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Flexible ultra-thin super-resolution endoscopy

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In recent years, multimode fiber (MMF) has become an important tool for high-resolution endoscopic imaging in narrow channels (e.g., in the brain via needles or inside blood vessels) due to its high mode density and fine diameter, typically <0.125 mm [1-6]. However, a major obstacle to widespread deployment in applications is that realistic perturbations, including bending, twisting and changes in temperature, cause unacceptable image degradation. Further, any perturbation compensation must be done in real-time and with access to only the part of the fiber outside the body, the proximal end. Much recent research has been devoted to compensating fiber perturbations: this typically involves recording emission or reflection from areas on the distal fiber tip using techniques such as holographic beacons, guidestars and metasurface reflectors [7-9]. In principle, these approaches are able to compensate fiber perturbations but they suffer limitations that have prevented widespread deployment, specifically: the need to engineer structures on the distal facet and slow measurement and image reconstruction steps.

Recently, a team led by Qing Yang and Xu Liu (Zhejiang University) reported in *Nature Photonics* a new real-time MMF tracking system termed STABLE endoscopy (Spatial-frequency Tracking Adaptive Beacon Light-field-Encoded), which overcomes these limitations and provides a path to single MMF endoscopic imaging with superior resolution. The STABLE concept is illustrated in Figure 1. A complex light pattern is projected onto the proximal fiber facet and then propagates down the fiber, where it partially reflects off the distal facet due to Fresnel reflection. The reflected light then propagates back up the fiber and exits the proximal fiber facet, passing through a lens onto a single-pixel photodetector (e.g., photodiode or PMT). This measurement at a single point in the plane conjugate to the proximal facet (related by Fourier transform), forms the spatial frequency beacon. The power detected at this beacon is maximized when the reflected light forms a focus, which in turn occurs when the complex input pattern perfectly compensates the instantaneous fiber perturbation. Fiber perturbation states are represented mathematically by transmission matrices but the space of possible transmission matrices contains ambiguities and is too large to comprehensively explore. However, the authors cleverly avoid these problems by searching a much smaller space of transmission matrices representing perturbations likely to be encountered in realistic usage. To define this space, a pre-calibration is performed in which the transmission matrix of the fiber is measured under several hundred realistic bending, twisting and movement conditions. During real usage, the system evaluates each of these pre-calibrated transmission matrices in quick succession and measures the resultant power focused on the single pixel detector. The powers recorded are then used to estimate the fiber perturbation state within this restricted space. By using high-speed photodetectors for power measurements and digital micromirror devices for displaying complex input patterns, this estimation of fiber perturbation state can be achieved on the order of milliseconds, enabling real-time tracking and perturbation compensation.

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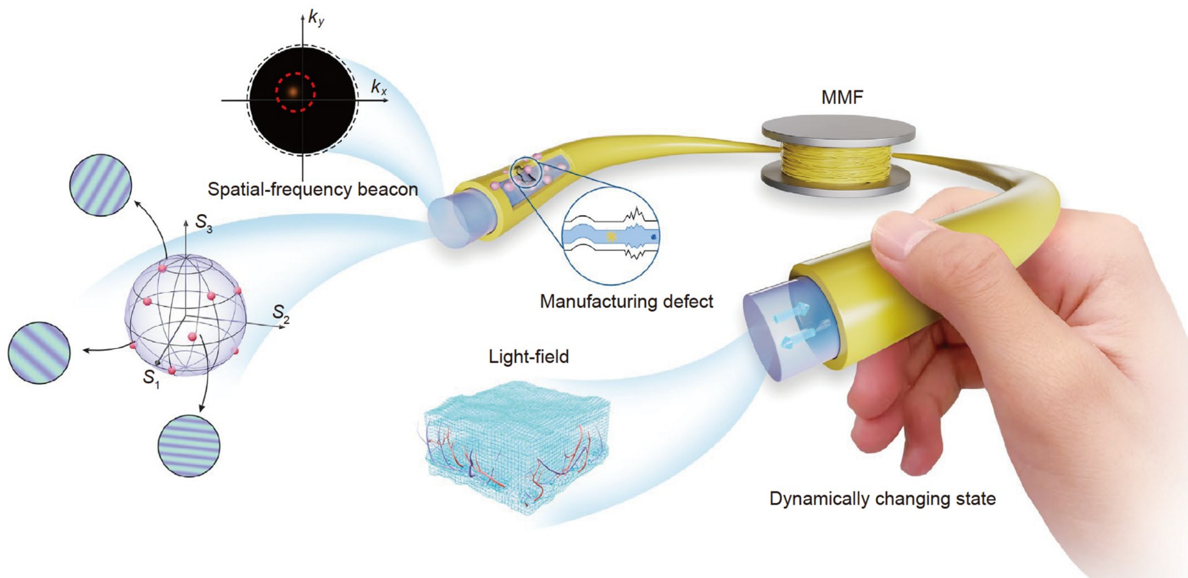

Figure 1 (Color online) Principle of the STABLE endoscopy system. STABLE can detect and track perturbations in MMF introduced by motion or temperature changes, thus maintaining high quality imaging in real time. The input light consists of a complex illumination pattern modulated in amplitude, phase and polarization (denoted by the Poincare sphere with axes S_1 to S_3). A spatial frequency beacon is located in the conjugate (Fourier) plane to the proximal end of the fiber. Reproduced with permission from ref. [10].

Real-time perturbation compensation in turn enables real-time high-quality imaging through these fibers, including both projection of complex illumination patterns (e.g. confocal scanning, structured illumination) and wide-field image reconstruction. The authors therefore demonstrate donut-shaped illumination to implement fluorescence emission difference imaging. Using this modality, they achieve improved image signal-to-noise ratio and increase resolution to the sub-diffraction limit of 250 nm (λ/3 NA). They also exploit the full control and detection of phase to demonstrate imaging different focal planes (depth sectioning) and imaging across scales. Further, they integrate their STABLE endoscope with a conventional white light endoscope (WLE) to show how it might be used in clinical applications: WLE provides a wide field-of-view (120°) to locate target areas to be inspected and STABLE endoscopy provides microscopic super-resolution for precise analysis e.g. optical biopsy.

This combined endoscopic system is then demonstrated for *ex vivo* imaging of a bronchus model and pig esophagus and *in vivo* imaging of mouse gastrointestinal tracts, achieving remarkably high resolution imaging of the oral cavity, esophagus, colon, stomach, and small intestine. These experimental results suggest many exciting future possibilities for further applications of STABLE. In the life sciences it could be used to enable ultra-thin probes for neuroimaging and optogenetics in freely moving animals, in industrial inspection it could be used to inspect ultra-small cavities, and in medicine it could bring high-quality optical imaging to difficult-to-access areas including deep in the bile ducts or inside tiny blood vessels (venules, arterioles). The combination of high-resolution imaging with ultra-thin flexible form factor could make STABLE the key next-generation tool for biomedical imaging.

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