A Computational Fluorescent Microscopy Through a Glass Needle

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For the last few decades, fiber bundles have been widely used for minimally invasive imaging, owing to its size and flexibility. However, fiber bundle imaging has suffered from low resolution and pixelation. To overcome these problems, imaging through a single multimode fiber has proposed as an alternative. Different computational techniques were developed to compensate for modal dispersion[1-2]. Most of these techniques use coherent phase correction, hence not suited to perform incoherent imaging. In addition, some techniques need the fiber fixed while imaging, and require re-calibration when it bends eliminating the benefit of flexible fiber. Furthermore, they often required complex electrical and optical hardware, such as a spatial light modulator (SLM).

In order to address the problems of existing computational methods, we recently developed an incoherent imaging method only to use a solid glass cannula[3]. Because light goes through multiple reflections inside cannula while propagating, the outcome light distribution is highly scrambled. To unscramble the image, we first calibrate the system by recording point spread function image e_i when a point source is place at i. Actual calibration images are shown in Figure 1 with a brief description of the principle. Once we collect e_i at every location within the field of view, we formed the complete transmission matrix E. When an arbitrary object x is placed in front of cannula, it produces scrambled image y. Since we know the transmission matrix E, we can represent any cannula image y as a linear combination of e_i. At this point, the reconstruction problem is reduced to solving a linear equation $y = Ex$, or $x = E^{-1}y$. In practice, we used nonlinear optimization algorithm to find the linear coefficient x_i to best match y, which showed a much better reconstruction performance than a traditional least-square method.

For the experiment, we used an off-the-shelf glass cannula with 220μm in diameter and 17mm in length. For calibration we used a single 1μm microbead stained with orange dye as a point source. After calibration, we imaged set of fluorescent microbeads using a conventional widefield fluorescent microscope and compared it to the cannula microscope to confirm a diffraction-limited resolution of ~1μm (Figure. 2a). Figure 2b show two pairs of images of a microglial cell from P0 stage mouse embryo labeled with tdTomato, confirming the viability of the cannula microscope in brain slices, and potentially as a miniature implantable device for imaging deep inside a brain.

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[1] Y. Choi *et al*, *Phys. Rev. Lett.* 109, 203901 (2012).
[2] T. Čižmár and K. Dholakia, *Nat. Comm.* 3, 1027 (2012).
[3] G. Kim and R. Menon, *Appl. Phys. Lett.* **105**, 061114 (2014).

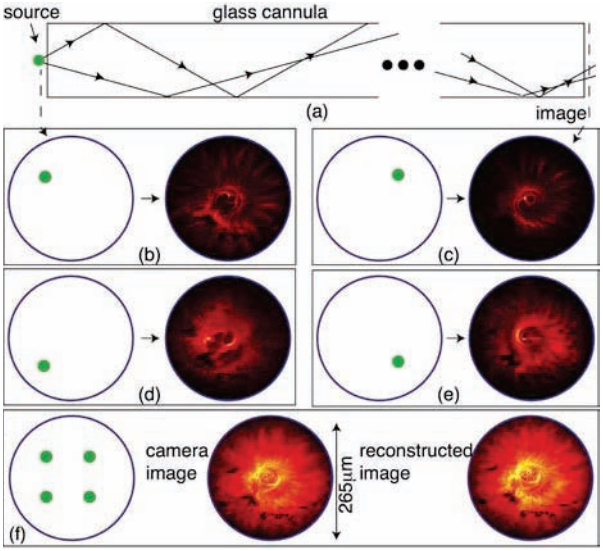

Figure 1: (a) Light rays from a point source propagate down the length of a glass cannula to form a unique light intensity distribution at the other end. (b) The image formed by a source near the top-left of the cannula. (c) The image changes as the source moves to (c) top-right, (d) bottom-left and (e) bottom-right. (f) The image formed by four point sources is the linear superposition of the images formed by the individual point sources. The actual camera image and the image reconstructed using a reconstruction algorithm is shown.

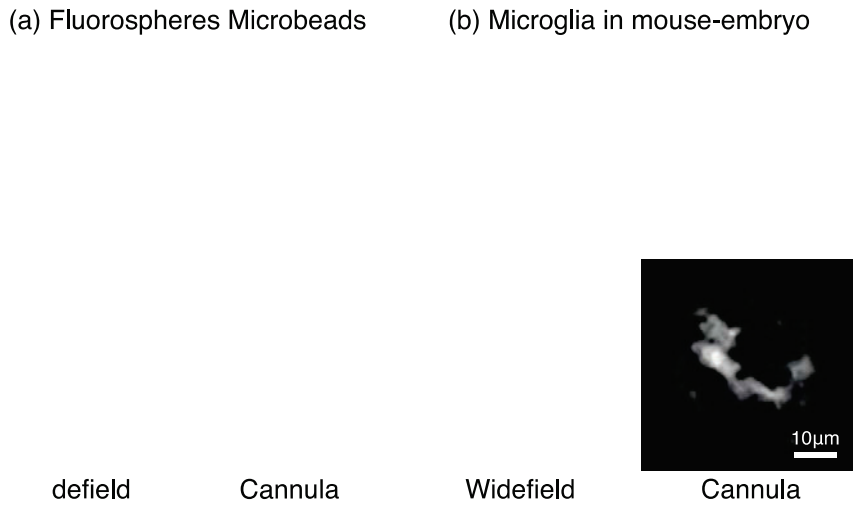

Figure 2: (a) Images of closely spaced fluorescent spheres (Fluorosphere, orange dye, diameter=1µm) and (b) microglia in mouse-embryo brain slice. We measured 1.09µm distance between the two centers of closely placed microbeads in the first image in (a). In all cases, cannula images show a great agreement with the reference image taken with widefield fluorescent microscope.