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Fiber endface illumination diffuser for endo-cavity photoacoustic imaging

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Abstract

The laser illumination delivery method is important in designing probes that achieve high imaging quality and deep tissue penetration. Here we present a novel, to the best of our knowledge, fiber diffuser tip using microspheres dispersed within an ultraviolet adhesive to scatter light. This diffuser keeps the skin surface fluence under the maximum permissible exposure, while enabling higher laser energy injection to enhance the photoacoustic (PA) signal generated from the tissue. We compare the light diffusion effects of different microsphere materials, sizes, and concentrations, and find that 10 μm silica microspheres provide the best light scattering with minimal 5% output energy loss. With the Zemax simulation and experimental validation, we show that this fiber diffuser tip is a valuable tool for endo-cavity PA imaging.

Capitalizing on developments in laser and ultrasound detection, our earlier studies reported in vivo transvaginal imaging using co-registered ultrasound and photoacoustic (PA) tomography (PAT) [1–4]. To deliver light into the PAT imaging probe, the multimode fiber is a typical choice. However, the available fiber diameters and numerical apertures (NAs) are limited, leading to a small divergence angle and a high light fluence hot spot on the tissue surface. If the fiber is directly in contact with tissue, the light fluence can easily exceed the maximum permissible exposure (MPE) ($\sim 28 \text{ mJ/cm}^2$ at 780 nm) [5]. Although several research papers have reported methods to reduce the fluence and hot spot at the skin surface [6–8], energy loss and manufacturing difficulty still remain as significant challenges.

Diffusion is an excellent method to reduce the fluence on the tissue surface, and a fiber diffuser tip is relatively compact and well suited for endoscopic imaging. Several research papers and patents have described fiber diffuser tips of various kinds. For example, Lee *et al.* [9] described a conical air-pocket fiber tip made by fusing a section of hollow optical fiber

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using an electric arc-discharge process. The laser beam entering the air-pocket fiber interface is reflected by total internal reflection that changes its direction multiple times, thus generating a larger laser spot or even side illumination. Reference [10] formed cracks on a fiber tip to generate reflections and refractions, thus diffusing light. Reference [11] described a bullet-shaped tip for deflecting and refracting light. However, these kinds of shape/structure-based fiber diffusers are relatively difficult to make in practice; the customized shape and cracks make fiber fragile, and the scattered light distribution and spot size are difficult to control.

Additionally, researchers have tried to use particles or air bubbles as a scattering medium for light diffusing. In Ref. [12], the author used a spherical shape radiator composed of adhesive and quartz powder, which is manufactured on the bare fiber core to generate a spherical pattern illumination for photodynamic therapy. However, this structure needed a large size scattering sphere compared with fiber dimension for a good spherical pattern scattering effect. Reference [13] described a diffusive tip for phototherapy in surgery made by an optical scattering medium enclosed in a light transmissive cap, which is attached to fiber tip, with 2π steradians illumination. However, for PA imaging, the large diffusing divergence angle in Refs. [12,13] is undesirable, where the back-scattered light could not be injected into tissue effectively and, thus, utilized for imaging.

To address these problems, we have developed an effective fiber diffuser tip to reduce the fluence on the target tissue surface, while injecting more laser energy and enhancing the PA signal generated from the tissue.

The fiber diffuser tip, as depicted in Fig. 1(a), is made of silica microspheres (10 μm diameter, refractive index = 1.458) mixed within ultraviolet (UV) adhesive (Norland Optical Adhesive 63, refractive index = 1.56). By simple steering, the mixture can be made. After that, the mixture is set aside or put into a vacuum chamber for degassing till all the air bubbles in the mixture are gone. Before applying the mixture onto fiber tip, the homogeneity of mixture is inspected under microscope.

After adhesive mixture preparation, the fiber endface is polished, and then it is dipped into the mixture of microspheres and adhesive. Thus, a partial sphere tip is formed by the surface tension of the adhesive. After curing for several minutes under UV light exposure, the fiber diffuser tip is complete. The thickness and curvature of the diffuser tip surface will influence the diffusive effect slightly. In our experiment and simulation, the curvature of the surface is considered as partial sphere, the surface radius is around 0.55 mm and the diffuser tip thickness is around 0.32 mm as marked in Fig. 1(a). When photons enter the tip scattering region, they undergo Mie scattering caused by the refractive index difference between the microspheres and the surrounding UV adhesive, thus scattering the photons and reducing the output fluence. This diffuser structure is compact, with the same dimension as the fiber diameter, and is easy to manufacture in lab.

Here the diffusing mixture concentration is calculated as the ratio between the mass of the UV adhesive and the microspheres. For example, a 20:10 diffuser is a mixture of 0.20 g UV adhesive and 0.10 g silica microspheres. On the one hand, with a higher concentration of

silica microspheres, the photons experience more scattering events, and thus light is more diffused at the output end. On the other hand, when mixing more and more silica microspheres with the UV adhesive, the solution will eventually become saturated as a clump which is hard to apply onto fiber tip. A 20:10 ratio is the highest microsphere concentration we could make before the clumping of microspheres in the UV adhesive.

The measured output cross-sectional patterns of a normal fiber tip and a 20:10 fiber diffuser tip are shown in Fig. 1(b) with the same input laser energy. As can be seen, with the diffuser tip, a larger spot is observed, and the laser intensity distribution is more homogenized than with the normal fiber tip output. Figure 1(c) shows the axial output patterns of a normal fiber tip and a 20:10 fiber diffuser tip. The light is diffused fast at the output of 20:10 fiber diffuser tip, while the laser output of the normal fiber tip is more concentrated to the axis with a smaller divergence angle.

Another advantage of this fiber diffuser tip is its controllable scattering effect, with varying microspheres sizes, materials and concentrations. To evaluate the fiber diffuser tip parameters and scattering effect, simulations were performed to examine the influences of the microsphere size and material refractive index, as shown in Figs. 2(a) and 2(b). Using Zemax's Mie scattering model, Fig. 2(a) shows the output laser patterns in water of different diffuser tips made of different microspheres manufactured on 1 mm core diameter multimode fibers (0.5 N.A., Thorlabs). To determine by simulation the best scattering effect achievable, we examined the maximum 20:10 concentrations of microspheres made of commonly used materials, such as soda-lime glass ($n = 1.52$), methyl methacrylate (PMMA) ($n = 1.49$), and silica ($n = 1.458$).

As expected, different materials and different microsphere sizes had distinct scattering effects. Figure 2(b) depicts the output fluence (blue lines) and energy loss (red lines) of different materials with varying microsphere diameters in a water medium. The output fluence here is defined as the total energy divided by the cross sectional area at the 1/e points (the points where the fluence has dropped to a value 1/e times the maximum) [5]. The energy loss here is a percentage defined as the back-scattered energy (energy that does not propagate in the forward direction after diffuser tip scattering) over the input energy. With a smaller microsphere diameter, the scattering effect is stronger, thus realizing lower output fluence. Meanwhile, energy loss increases with the reduction of microspheres diameter, especially when the diameter is less than 5 μm . Among all the simulated materials, silica microspheres exhibit the best scattering effects, but also have the highest energy loss. By using 10 μm diameter silica microspheres (gray dashed-dotted vertical line), a reasonable scattering effect of 6.5 times fluence reduction with acceptable laser energy loss (<5%) can be realized.

The concentration of silica microspheres is another important parameter, which we studied with both simulations and experiments in water. Figure 3(a) plots fluence (blue lines) and the maximum input laser energy at MPE (red lines) variations with different fiber diffuser tip microspheres concentrations (from 20:0 to 20:10). At the same input energy level (i.e., 4 mJ/pulse in the simulation and experiment), the output fluence drops from around 130 mJ/cm^2 for a normal fiber tip to 20 mJ/cm^2 for a 20:10 fiber diffuser tip. On the other hand, with its

increased silica microsphere concentration, the maximum input laser energy without exceeding the tissue surface MPE also increases, from 0.9 mJ/pulse with a normal fiber tip to 5.7 mJ/pulse with a 20:10 fiber diffuser tip. This input energy increase will greatly increase the PA signal without exceeding the surface MPE due to the diffused laser spot, as will be demonstrated later. A slight diffusive effect was also observed for 20:0 diffusing tip. It is due to the NA increase after UV adhesive application, which compromises the relatively weak partial-spherical tip curvature focusing effect in a water coupling medium [14].

In order to analyze the fiber diffuser tip's light scattering effect within tissue, we conducted simulations and experiments using a calibrated 0.4% intralipid solution with a 4 cm^{-1} reduced scattering coefficient (μ'_s) and a 0.02 cm^{-1} absorption coefficient (μ_a).

In the experiments, light scattered quickly in the intralipid solution. To show the average fluence distribution in the intralipid solution, here we defined a parameter, named average energy, as the total detected energy averaged by the entire energy detector sensing area. Based on this definition, a higher average energy corresponds to a higher fluence over the energy detector sensing area. In simulation, the Henyey-Greenstein scattering model in Zemax was applied for simulating biological tissue, and a 25 mm diameter detector area was used to simulate the 25 mm diameter energy detector (Coherent Inc., J-25 MB-HE) used in our experiment. Figure 3(b) shows both the simulated and experimental energy distributions at different depths in a 0.4% intralipid solution. The performances of a single 20:10 fiber diffuser tip and a normal fiber tip were compared by measuring the fluence propagating through 5–50 mm thickness of a calibrated intralipid solution. During the simulation and experiment, both the 20:10 diffuser tip and normal fiber tip were controlled at the MPE input energy at the tissue surface. Both the 20:10 diffuser tip and a normal fiber tip showed good agreement between the simulation and experiment, with fluence decreasing with increased depth, due to scattering-induced laser spot expansion. Additionally, with the lower laser energy input, limited by the MPE, the normal fiber (at 0.9 mJ/pulse) shows much weaker average energy at all depths, nearly 1/6 that of the 20:10 diffuser (at 5.7 mJ/pulse).

Figure 3(c) depicts the peak fluence depth distribution along fiber axis when the surface fluence is controlled at the value of MPE. As can be seen in Fig. 3(c), with the increase of depth, the fluence of a normal fiber and diffuser tip both decrease. However, with a normal fiber, the fluence along fiber axis decreases much faster than the circumstance with diffuser tip. As marked with the gray dashed line in Fig. 3(c), the peak fluence at 5 cm depth of a diffuser tip is similar to the peak fluence at 3 cm depth of a normal fiber case.

According to the well-established relationship between the PA signal strength and laser fluence [15,16], the initial pressure generated by the PA effect has a linear relationship with laser fluence and tissue absorption. With a high fluence distribution inside the tissue, a high PA signal should be generated under the same tissue absorption parameter. Thus, according to Figs. 3(b) and 3(c), a stronger PA signal is expected using a diffuser with a higher energy input than a normal fiber with limited input energy.

To demonstrate, we used a four-fiber transvaginal probe configuration reported in our previous study [7] to perform the experiment and acquire PA signal in the calibrated 0.4%

intralipid emulating biological tissue. A carbon fiber was located in different depths as an imaging target. Additionally, fluence distribution at different depths was simulated. In this configuration, the horizontal spacing between fibers was 21 mm, and the vertical spacing was 12 mm. The ultrasound probe (EC3–10, Alpinion Medical Systems, Republic of Korea) was placed in the center of these four fibers to acquire a PA signal. The fiber tip displacement from the probe base is zero. The PA system setup consisted of a fully programmable clinical ultrasound (US) system (EC-12 R, Alpinion Medical Systems, Republic of Korea), and a Nd:YAG laser (Symphotics-TII, LS-2134, Camarillo, California) pumping a pulsed, tunable (690–900 nm) Tisapphire laser (Symphotics TII, LS-2122). Figures 4(a) and 4(b) show the simulated laser fluence distributions at different depths (5–40 mm) inside the calibrated intralipid solution under surface MPE conditions, with (a) the normal fiber and (b) the 20:10 diffuser. Figures 4(c) and 4(d) depict the normalized fluence distribution along the dashed diagonal line crossing two hot spots in Figs. 4(a) and 4(b), with (c) the normal fiber and (d) the 20:10 diffuser. As can be seen, with the 20:10 diffuser, the four laser spots merged faster than with the normal fiber.

Figure 5(a) shows the simulated fluence depth information in the 0.4% intralipid solution at the center region of the four fibers, where the imaging target is located, as marked in the white circular areas in Figs. 4(a) and 4(b). Based on the simulations, the fluence in intralipid first increases and then decreases with increasing depth. For the 20:10 diffuser tip, the fluence peak is around 1–1.5 cm. For the normal fiber tip, the peak is at around 1.5–2 cm. At 1 cm depth, a 15 dB fluence enhancement is observed with the 20:10 diffuser (green line, 5.7 mJ/pulse) over that of a normal fiber (blue line, 0.9 mJ/pulse). In contrast, with the same laser energy input (4 mJ/pulse), no big difference is observed in the fluence value distributions of the different diffuser concentrations (purple, orange lines). Figure 5(b) depicts the experimental results of the recorded amplified PA signal from the commercial ultrasound transducer (EC3–10), we see expected similar trends in the experiments and the simulations.

Figures 5(c) and 5(d) depict the fluence and PA signal change with depths in a 0.8% calibrated intralipid solution, which has an 8 cm^{-1} reduced scattering coefficient (μ'_s) and a 0.02 cm^{-1} absorption coefficient (μ_a). As can be seen, both the fluence peak in Fig. 5(c) and the PA signal peak in Fig. 5(d) shifted down to around 1 cm depth in a 0.8% calibrated intralipid solution due to an increased scattering coefficient. Both 0.4% and a 0.8% calibrated intralipid solution experiments show that, with the high concentration 20:10 diffuser tip, more energy can be injected into the tissue without exceeding the tissue surface MPE, while generating a higher PA signal without damaging the tissue surface. In our experiments, the four-fiber diffuser tips did not reach the MPE energy input level (5.7 mJ/pulse) due to the total energy limitation of our Ti:sapphire laser, which could reach only 4.5 mJ/pulse per fiber for four fibers.

The advantages of this fiber diffuser tip include controllability (different diffusion effects generated by different concentration, material or microsphere size), compactness (same as the dimension of a fiber tip), compatibility (suitable for various fiber tip with different diameters), and high feasibility (easy to make in lab with simple procedures and no requirement for expensive machine). We believe that this fiber diffuser tip could be a useful

tool for PA signal enhancement in many endo-cavity PA imaging applications, such as *in-vivo* colorectal cancer, cervical cancer, and ovarian cancer.

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Fig. 1.

(a) Fiber diffuser tip, (b) fiber tip output cross-sectional pattern recorded by a camera, and (c) fiber tip output axial pattern recorded by a camera.

Fig. 2.

(a) Simulation of the fiber diffuser tip output pattern: normal fiber tip (upper-left), soda-lime glass ($n = 1.52$) (upper-right) PMMA ($n = 1.49$) (lower-left), and silica ($n = 1.458$) (lower-right), and (b) comparison of the fluence and energy loss of different microsphere materials and sizes.

Fig. 3.

(a) Fluence distribution and maximum input energy with different diffuser concentrations, (b) fluence distribution in a calibrated intralipid solution at different depths, and (c) peak fluence along fiber axis.

Fig. 4.

(a) Simulation of four-fiber transvaginal probe output fluence in a calibrated intralipid solution—normal fiber tip, (b) four-fiber transvaginal probe output fluence in a calibrated intralipid solution—20:10 diffuser tip, (c) normalized fluence at the diagonal line crossing two hot spots—normal fiber tip, and (d) normalized fluence at the diagonal line crossing two hot spots—20:10 diffuser tip.

Fig. 5.

(a) Simulation of four-fiber transvaginal probe fluence distribution in a 0.4% calibrated intralipid solution at different depths, (b) experiment PA signal distribution at different depths in a 0.4% calibrated intralipid solution, (c) the simulation of four-fiber transvaginal probe fluence distribution in a 0.8% calibrated intralipid solution at different depths, and (d) experiment PA signal distribution at different depths in a 0.8% calibrated intralipid solution.