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Optofluidic needle probe integrating targeted delivery of fluid with optical coherence tomography imaging

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We present an optofluidic optical coherence tomography (OCT) needle probe capable of modifying the local optical properties of tissue to improve needle-probe imaging performance. The side-viewing probe comprises of an all-fiber-optic design encased in a hypodermic needle (outer diameter 720 μ m) and integrates a coaxial fluid-filled channel, terminated by an outlet adjacent to the imaging window, allowing focal injection of fluid to a target tissue. This is the first fully-integrated OCT needle probe design to incorporate fluid injection into the imaging mechanism. The utility of this probe is demonstrated in air-filled sheep lungs, where injection of small quantities of saline is shown, by refractive index matching, to greatly improve image penetration through multiple layers of alveoli. 3D OCT images are correlated against histology, showing improvement in the capability to image lung structures such as bronchioles and blood vessels.

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Optical coherence tomography (OCT) imaging of the microstructure of tissue is demonstrating value in an increasing range of clinical applications, but multiple backscatter and absorption of the light beam limit imaging to 2-3 mm of tissue. OCT needle probes [1-4], consisting of a miniaturized fiber-optic probe encased within a medical needle, provide one solution, allowing imaging deep within tissue by interstitial insertion of the probe. OCT needle probes with an outer diameter as small as 310 μ m have been used to image tissue structure [5]. However, image penetration is still limited to tissue immediately adjacent to the needle's imaging window.

In other (non-needle) OCT set-ups, fluid has been used to increase image penetration. In intravascular OCT, highly scattering blood cells are temporarily cleared from the field of view through the use of a saline flush delivered via a guide catheter [6]. With benchtop scanners, optical clearing agents [7] and refractive index matching fluids [8] have been used to improve image penetration depth in turbid tissue. Extending the localized application of fluid to needle probes is challenging as the OCT probe is interstitially embedded deep in solid tissue. Previous OCT needle probe designs have not integrated any mechanism to enable the local application of a fluid. This is both because of the highly restrictive size constraints inherent in such miniaturized probes, and because the inner lumen of the needle is often fully occluded, either by the imaging optics or with optical adhesive to rigidly constrain the optics to be aligned with the imaging window through which the light beam is emitted.

In earlier work, Jafri *et al.* [9] proposed the use of a blunt-tip dual-barrel endoscopic guide tube as a method to couple interstitial imaging with application of a fluid. They introduced a catheter probe through one barrel, and demonstrated insertion of a separate injection needle to deliver a therapeutic fluid through the second barrel.

We present the first side-facing OCT needle probe with an integrated channel to deliver fluid focally to the region being imaged. We demonstrate this optofluidic needle probe by delivering refractive index-matching fluid during lung imaging. The delivery of milliliter volumes of fluid enable acquisition of images of a quality previously only attained in lungs globally perfused with fluid [10].

The focusing optics of the probe (Fig. 1) were fabricated by splicing 270- μ m of graded-index fiber (GRIN) (GIF625, Thorlabs, USA) to a length of single-mode fiber (SMF) interfaced to the OCT scanner. The optics are encased within a 22-gauge needle (outer diameter 720 μ m) and held rigidly in a borosilicate mounting capillary (ID 200 μ m, OD 330 μ m, VitroCom, NJ, USA). A copper mirror, angle-polished at $\sim 45^\circ$, deflects the light beam through an imaging window electrochemically etched into the side of the needle. The optics were rigidly affixed with UV-curing optical adhesive (NOA81, Norland, USA), such that the adhesive formed an optical surface sealing the imaging window. The average transverse resolution of the probe is 15 μ m in tissue, over a range of 700 μ m. A second hole, 0.3mm in diameter, was also etched into the needle, 5 mm proximal to the imaging window. This hole formed the fluid-delivery outlet for a channel inside the needle.

Fig. 1: Schematic of the optofluidic needle probe. Outer diameter of needle is $720\mu\text{m}$.

The optofluidic needle probe was mounted on a brass manifold with two inlets, the first carrying the SMF from the OCT scanner; and the second coupled to a length of flexible tubing which carried fluid to the needle. The fluid channel was connected to an electronically controlled syringe pump which allowed fluid to be injected through the probe at a constant rate. The manifold was mounted on a stepper motor allowing it to be counter-rotated at 2 Hz for radial scanning, enabling the acquisition of 2D radial B-scans. To eliminate tissue drag artifacts between needle rotation and counter-rotation, only forward rotations were used for image reconstruction. A linear translation stage was used to insert and retract the assembly at $7\mu\text{m}$ per rotation, allowing acquisition of a 3D OCT data volume. The scanning speed of this prototype system is comparable to that previously published for *ex vivo* measurements [2-4], although more rapid needle scanning is feasible [1].

A schematic of the system is shown in Fig. 2. The optofluidic needle probe was interfaced to a swept-source OCT system. The light source (Axsun, MA, USA) has a central wavelength of 1310 nm, sweep rate of 50 kHz, average output power of 31 mW, and sweep range of 100 nm. After application of the Hann window to reduce sidelobes in the axial point-spread function, this yields a FWHM axial resolution of $21\mu\text{m}$ in air. This common-path OCT system used the GRIN fiber-glass interface as the reference reflection, as described previously [4]. Backscattered light was detected with an InGaAs balanced photodetector (ThorLabs, NJ, USA) and digitized using a 720 MB/s data acquisition card (AlazarTech Inc., Quebec, Canada).

To assess this device, freshly excised, intact lungs were obtained from two sheep under institutional tissue sharing protocols. Air-filled lungs present significant challenges for OCT because of the large refractive-index mismatch between alveoli walls and the enclosed air-filled region. At each air-tissue interface, the light is strongly backscattered, such that image penetration is typically limited to a single alveolus. Previous work with OCT needle probes has addressed this issue by performing a whole lung lavage, where the lung is flooded with saline [10]. However, this is undesirably invasive and logistically challenging *in vivo*. Utilizing the optofluidic needle probe, we delivered a small fluid payload of saline to the area

Fig. 2: Schematic of the experimental setup with the optofluidic needle probe. Label: VOA: variable optical attenuator.

being imaged, locally displacing the air without effecting the remainder of the lung. In addition to its utility as a protocol for OCT lung imaging, we found this to be a useful model to assess the extent of fluid perfusion, as areas perfused with saline show a marked improvement in image quality and image penetration depth.

To prepare the tissue, the trachea was cannulated immediately after excision of the lungs and occluded to minimize deflation. The lung was kept moist until scanning (within 2 hours) by the application of saline. Immediately prior to imaging, each lung was air-inflated to 20 cm H₂O and held at this pressure for 10 minutes to allow for alveoli recruitment. The pressure was then reduced to 15 cm H₂O for imaging, as we found the lower pressure more reliably maintained during lung puncture.

Two experimental scanning protocols were implemented. The aim of the first was to assess the effect of saline infusion through the imaging needle during scanning at a fixed location. The probe was inserted into the lung parenchyma and counter-rotated to acquire radial B-scans, without the injection of saline. After 10 counter-rotations, the syringe pump was engaged and saline introduced at a rate of $14\mu\text{L/s}$. Scanning continued uninterrupted for 20 counter-rotations, delivering a total fluid payload of $140\mu\text{L}$. This process was repeated several times at well separated locations in the lung. After withdrawal of the needle at the completion of each scan, the needle puncture was sealed with cyanoacrylate.

The aim of the second scanning protocol was to compare 3D scans of air-filled lungs acquired with and without probe-delivered saline. The probe was inserted into an unpunctured, air-filled lung lobe and a 3D OCT volume acquired without saline infusion, over a pullback distance of 4 mm. The scan was repeated at a nearby location, with the syringe pump engaged at $14\mu\text{L/s}$, delivering 4mL of saline over a 4 mm pullback. The needle probe was left in place to mark the area scanned. A slice of tissue was then excised adjacent to the length of the needle and a hematoxylin and eosin (H&E) -stained section prepared.

Fig. 3: (a) Optofluidic needle probe image of air-filled lungs: (a) prior to; and (b) after commencement of saline injection. Arrows indicate representative alveoli.

Results from the first experimental protocol are shown in Fig. 3, displayed at high contrast to allow delineation of the alveoli. A radial B-scan acquired in air-filled lung prior to injection of fluid is shown in Fig. 3a. The black disc in the center of the image is the needle. Note the lack of alveolar structures; high degree of backreflection at the initial air-tissue interface; and rapid attenuation of the OCT light beam. Fig. 3b shows the same location 6 seconds after the commencement of saline perfusion. The dense network of alveoli surrounding the needle probe became visible, with the OCT light beam penetrating typically through ~ 5 alveoli. We found the imaging results to be robust under minor perturbations in the flow rate, with increases up to $28 \mu\text{L/s}$ resulting in negligible differences in image quality and penetration.

Figure 4 compares results for the second experiment. The volume-rendered images are cropped to reveal airway structures. The needle appears at the center of each volume, labeled N, and a longitudinal plane is visualized at a distance of $150 \mu\text{m}$ from the needle. Fig. 4a (Media 1) is the OCT image acquired in air-filled lungs without fluid, showing few discernible features, again due to the high backscatter at the initial air-tissue interface. Fig. 4b (Media 2) shows OCT acquired during fluid injection, revealing a network of alveoli (labeled A), interspersed with bronchioles (labeled B) and a vessel (labeled V).

Fig. 5a shows a longitudinal image extracted from data acquired during fluid injection and pullback, and the corresponding H&E histological section. The OCT image was constructed by extracting an imaging plane from the

Fig. 4: Images from 3D visualizations of sheep lung, showing cross-sectional views: (a) without (Media 1); and (b) with saline injection (Media 2). V, blood vessel; B, bronchiole; A, alveoli. The length of the cylindrical data volume is 4 mm.

data volume, where the horizontal axis of the image is aligned with the direction of needle retraction. Each vertical column of the image intersects a different radial B-scan. The thin black horizontal line running through the image marks where the counter-rotating needle probe completed rotation and reversed direction. The horizontal section through the center of the image is closest to the probe. The reduced signal at the top and bottom of the image correspond to tissue that is further from the probe.

A bifurcating vessel is visible (labeled V) and two bronchioles are shown in cross-section (labeled B). Alveoli appear as regions of low backscatter enclosed by highly backscattering walls. These images acquired in predominantly air-filled lungs show comparable quality to OCT images acquired in saline-flooded lungs [5, 10].

The extent of the visible lung parenchyma provides an indication of fluid penetration. We found the airway structures to be more extensive when fluid injection occurred during pullback (Fig 4b) than when held at one position (Fig. 3b). We hypothesize that this is partially because the imaging window is retracted directly through the point of fluid injection, and also that fluid injection during pullback allows additional pathways for diffusion through airspaces compared to static injection. We note that, while injection of the fluid is fixed relative to the imaging window, subsequent diffusion of the fluid will be tissue-dependent.

Fig. 5: (a) Longitudinal reconstructed OCT image of a sheep lung acquired in pullback mode with saline injection through an optofluidic needle probe. The horizontal axis is aligned with the direction of needle retraction during scanning. (b) Co-located H&E section. A, alveoli; B, bronchioles; V, vessel.

The integrated probe design rigidly controls the relative location of the area imaged to that infused with fluid, and also reduces the overall probe outer diameter to 0.72 mm, from 0.9 mm in the dual-barrel design of [9]. The distance between the imaging window and fluid-delivery outlet in this prototype was restricted by the electrochemical etching process used. However, smaller and more localized openings are possible through the use of laser ablation [11]. The optimal hole size and position will depend on scan rate, fluid delivery rate and the tissue being imaged. Placement of the hole too close to the imaging window may cause artefacts related to fluid motion, but this was not observed here.

Localized delivery of saline lends itself more to an *in vivo* setting than earlier work requiring flooding of the lung [10], but challenges remain. Reduction of respiratory motion artifact places more stringent requirements on image acquisition time, although use of respiratory gating techniques provide an alternative approach [12]. Such refinements represent future engineering challenges.

The ability to directly inject fluid into the area being imaged has a number of potential applications, such as optical clearing agents, contrast agents and therapeutic agents. In the specific example of gold nanoparticle solutions, an optofluidic needle probe with the ability to deliver focused light could both image tissue perfused with nanoparticles, and enable localized ablation [13]. While the *in vivo* toxicity of nanoparticles is poorly understood, complications become more pronounced at higher concentrations [14], making targeted delivery of nanoparticles highly desirable. For improved tissue targeting, tumor-specific fluorescent contrast agents have been demonstrated [15]. Recent advances in needle probes

have demonstrated dual-modality probes capable of simultaneous OCT and fluorescence imaging [16]. Incorporated into an optofluidic needle, such a design could complement OCT tissue imaging with targeted fluorescence contrast.

In conclusion, we have presented the first optofluidic needle probe integrating imaging and fluid injection. Integrating these into a single needle has allowed a reduction in the size of the device, and ensures a fixed, rigid relationship between the point of imaging and fluid delivery to help facilitate targeting. Results in a lung model demonstrated the ability of this probe to modify optical properties in a localized area through delivery of milliliter quantities of fluid. We believe that such integrated probes will improve the capabilities of OCT needle probes, supplementing imaging with a range of image-enhancing, diagnostic and therapeutic fluids.

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