In vivo three-dimensional photoacoustic imaging based on a clinical matrix array ultrasound probe

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Abstract. We present an integrated photoacoustic and ultrasonic three-dimensional (3-D) volumetric imaging system based on a two-dimensional (2-D) matrix array ultrasound probe. A wavelength-tunable dye laser pumped by a Q-switched Nd:YAG laser serves as the light source and a modified commercial ultrasound imaging system (iU22, Phillips Healthcare) with a 2-D array transducer (X7-2, Philips Healthcare) detects both the pulse-echo ultrasound and photoacoustic signals. A multichannel data acquisition system acquires the RF channel data. The imaging system enables rendering of co-registered 3-D ultrasound and photoacoustic images without mechanical scanning. The resolution along the azimuth, elevation, and axial direction are measured to be 0.69, 0.90 and 0.84 mm for photoacoustic imaging. In vivo 3-D photoacoustic mapping of the sentinel lymph node was demonstrated in a rat model using methylene blue dye. These results highlight the clinical potential of 3-D PA imaging for identification of sentinel lymph nodes for cancer staging in humans. © 2012 Society of Photo-Optical Instrumentation Engineers (SPIE). [DOI: 10.1117/1.JBO.17.6.061208]

Keywords: photoacoustic imaging; ultrasound imaging; three-dimensional imaging; sentinel lymph node.

1 Introduction

Photoacoustic (PA) imaging, combining optical absorption contrast with fine ultrasonic resolution, enables deeply penetrating in vivo imaging.1 Pure optical imaging modalities (e.g., optical coherence tomography and diffuse optical tomography) encounter a fundamental limitation of either penetration or spatial resolution at depths beyond one optical transport mean free path (~1 mm) due to strong light scattering by biological tissue. PA imaging, however, provides a high ultrasonic spatial resolution for deep imaging by utilizing ultrasonic detection of the PA wave generated by absorbed diffuse light.2–5 Deep PA imaging has been used to image both biological structure (e.g., internal organs,6,7 and sentinel lymph nodes8) and function (e.g., tumor hypoxia,9 and brain oxygenation10). The ability of PA imaging (PA microscopy and PA computed tomography1) systems to render three-dimensional (3-D) volumetric images relies on recording the PA time-of-flight signals on a two-dimensional (2-D) surface facing the photoacoustic source, light-absorbing chromophores. Due to the system cost and complexity when employing a large number of data acquisition (DAQ) channels, currently most PA imaging systems utilize a single-element ultrasound (US) transducer2–10 or a one-dimensional (1-D) array US probe.4,6,11 Mechanical scanning of the US probe required by these systems to form 3-D PA images limits the volumetric imaging frame rate. Thus, 3-D PA imaging systems using 2-D array US probes have been recently studied. Khuri-Yakub et al. have fabricated a 2-D capacitive micromachined ultrasonic transducer (CMUT) with 16 × 16 elements (pitch size, 250 μm) for PA and US imaging.12 Mechanical scanning was needed to form a large detection aperture to improve the image quality. Zhu et al. have developed a 2-D array US transducer with 10 × 128 elements for US and PA characterization of ovarian tissue.13 This imaging system is limited in the beam steering angle and elevational resolution. Van Leeuwen et al. have used a polyvinylidene fluoride (PVDF) based hydrophone matrix consisting of 590 elements in a research prototype system for breast cancer detection.14,15 The large detector element size of 2 × 2 mm2 limits the spatial resolution of the imaging system. We developed a 3-D PA imaging system based on a clinical 2-D matrix array US probe with the modified US scanner to enable 3-D PA and US imaging without mechanical scanning. Optical fiber bundles for light delivery were physically integrated with the matrix array US probe (2500 elements), while the capability of real-time 3-D US imaging was maintained.

Sentinel lymph node biopsy (SLNB) is an emerging method for axillary lymph node staging in clinically node-negative breast cancer patients.16 The current SLNB technique requires an injection of radioactive colloids and blue dyes for identification of sentinel lymph nodes (SLNs). Following invasive visual confirmation, SLNs are surgically resected for pathological examination of the excised tissue. The invasive surgical procedure leads to potential postoperative complications, such as lymphedema, seroma formation, sensory nerve injury, and limitation in the range of motion.17 Therefore, PA imaging has been proposed as an alternative method of noninvasive SLN identification and photoacoustically-guided minimally invasive fine-needle aspiration biopsy.18 Noninvasive mapping of SLNs using PA imaging of the injected blue dye accumulated...
in the SLNs would enable targeted needle biopsy. Moreover, PA imaging features lower speckle signal from the background biological tissue than US imaging.6

Our group previously reported a modified clinical US scanner using a linear US array for clinical translation of PA sentinel lymph node mapping.6 In this report, we evaluated the performance of the matrix US array based multi-modal 3-D imaging system using a resolution phantom, and demonstrated 3-D in vivo PA SLN mapping in a rat model.

2 Methods and Materials

2.1 Imaging System Description

The PA imaging system adapted from a clinical US scanner (iU22, Philips Healthcare, Andover, MA) is shown in Fig. 1. The channel board architecture was modified to allow acquisition of the raw per-channel PA and US data. The dual-modality image data were transferred to a custom-built data acquisition (DAQ) system for image reconstruction and display. For 3-D PA and US imaging, we used the 2-D matrix array US probe (X7-2, Philips Healthcare) which has 2500 elements and a nominal bandwidth of 2 to 7 MHz. Each frame of the PA volumetric image requires 36 laser shots and takes 20 sec, limited by the current DAQ system performance. The DAQ system was synchronized with laser firings by an FPGA-based electronic board and digital delay generator (Stanford Research Systems, Sunnyvale, CA). A 3-D back-projection algorithm was implemented using Matlab (MathWorks Inc., Natick, MA) to reconstruct PA images.19 The resolution of the matrix array US probe was estimated using a wavelength tunable dye laser (PrecisionScan-P, Sirah, Rheinbach, Germany) integrated with the matrix array US probe. The laser pulse is coupled along the elevation direction. PA B-mode image of the hair positioned along the (a) azimuth and (f) axial directions. (c) PA B-mode image of the hair positioned along the elevation direction. PA amplitude profiles crossing the hair along the (d) elevation, (e) azimuth, and (f) axial directions, respectively. PA, photoacoustic; US, ultrasound; and DAQ, data acquisition.

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Fig. 3  (a) Photograph of the gelatin phantom consisting of one white hair, one black hair, and a gelatin slab dyed with black ink. (b) PA MAP image showing the black hair and the ink dyed gelatin slab. (c) US MAP image showing the white hair and the black hair. (d) PA 3-D image. (e) US 3-D image. PA, photoacoustic; and US, ultrasound.

the probe and then imaged with the hair placed along the elevation direction. The PA maximum amplitude projection (MAP) images are formed by projecting the 3-D PA image onto the surface plane of the probe. Figure 2(a) and 2(b) shows the PA MAP images of the hair positioned along the azimuth and elevation directions, respectively. Figure 1(c) displays the PA B-mode image of the hair positioned along the elevation direction. Figure 2(d)–2(f) displays the 1-D PA amplitude profiles crossing the hair along the elevation, azimuth, and axial directions as indicated by the dashed lines in Fig. 2(a)–2(c). We used the full width at half maximum of each 1-D PA amplitude profile to quantify the corresponding spatial resolution. At a depth of ~2 cm, the spatial resolution was found to be 0.69 ± 0.05 (mean ± standard deviation) mm in the azimuth direction, 0.90 ± 0.03 mm in the elevation direction, and 0.84 ± 0.04 mm in the axial direction.

Figure 3(a) shows a photograph of the second gelatin phantom. The PA MAP image [Fig. 3(b)] only shows the black hair and the ink-dyed gelatin slab because of the PA wave generation by the light absorbing chromophores. In the pulse-echo US MAP image [Fig. 3(c)], two hairs are seen, but not the ink-dyed gelatin, because the acoustic impedance mismatch between the hair and the gelatin produces a strong US reflection, while the acoustic impedance mismatch between the ink-dyed gelatin and surrounding gelatin is too small. The 1 × 1 × 1 cm² volumetric PA and US images of the phantom are shown in Fig. 3(d) and 3(e). Figure 4(a) shows a photograph of the third gelatin phantom from top view. In the PA 3-D volumetric images [Fig. 4(b) and 4(c)], all three hairs at different depths were seen.

3.2 Rat SLN Mapping

To explore 3-D PA mapping of SLNs with methylene blue dye, we used the matrix array US probe to image the axillary region in a rat. A control PA MAP image was acquired before injection of methylene blue dye [Fig. 5(a)]. After injection, the blue dye accumulated in the SLNs by lymphatic drainage. Figure 5(b) and 5(c) shows the PA MAP images acquired at 5 and 30 min post-injection, respectively. The uptake of methylene blue in the rat SLN was clearly observed in the PA MAP images, which are all displayed with the same dynamic range. After dissection, the methylene blue-dyed SLN was visually identified as shown in the post-mortem photograph [Fig. 5(d)]. The 3-D photoacoustic image from the rat SLN acquired at 30 min post-injection is rendered volumetrically in Fig. 5(e). The dynamics of the methylene blue accumulation in the SLN following injection for three rats is plotted in Fig. 5(f).

A single-compartment model was used to fit the methylene blue dye accumulation in the SLN.

\[ \frac{dC}{dt} = k_{in}C_0 - k_{out}C, \]  

where \( C_0 \) and \( C \) represent the methylene blue concentration in the bolus injection site (left forepaw pad) and the SLN, respectively; \( k_{in} \) and \( k_{out} \) are rate constants for the SLN’s inward and outward transport of the blue dye; and \( t \) is the post-injection time. The solution to Eq. (1) is

\[ C = C_0 \frac{k_{in}}{k_{out}} \left( 1 - e^{-k_{out}t} \right). \]  

The fitted curve, \( C = 16.1 (1 - e^{-0.142t}) + 4.03 \), with an \( R^2 \) value of 0.785 is shown in Fig. 5(f). The mean PA signal amplitude enhancement at 30 min post-injection was ~20 fold, compared to the pre-injection baseline signal amplitude.

4 Discussion and Conclusions

We have developed a 3-D PA and US imaging system comprised of a 2-D matrix array US probe and a modified clinical US system. Compared to previous PA imaging systems employing 2-D array US transducers, this system provides...
sub-millimeter spatial resolution, enables fast PA data acquisition, and incorporates real-time 3-D US imaging functionality of the commercial US scanner system. The current DAQ system acquires the PA data set for one volumetric frame in ~20 sec from 36 laser firings. To fully realize the potential of 3-D PA imaging, further system development will concentrate on improving the speed of data acquisition and utilizing fast Fourier transform (FFT) based 3-D reconstruction algorithm.

Previous reports support the potential for PA SLNs mapping with a 2-D PA imaging system that employs a commercial linear array US probe. Here, we present 3-D PA imaging of rat SLNs in vivo following accumulation of methylene blue dye. This new 3-D imaging system improves on earlier advancements of SLNs PA imaging by more efficiently and effectively acquiring 3-D images, and should facilitate the clinical application of PA imaging for SLNs mapping and image-guided SLN biopsy.

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