Three-dimensional photoacoustic imaging system in line confocal mode for breast cancer detection

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We present a three-dimensional (3-D) photoacoustic imaging system (PAIS) in line confocal mode for breast cancer detection. With the line confocal mode, the spatial resolution of the PAIS was tested to be improved about three times compared with the nonconfocal mode PAIS. Furthermore, with a flexible scanning system and no compression on the breast, the PAIS could supply a comfortable and safe diagnosis process for the patient. An *ex vivo* breast tumor imaging experiment was performed and the tumor was visualized by the 3-D photoacoustic image. The experimental result demonstrated that the system had great potential of application in breast cancer detection. [doi:10.1063/1.3518704]

Breast cancer is one of the most common cancers striking women worldwide and became the second leading cause of death in women in recent years. The incidence of breast cancer is still climbing due to the increase of life expectancy and urbanization.[1] Currently, several methods are employed for breast cancer diagnosis, including x-ray mammography, ultrasonography, and nuclear magnetic resonance imaging (MRI).[2] X-ray mammography is widely used in breast cancer detection, but it is a radiating imaging method and its sensitivity is limited when the lesions are small. Ultrasonography is a safe method for breast cancer detection, but suffers from its high false-positive rate. MRI can supply excellent resolution; nevertheless it is not widely available because of the high price. The burden of breast cancer on society and drawbacks of conventional mammography are impelling the development of breast cancer detection modalities.

Photoacoustic imaging (PAI) combines the advances of the high optical contrast and the high ultrasound resolution[3–5] and it is a promising method for breast cancer detection.[6] PA imaging is based on thermoacoustic effect caused by energy absorption in the investigated tissue. PA waves travel through the boundary of the tissue and can be captured by ultrasonic transducers. With the acquired PA waves, the optical absorption difference of the tissues can be shown in the reconstructed energy absorption image.[7–9] Owing to the great need of blood in fast growing malignant tumor, the blood vessels are relatively rich, which causes an enhancement of light absorption in the lesion area.[10] Besides, fat is the main component of the breast, which is relatively transparent for the near infrared (NIR) laser. Hence, PA imaging can play an important role in the breast cancer detection.

Several PAI systems for breast cancer detection have been reported. Oraevsky *et al.*[11] exploited a laser optoacoustic imaging system with an arc shaped detection array for two-dimensional image of the breast. Steenbergen *et al.*[12] developed a photoacoustic mammoscope system with a 590-element plane detector for three-dimensional breast imaging. Wang *et al.*[2] combined thermoacoustic and photoacoustic tomography for breast cancer detection, which could provide dual-contrast image. These systems demonstrated the feasibility of PAI technique application in breast cancer detection. However, the sensitivity was still not good enough due to the limited spatial resolution.

In our design, a 3-D PAI system in line confocal mode was developed and assembled for breast cancer detection. In the system, line confocal mode was used to improve the spatial resolution and 3-D image of the investigated sample could be acquired by the spatial scan. Compared with point detection scheme photoacoustic microscopy, the line confocal mode photoacoustic imaging system has higher acquisition efficiency. Owing to the high spatial resolution and the 3-D visualization, the system had great potential of application in breast cancer detection. In this paper, details of the system were depicted and discussed. Resolution improvement of the PAIS in line confocal mode compared with that of nonconfocal mode was demonstrated by a phantom experiment. Furthermore, an *ex vivo* tumor imaging experiment was conducted to verify the potential application of the system in medical application.

The schematic of the line confocal mode is shown in Fig. 1(a). A Q-switched Nd:YAG laser with a wavelength of 1064 nm, a pulse width of 6 ns at 40 mJ $pulse^{-1}$, and a repetition rate of 15 Hz was used to generate PA signals. The laser was coupled into an optical fiber (core diameter

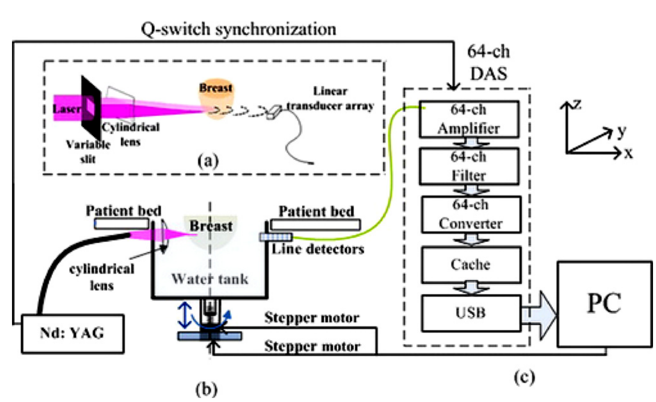

FIG. 1. (Color online) (a) Schematic of the line confocal mode. (b) Diagram of the incorporated excitation and detection device. (c) Parallel DAS.

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600 μm) and then expanded by a negative lens. The expanded laser was filtered by a variable slit to get a rectangular cross homogenous light. With an optical cylindrical lens (focus length 100 mm in the vacuum), the laser was focused into a line and illuminated into the sample. A transducer array (L7L38A-S, SIUI, China) with 64 elements was used to collect photoacoustic signals. The central frequency of the linear multielement transducer array was 7.5 MHz with a bandwidth of 70%. With an acoustic cylindrical lens in the front of the transducer array, the signals from its focal line could be selected. The focal line of the optical cylindrical lens and the acoustic cylindrical lens were set to collinear and thus the line confocal mode was formed. With the line confocal mode, the resolution of the imaging system could be improved compared with nonconfocal mode PA tomography.

Since the long focus optical cylindrical lens (focus length 100 mm) and acoustic cylindrical lens (focus length 35 mm) were used in the system, the illuminated area and the signal receiving area of the transducer array could be seen as a plane, respectively, and the two planes were coplanar. Therefore, plane information could be selected and acquired accurately with one laser pulse.

The schematic of scanning system is shown in Fig. 1(b). Through the aperture of the patient bed, the investigated breast can be suspended in a custom water tank naturally. To acquire volume information of the sample, the excitation and detection system incorporated with the custom water tank first scanned around the axial of the water tank for 20 steps, with each step of 18°, and then along the axial of the water tank for 40 steps, with each step of 0.5 mm. The whole scan process lasts about 5 min. During the process of the diagnosis, the patient's breast will be immersed in warm water with no compression.

A custom 64-ch data acquisition system (DAS) was employed to transmit the acquired raw PA signals from the transducer array. Figure 1(c) shows the schematic of the parallel acquisition system. The parallel DAS was triggered by the Q-switch synchronization of the laser. With the parallel DAS, a frame of the 64-ch data was acquired and transmitted in 1/100 s. Nevertheless, the repetition of the laser was 15 Hz, so the acquisition speed was limited by the laser. With the improvement of repetition frequency of laser in future, the frame rate of the system could be up to 100 Hz.

The signals acquired from each horizontal plane of the sample were calculated by a image reconstruction program, which implements the filtered backprojection algorithm.[13] By 3D-Med (Institute of Automation, Chinese Academy of Sciences), slices of the sample could be composed into a volume image.

To verify that the spatial resolution of the line confocal mode PAIS was superior to nonconfocal mode PAIS, two carbon points (with diameter of 0.5 mm) embedded in the phantom was used to simulate the optical properties of human breast, made with 13% gelatin, 12.5% milk, and 74.5% water,[14] and had an effective attenuation coefficient 1.2 cm^{-1}, with 10 mm distance from the surface of the phantom. Also, the center distance of the two carbon points was 2 mm. They were imaged by both nonconfocal mode and confocal mode PAIS. In the next experiment, a spherical breast tumor specimen with diameter of 10 mm (supplied by the First Affiliated Hospital of Ji'nan University) was used for the *ex vivo* imaging experiment. The experiment was performed immediately after the tumor excision surgical operation. The breast tumor specimen was hidden in the fat tissue and then the hybrid tissue was fixed in the phantom (as mentioned above) with a distance of 2 mm from its surface and shaped as a breast to simulate the diagnosis process. The sample was suspended in the water tank for spatial scan. After the experiment, the tumor specimen was cut open at its middle height to compare with PA image.

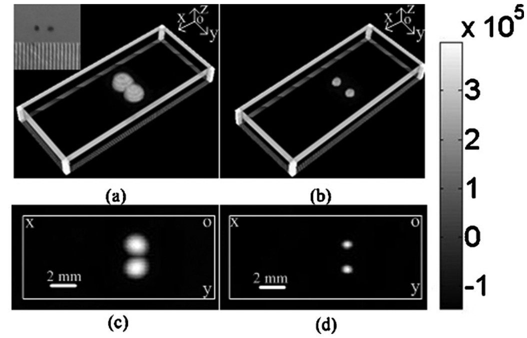

FIG. 2. (a) The 3-D PA image of two carbon points with nonconfocal mode PAIS. (b) The 3-D PA image of two carbon points with line confocal mode PAIS. (c) The middle slice of the 3-D reconstructed images with nonconfocal mode PAIS. (d) The middle slice of 3-D reconstructed images with line confocal mode PAIS.

Figures 2(a) and 2(b) show the 3-D reconstructed images of two point sources with both nonconfocal mode and line confocal mode PAIS. Figures 2(c) and 2(d) show the middle slice of the 3-D reconstructed images with nonconfocal mode and line confocal mode PAIS. Figures 2(a) and 2(b) agree with each other basically, but the spatial resolution is better in line confocal mode PAIS. With the resolution calculation method mentioned in Ref. 14, the spatial resolution improvement of line confocal mode PA tomography is estimated about three times compared with nonconfocal mode PA tomography according to Figs. 2(c) and 2(d). In the line confocal mode PAIS, the influence to the investigated plane from the noninvestigated plane is much less compared with nonconfocal mode PAIS. Therefore, we can conclude that the line confocal mode PAIS is superior to nonconfocal mode on spatial resolution.

Figure 3(a) shows the photograph of the middle cross section of the human breast tumor. A view of 3-D PA image of the human breast tumor is shown in Fig. 3(b). Figure 3(c) shows slices of the sample from which the internal information is shown. The third slice of Fig. 3(c) is the PA image of the middle cross section of the sample and it corresponds to the middle cross section photograph in Fig. 3(a). They match each other very well.

In conclusion, a 3-D PAIS was developed for breast cancer detection and line confocal mode was employed to improve the spatial resolution of the system. Phantom experiments demonstrated that line confocal mode PA tomography had higher spatial resolution than nonconfocal mode PA tomography. *Ex vivo* tumor imaging experiment showed that the system could visualize breast tumor in normal biological tissue. Owing to high spatial resolution, high acquisition speed, and painlessness diagnosis process, the 3-D PAIS had great potential of application in clinic for tumor imaging and the intraoperative margin assessment of the microscopic status of lumpectomy margins.

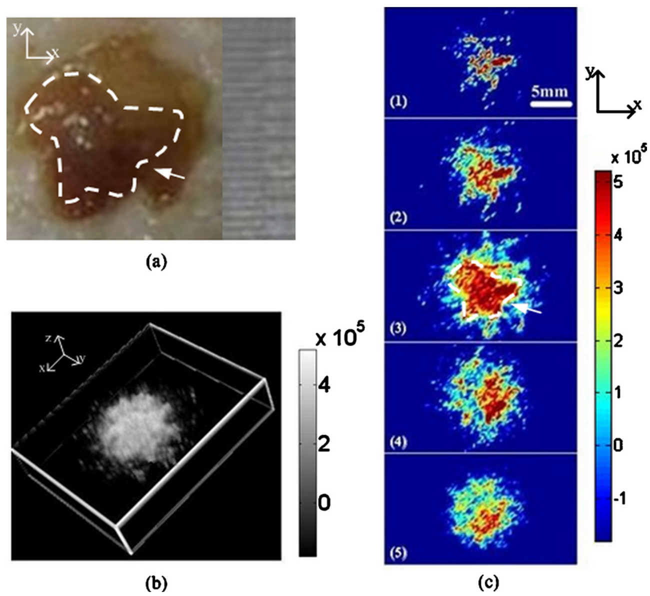

FIG. 3. (Color online) (a) The middle cross section of the human breast tumor; the tissue in the dashed circle was the area that was rich in blood vessels. (b) The 3-D PA image of the breast tumor. (c) PA slices of the breast tumor, the area in the third slice in the dashed circle area was the area with high optical absorption coefficient.

As a result of high scattering property of the tissue, the focused laser can only penetrate shallow depth of the tissue. However, it is a compromise proposal, which can improve the resolution but relatively decrease the imaging depth. The challenge of laser focusing becomes greater for the deeper area of the biological tissue, so the spatial resolution deteriorates as the depth increasing in the biological tissue. In the experiment, NIR laser (with the wavelength 1064 nm) was used to improve the imaging depth and a long focus cylindrical optics lens was used to create a thin light plane in the deeper area of the sample. With these methods, the vertical resolution of the PAIS can reach 0.6 mm in the depth of 10 mm (see Ref. 15 for details about phantom resolution test). However, there is still a lot of work to be done for *in vivo* imaging of breast cancer. For one thing, to achieve a deeper imaging depth, much longer wavelength laser should be employed. In our following work, we will use microwave as the exciting source because it can penetrate the tissue much deeper. For another, the much longer focus length acoustic lens will be employed deeper depth imaging with good resolution.

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[15]See supplementary material at http://dx.doi.org/10.1063/1.3518704 details about the phantom resolution test.