig. 3a). Performing bicubic interpolation on this image does not significantly improve the image quality (Fig. 3b). When the target was imaged using our CS method, several elements within group 3 became distinguishable and the group 2 element numbers down the left side are also more clearly resolved defined (Fig. 3c). The textured appearance of the CS reconstruction image (Fig. 3c) is an artifact of the reconstruction algorithm and can be reduced by more accurate characterization of the system-specific optical effects, or by increasing the number of masked measurements.

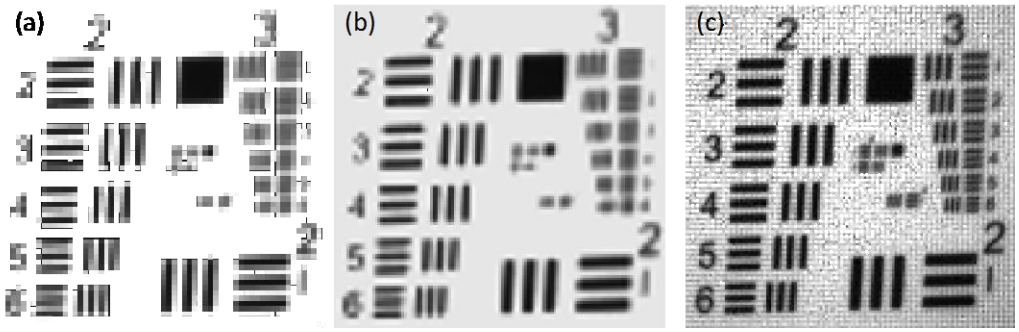

Fig. 3. Results for USAF target imaging. (a) Direct imaging of the resolution target with no intermediate mask. (b) Non-CS reconstruction using bicubic interpolation on the unmasked image in (a). (c) NPG-based CS reconstruction of the target using 20 masked measurements.

4. Discussion

While several fiber-bundle-based endomicroscopy technologies are currently under investigation for cancer detection in pre-clinical studies, all are inevitably limited in resolution by the size and packing of individual optical fibers within the bundle. The system described here aims to escape this resolution limitation and improve the ability of minimally invasive probes to discern subcellular detail. Our initial proof-of-concept experiments have established our system's efficacy for improving image detail over the sensor's native capability and provides a base for advancing fiber-bundle CS-based imaging. While the data presented hear uses an undersampling factor of 4, we are also examining larger undersampling factors with the aim of further improving resolution. The transition from mapping mask elements onto CCD pixels to true fiber-bundle imaging will require some additional considerations. Most notably, the non-orthogonal organization of individual fibers in the bundle will need to be accounted for by adding a grid mapping term to the reconstruction algorithm. We are currently evaluating different CS architectures to establish which is most efficient and achieves the best reconstruction and we aim to replace the CCD sensor with a fiber-optic bundle in the near future.

Acknowledgments:

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