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Mid-infrared fiber-coupled supercontinuum spectroscopic imaging using a tapered chalcogenide photonic crystal fiber

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ABSTRACT

We present the first demonstration of mid-infrared spectroscopic imaging of human tissue using a fiber-coupled supercontinuum source spanning from 2-7.5 μm . The supercontinuum was generated in a tapered large mode area chalcogenide photonic crystal fiber in order to obtain broad bandwidth, high average power, and single-mode output for good imaging properties. Tissue imaging was demonstrated in transmission by raster scanning over a sub-mm region of paraffinized colon tissue on CaF_2 substrate, and the signal was measured using a fiber-coupled grating spectrometer. This demonstration has shown that we can distinguish between epithelial and surrounding connective tissues within a paraffinized section of colon tissue by imaging at discrete wavelengths related to distinct chemical absorption features.

1. INTRODUCTION

Mid-infrared (mid-IR) spectroscopic imaging is a promising label-free technique with the potential for aiding researchers and clinicians in the study and diagnosis of cancer and other malignant diseases, but in order to transfer the technology from the lab and into the clinic it must be able to compete with conventional histopathology in terms of speed and reliability. Key to this is the development of compact, portable, turn-key systems relying on high brightness laser sources to provide a high signal-to-noise ratio for real-time measurements. In recent years, several demonstrations of mid-IR spectroscopic imaging using quantum cascade lasers (QCL) [1,2] has emerged resulting in a drastic reduction in acquisition time from hours to minutes, which makes it very attractive for clinical applications. However, only preliminary work has been performed with using supercontinuum (SC) sources for spectroscopic imaging in the mid-IR region [3–5]. The use of mid-IR supercontinuum sources for spectroscopic imaging has the potential for covering both the functional group region (2.5-6.7 μm) and part of the fingerprint region (6.7-15 μm) from a single compact source [6–9], that can be several orders of magnitude brighter than a synchrotron IR beamline [5] whilst being compatible with existing broadband technologies such as Fourier-transform infrared (FTIR) spectrometry and array detectors. This demonstration represents one of the first steps toward developing SC-based spectroscopic imaging in the mid-IR and is among

several results of the European research project MINERVA: MID- to NEaR infrared spectroscopy for improVed medical diAgnostics, that was a collaboration between thirteen organizations from industry and academia across seven European nations with the goal of developing mid-IR technologies for high-volume pathology screening and in-vivo skin surface examination for the early diagnosis of cancer.

2. FIBER-COUPLED SUPERCONTINUUM SOURCE

The fiber-coupled SC source was based on a tapered large mode area chalcogenide (ChG) photonic crystal fiber (PCF). The ChG PCF was fabricated from highly purified $\text{Ge}_{10}\text{As}_{22}\text{Se}_{68}$ glass by SelenOptics using the preform casting method producing low-loss PCFs with a core/cladding diameter of 11.6/125 μm , hole diameter $d=3.4\pm 0.1$ μm and pitch $\Lambda=7.6\pm 0.1$ μm , resulting in $d/\Lambda=0.45$. The large initial mode area allowed for high damage threshold and ease of coupling to the fiber, while the PCF structure enabled single-mode beam quality for diffraction-limited imaging. The taper was made post-drawing post-drawing using a filament-based tapering system operating at 258 $^{\circ}\text{C}$. The fiber was pulled with a translation speed of 3.8 mm/min, starting tensile strength of 40-50 g, and 15 g in the waist section. The taper was translated with a speed of 4 cm/min to obtain a 4 cm uniform waist section with 6.6 μm core diameter. The transition regions measured 2 cm and 3 cm on the input and output side, respectively. A total fiber length of around 1 m was used for flexible beam delivery, and the fiber was subsequently end-capped, polished and fitted with FC connectors as seen in Fig. 1(a) for better environmental stability, robustness, and ease of coupling to the scanning system. After fabrication the transmission of the fiber cable was tested using a Fourier transform infrared (FTIR) spectrometer, which indicated guidance up to 10 μm as seen in Fig. 1(b). The FTIR transmission spectrum also revealed several impurity absorption peaks from Se-H at 4.5 μm , H-O-H at 6.3 μm and Ge-O at 7.9 μm . The absorption features at 4.25 μm and 5.5-7.5 μm was due to atmospheric absorption from CO_2 and H_2O , respectively.

Broadband SC generation spanning 2-7.5 μm was achieved by pumping the ChG PCF with around 250 fs pulses at 4.35 μm (85 nm bandwidth) from a single-pass MHz optical parametric amplifier [6]. The pump wavelength was chosen to fit between the CO_2 and Se-H absorption features to reduce losses and avoid damage at the input. To reduce the intensity on the sample the spectrum was long-pass filtered at 4.5 μm as shown in Fig. 1(c), resulting in around 9 mW of power delivered to the sample. At this power level no tissue damage was observed, and during the scan the laser exposure remained around 15 times below than the maximum permissible exposure (MPE) level recommended for skin in the IEC 60825-1:2014 international standard. The SC spectrum display clear signs of water absorption from 5.5-7.5 μm due to the atmosphere, and the sharp dip at 6.3 μm coincide with the water impurity absorption in the ChG glass. Unlike previous experiments with similar tapered ChG PCFs reported in [6] the spectrum did not extend beyond 7.5 μm due to a series of design compromises, such as a long uniform fiber length and a fiber geometry suitable for end-capping and connectorization.

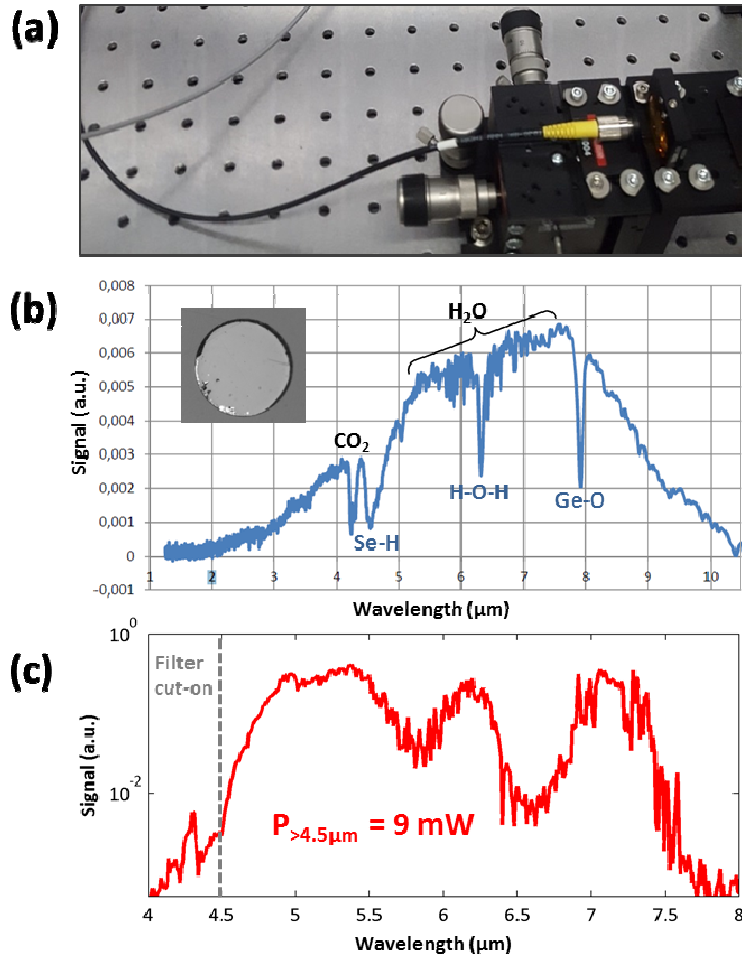


Figure 1. (a) Photograph of the tapered ChG PCF cable mounted on a translation stage for pump laser coupling. The white tape indicates the start of the tapered region. (b) FTIR transmission test demonstrating guidance up to 10 μm with various absorption features from the fiber (Se-H, H-O-H, Ge-H) and surrounding atmosphere (CO_2 , H_2O). The insert shows a microscope image of the polished end-cap on the input side of the fiber cable. (c) Spectrum of the filtered SC used for imaging.

3. SAMPLE PREPARATION

The sample was a non-tumoral colon tissue section obtained from the Gloucestershire Royal Hospital with the approval of the local research ethics committee. Two tissue sections were cut from this block, where the first 3 μm section was used for standard haematoxylin and eosin (H&E) staining on a glass slide for confocal microscopic examination and a second adjacent 7 μm thick section was mounted on a calcium fluoride (CaF_2) substrate for mid-IR imaging. Figure 2 shows a confocal image of the H&E stained tissue section, in which the various histological regions are clearly distinguished. The main objects of interest are the circular structures - the colonic crypts - which consist of a darkly stained outer layer (nuclear region) and a lightly stained interior (cytoplasmic region).



Figure 2. Confocal microscope reflection image of the 3 μm thick H&E stained colon tissue section.

4. SPECTROSCOPIC IMAGING SYSTEM AND RESULTS

Figure 3 shows the scanning system used for spectroscopic imaging.

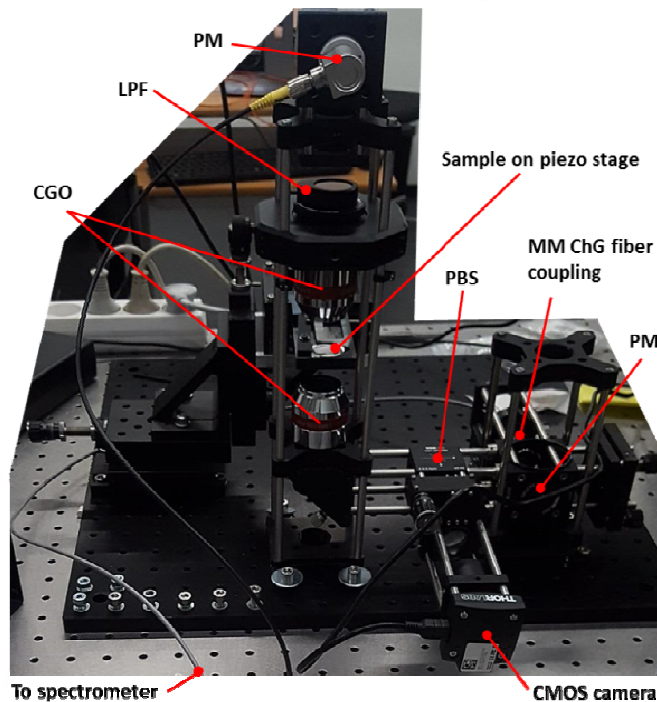


Figure 3. Fiber-coupled scanning system for spectroscopic imaging. PM: Parabolic mirror, LPF: Long-pass filter, CGO: Cassegrain objective, PBS: Pellicle beam splitter.

The system is fiber coupled and has a multimode fiber output for the spectrometer enabled by FC/PC parabolic mirror collimators. The system employed a pair of 15x reflective Cassegrain objectives for achromatic diffraction-limited imaging, as well as a CMOS camera for visual alignment of the sample. The CaF_2 sample plate was mounted on a piezo-stage and tissue imaging was demonstrated by raster in 5 μm steps over a 600x600 μm region of the sample. The signal was measured in transmission using a fiber-coupled grating spectrometer and MCT detector in combination with lock-

in amplification. The signal was chopped at 4 kHz in order to use lock-in detection, and a 50 ms time constant was needed for maximum dynamic range due to significant loss in the beam-splitter and fiber-coupling to the spectrometer. The acquisition rate was further limited to 100 ms in order to avoid motion artifacts, which resulted in a 24 minute acquisition time for a single-wavelength point-scan image. However, this was a first proof-of-principle demonstration, and the acquisition rate can easily be improved by using a camera or array detector in combination with acousto-optic- or linear variable filters. Figure 4(a-d) show a comparison between the H&E stained tissue section and the mid-IR sample visualized using the CMOS camera, SC source and a state-of-the-art FTIR focal-plane array system, respectively. The SC and FTIR images are captured at 6.45 μm where the SC is low; however, it is still possible to distinguish between epithelial and surrounding connective tissues, and with further improvements to the technology we expect to be able to obtain high quality images within few seconds, similar to what was demonstrated at shorter wavelengths in [1].

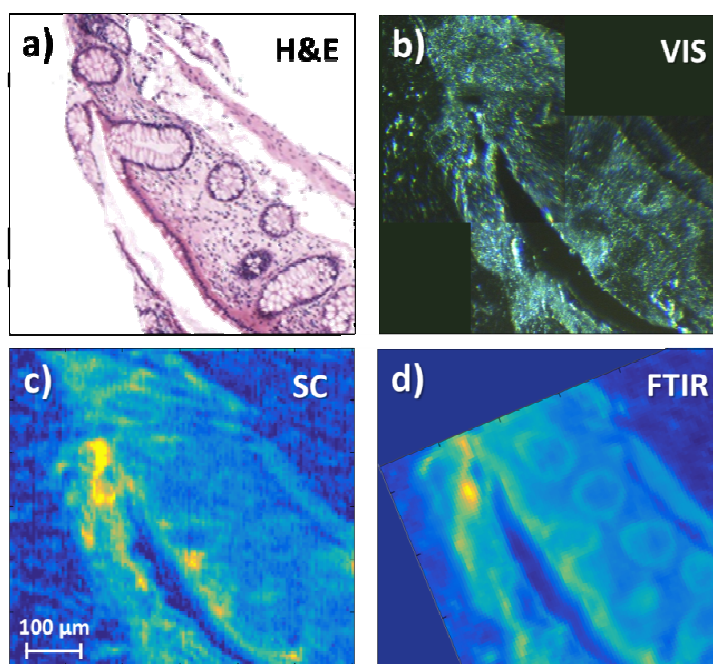


Figure 4. Comparison between (a) H&E stained tissue section, and (b,c,d) mid-IR sample visualized using the CMOS camera (b), SC source (c) and FT-IR focal-plane array system (d).

5. CONCLUSION

In conclusion, we have demonstrated the feasibility of using a broadband fiber-coupled mid-IR SC source in combination with a scanning system for spectroscopic imaging of tissue.

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