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Design of optimal light delivery system for co-registered transvaginal ultrasound and photoacoustic imaging of ovarian tissue

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ABSTRACT

A hand-held transvaginal probe suitable for co-registered photoacoustic and ultrasound imaging of ovarian tissue was designed and evaluated. The imaging probe consists of an ultrasound transducer and four 1-mm-core multi-mode optical fibers both housed in a custom-made sheath. The probe was optimized for the highest light delivery output and best beam uniformity on tissue surface, by simulating the light fluence and power output for different design parameters. The laser fluence profiles were experimentally measured through chicken breast tissue and calibrated intralipid solution at various imaging depths. Polyethylene tubing filled with rat blood mimicking a blood vessel was successfully imaged up to ~30 mm depth through porcine vaginal tissue at 750 nm. This imaging depth was achieved with a laser fluence on the tissue surface of 20 mJ/cm^2, which is below the maximum permissible exposure (MPE) of 25 mJ/cm^2 recommended by the American National Standards Institute (ANSI). Furthermore, the probe imaging capability was verified with *ex vivo* imaging of benign and malignant human ovaries. The co-registered images clearly showed different vasculature distributions on the surface of the benign cyst and the malignant ovary. These results suggest that our imaging system has the clinical potential for *in vivo* imaging and characterization of ovarian tissues.

1. Introduction

Ovarian cancer has the highest mortality rate of all gynecologic cancers, and is estimated to be the ninth most common cancer and the fifth leading cause of death among all cancers in the United States [1,2]. The lifetime risk of invasive ovarian cancer is approximately 1.4% (1 in 71) and the lifetime risk of death is about 1 in 95 [1]. More than two thirds of ovarian cancer cases are diagnosed in stages III or IV with invasion to the peritoneum and other organs due to nonspecific associated symptoms as well as lack of efficacious screening techniques at the disposal of patients [1–3]. The 5-year survival rate is 94% at the local stage (stage I), while only 15% of ovarian tumors are diagnosed at this stage. This is in sharp contrast to a rate of approximately 28% at the distant stage (stage IV), where 62% of the cases are diagnosed [2]. Unfortunately, there is no simple and reliable way to screen for ovarian cancer. For instance, tumor marker CA 125 along with transvaginal ultrasound (US) yield low positive predictive values (PPVs) of 40% [4–8]. Transvaginal ultrasound alone suffers from a low positive predictive value of 14.1% according to a study done on the annual screening of 25,327 women [9]. Therefore, there is an urgent need to improve the current diagnostic techniques and consequently increase the effectiveness of ovarian cancer screening.

Photoacoustic tomography (PAT) is an emerging imaging modality with great potential to assist transvaginal ultrasound for ovarian cancer screening. In PAT imaging, a short-pulsed laser beam penetrates into biological tissue diffusively. Due to tissue thermoelastic expansion resulting from a transient temperature rise caused by the laser irradiation, the photoacoustic waves are generated and measured by wideband ultrasound transducers [10–22]. The photoacoustic waves are utilized to reconstruct, at ultrasound resolution, the optical absorption distribution that reveals tissue optical contrast. Optical absorption is directly related to neovascularization associated with tumor angiogenesis and hypoxia. Tumor angiogenesis and oxygen consumption are significant factors promoting tumor growth and metastasis [23].

Several optical fiber-based photoacoustic imaging probes have been designed for various applications by several research groups

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[24–38]. Typically, to deliver light to the tissue, one or several optical fibers or fiber bundles are integrated with the ultrasound transducer. In the compact probe design for endoscopic and intravascular applications, single fibers with core diameters of a few to several hundred microns are utilized [24–27]. Due to the relatively small core area, the energy density of the coupled light at the fiber end face is high. In order not to damage the fiber, the available light energy at the end face is limited. As a result, these fibers are most suitable for imaging shallow lesions where the laser intensity required is relatively low. Fiber bundles on the other hand have the advantages of a relatively larger optically active areas and good mechanical flexibility and have been used in photoacoustic imaging probes [28–38]. However, their large diameter sizes make them unsuitable for transvaginal photoacoustic/ultrasound probes. Another drawback is their high loss in light transmission, which potentially reduces the signal-to-noise ratio (SNR) of the detected photoacoustic signals. In our earlier study, we designed a transvaginal photoacoustic/ultrasound probe suitable for imaging of human ovaries [39]. This probe consisted of 36, 200-micron core fibers from a pair of custom-made high-power fiber-optic beamsplitter assembly integrated with the ultrasound transducer. Unfortunately, this specialty beamsplitter is rather expensive and moreover prone to damage at the fiber input end and the junction between the input and output fibers with repeated use, when a high intensity ($>$ 20 mJ/pulse) laser source is employed.

In this paper, we report the optimal design, implementation, and evaluation of an optical fiber-based transvaginal photoacoustic/ultrasound imaging probe with significantly improved light delivery efficiency, low-cost, robust operation for extended use as well as a homogeneous distribution of irradiance. The light delivery system consists of light coupling optics, a custom-made transducer sheath internally lined with highly reflecting aluminum sheet, and four 1-mm-core multi-mode optical fibers surrounding the ultrasound transducer. The transducer and fibers are housed inside the sheath, and the aluminum material lining serves as a light tunnel for high-efficiency light transmission. The probe design was optimized by simulating the light fluence and power output efficiency, and was further evaluated by experimental measurements.

2. Methods and Materials

2.1. Optimization of imaging probe design

The probe design was optimized to deliver good light uniformity on tissue surface, high power output efficiency, and acceptable fluence levels below the ANSI safety limit (25 mJ/cm^2 at 750 nm wavelength) [40]. The power output efficiency is defined as the ratio of the total energy output from the probe to the total energy exiting the four fibers. The optimization was performed by simulating the fluence distribution of the four fibers using a 3D model in Zemax. The model of the imaging probe [41], shown in Fig. 1, consisted of two concentric hollow cylinders and represented the transvaginal ultrasound transducer and the probe sheath respectively. For a more realistic geometry, the cross-sectional area of the first cylinder, representing the ultrasound transducer, was gradually tapered down to a radius of 5 mm. This shape resembled closely the actual transvaginal probe used in the experiments. The diameter of the inner cylinder was chosen as 20 mm - same as the diameter of the transducer used in the experiments. The diameter of the outer cylinder however was varied to obtain one that provides the best results, as will be explained in the subsequent sections. The illumination fibers were sandwiched between the two hollow cylinders. Additionally, the surfaces of the cylinders bordering the fibers were chosen to have a

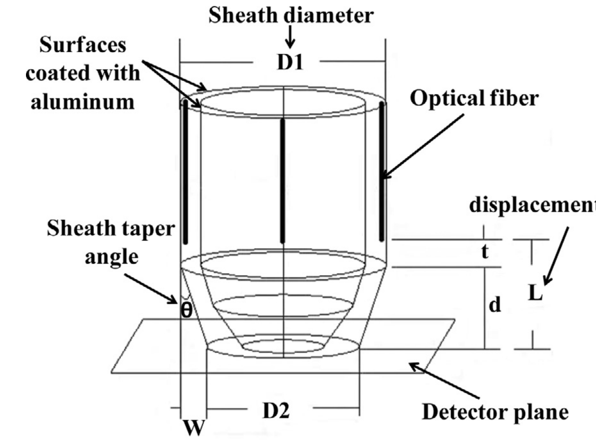

Fig. 1. The model of the imaging probe employed in the simulation with all the design parameters shown. L: fiber displacement, D1: probe diameter, and θ: sheath taper angle.

reflection coefficient of 85% at 750 nm, this is the same value as the reflection coefficient of the aluminum sheet that was used in the actual construction of the probe. The optical detection plane was chosen to be a plane parallel to the surface area of the probe base and just touching it (Fig. 1). In the simulation, a detector was placed at this plane to measure the laser fluence and power output efficiency. The fluence delivered to the tissue surface was calculated based on the incident optical energy and the illumination area.

Various parameters of the imaging probe were investigated in order to obtain acceptable fluence levels, while at the same time yielding high power output efficiencies. These parameters are: 1) fiber numerical aperture (NA); 2) fiber displacement from the probe base (L); 3) sheath diameter (D1); and 4) sheath taper angle (θ); for a definition of these terms, see Fig. 1.

Fiber numerical aperture and displacement from probe base (L): The first parameters that were investigated were the fiber numerical aperture and the longitudinal displacement (L) from the base of the probe. The angle of divergence of light exiting the fiber depends on the fiber's numerical aperture- higher numerical apertures yield greater divergences. Therefore, this numerical aperture effect was simulated in Zemax by adjusting the divergence of the light source to correspond to the fiber numerical aperture that would give the same divergence. The fiber numerical aperture was calculated by *sine (angle of divergence)*. The fiber displacement (L) was also accomplished in Zemax by changing the positions of the Gaussian light sources in the vertical direction. In all, four different numerical apertures, of values, 0.21, 0.36, 0.48, 0.65, and four displacements, 5, 10, 15, and 20 mm were simulated. For each displacement, the fluence and power output efficiency at the imaging plane were simulated for all the numerical aperture values and compared. The simulation results were obtained with the sheath diameter fixed at 25 mm and sheath taper angle at 0^o. The distance t was not varied and its purpose was to provide some space for the fiber holder. Moreover, Monte Carlo (MC) simulation was performed to estimate light reflection events of photons at the surfaces with various numerical apertures. A 2D model was used for the simulation. After the photon was generated, it reflected between the two surfaces according to the law of reflection, until it reached the detector plane. The MC code was a custom program written by the authors.

Sheath diameter (D1) and taper angle (θ): The next parameters that were investigated were the sheath diameter and taper angle. Different sheath diameters were simulated simply by changing the diameter of the outer cylinder. Diameters of 23, 24, 25, and 26 mm