

Biomedical Photoacoustic Imaging

Introduction

Medical imaging is very important for medical diagnostics and research. There are so many medical imaging techniques, and some of them have weaknesses. For instances, x-ray computerized tomography is limited by the accumulation of ionizing radiation which are harmful to the body, ultrasound imaging is limited by its poor contrast and pure optical imaging techniques are unable to effectively visualize the structures several centimeters deep in the tissue due to the strong scattering of biological tissue etc. However, existing high-resolution optical imaging technologies, including confocal microscopy, two-photon microscopy, and optical coherence tomography (OCT), do not sense optical absorption directly (Table 1). These techniques rely on ballistic photons for imaging, hence their imaging depths are limited due to the strong backscattering that related to tissue morphology (OCT imaging in relatively transparent tissues such as the eye is an exception). Mostly, imaging systems can only be used for detecting the prominent parts in our body e.g. brain and breast since the transducer circularly scans the object.

One of a new technique for non-invasive as well as non-destructive imaging is a hybrid biomedical imaging which is called photoacoustic (PA) imaging. It is developed based on the PA effect, a phenomena in which the absorbed energy from the light is transformed into kinetic energy of the sample by energy exchange processes, then results in local heating and thus a pressure wave or sound. In another words, PA effect is the generation of acoustic waves by the absorption of electromagnetic (EM) energy such as optical or radio-frequency (RF) waves. Observation of sound generated by light was first reported in 1880 by Alexander Graham Bell.

PA in tissues

EM energy in the optical (from visible (400–700 nm) to near-IR (700–1100 nm)) and RF regions is used for PA excitation in soft tissues because the waves in these regions are non-ionizing, safe for human and can provide the high contrast and enough penetration depths. Other EM spectrum seems not practical for PA generation in deep tissues. For instance, terahertz rays, lying between the above two EM spectra, do not well penetrate biological tissue due to water-dominated absorption. Below the visible region, such as UV rays, radiation is harmful to human regarding high photon energy.

The optical properties (include scattering and absorption) of biological tissues in the visible and near-IR regions are related to the molecular constituents of tissues and their electronic and/or vibrational structures. The RF properties of biological tissues are related to the physiological nature of their electrical properties. The electrical properties can be described by complex permittivity or complex conductivity.

Non-ionizing waves, such as short laser or RF pulses, are often used to excite megahertz ultrasound waves, referred to as PA or thermoacoustic signals, in biological tissues. So, no ionizing radiation is used in PA imaging, means no health hazard. PA imaging combines ultrasonic resolution with high contrast due to light, or RF, absorption, and does not rely on ballistic photons for excitation. Optical scattering in soft tissues degrades spatial resolution significantly with depth, while ultrasonic waves have 2-3 orders of magnitude weaker than optical waves scattering in biological tissues, hence ultrasound can provide a better resolution than optical imaging in depths greater than ~ 1 mm. Ultrasound imaging, which is relied on the detection of the mechanical properties in biological tissues, has weak

contrasts which are not capable of revealing early stage tumors. In addition, ultrasound is unable to image either oxygen saturation or the concentration of hemoglobin, while optical absorption is very sensitive to both of these parameters. Due to its long wavelength, pure rf imaging cannot provide good spatial resolution. Using the operating frequencies range of 500–900 MHz, pure rf imaging can only serve a spatial resolution of ~ 1 cm. PA imaging overcomes these problems and produces images of high EM contrast at high ultrasonic resolution at large depth. Similar to ultrasound imaging, the resolution and imaging depth of PA imaging is scalable, depending on the frequency of the ultrasound transducer used. Since the velocity of sound in soft tissues is ~ 1.5 mm/ μ s, PA signals with a 1 MHz bandwidth can provide around 1 mm spatial resolution. For 10 MHz, resolution of 0.1 mm can be achieved at the expense of ultrasonic penetration. Increasing the ultrasonic frequency too much will result in a small penetration depth since the ultrasonic attenuation in tissues linearly increases (for human skin, it is $0.7\text{--}3$ dB cm^{-1} MHz^{-1}).

Table 1. Comparison of some imaging modalities

Imaging modality	Primary contrast	Imaging depth	Resolution
Confocal microscopy	Fluorescence/scattering	~ 0.2 mm	$\sim 1\text{--}2$ microns
Two-photon microscopy	Fluorescence	~ 0.5 mm	$\sim 1\text{--}2$ microns
Optical coherence tomography	Optical scattering	$\sim 1\text{--}2$ mm	~ 10 microns
Ultrasonography (5 MHz)	Ultrasonic scattering	~ 60 mm	~ 300 microns
Photoacoustic microscopy (50 MHz)	Optical absorption	~ 3 mm	~ 15 microns
Photoacoustic tomography (3.5 MHz)	Optical absorption	~ 50 mm	~ 700 microns

The combination between the high optical absorption contrast and the high ultrasonic spatial resolution (low scattering) possessed by this technique make it a very useful technique. In PA imaging, non-ionizing laser pulses are delivered into biological tissues, absorbed by tissue chromophores (part or moiety of a molecule responsible for its color), then converted into heat, leading to transient thermoelastic expansion and then excites the spatial emissive distribution of the acoustic transient pressure inside the tissue that acts as the initial source for the acoustic waves. The generated ultrasonic waves reach the surface of the tissue with various time delays, and then detected by ultrasonic transducers placed around the tissues. These waves are used to determine ultrasonic source distribution by forming images revealing the distribution of optical absorption. Optical absorption is closely associated with physiological properties, such as Hb concentration and oxygen saturation. So, the magnitude of the ultrasonic emission (i.e. photoacoustic signal), which is proportional to the local energy deposition, reveals physiologically specific optical absorption contrast.

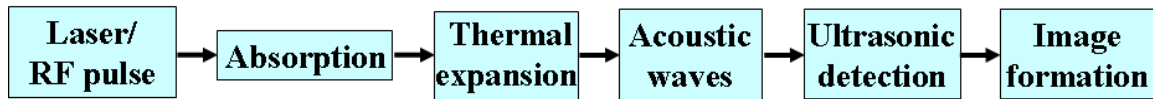


Fig. 1. Schematic illustration of PA imaging.

The optical absorption in biological tissues can be due to endogenous molecules such as Hb or melanin, or exogenously delivered contrast agents (exogenous Hb, for example). Blood usually has orders of magnitude larger absorption than surrounding tissues, so there is sufficient endogenous contrast for PA imaging to visualize blood vessels, for imaging *in vivo* subcutaneous vasculature (the arrangement or the distribution of blood vessels in an organ or body part) in small animals and human, monitoring tumor or cancer, mapping blood oxygenation, imaging functional brain, detecting skin melanoma (a malignant tumor of melanocytes which are found in skin, also in the bowel and the eye), monitoring of vascular damage during tumor photodynamic therapy.

Types of PA imaging systems

There are two types of PA imaging systems:

1. PA microscopy (PAM).

It uses spherically focused ultrasonic transducers with 2D point-by-point scanning to localize the PA sources in linear or sector scans and then reconstruct the image directly from the measured data set, as is often done in pulse-echo USG. So it requires no reconstruction algorithm. The imaging depth of PAM is mainly limited by the ultrasonic attenuation. The spatial and lateral resolutions depend on the ultrasound transducer used. To get high axial resolution, an ultrasound transducer with high central frequency and broader bandwidth are chosen. The lateral resolution is determined by the focal diameter of the transducer. Applications: to detect changes in oxygenated/deoxygenated Hb in small vessels and to image skin melanoma.

2. PA Tomography (PAT), or Thermoacoustic Tomography (TAT), or Optoacoustic Tomography (OAT).

It is used to image complicated structures. PAT uses a pulse laser as a pumping source to irradiate a medium. PAT makes use of PA signals measured at various locations around the subject under study. A typical PAT system uses an unfocused (wideband) ultrasound detector to get the PA signals, usually in a circular or spherical fashion, and then reconstructs the optical absorption distribution of the tissue. PAT imaging can reach a depth of 1 cm at $\lambda = 580$ nm with an axial resolution of less than $100 \mu\text{m}$, and at 1064 nm it can detect 2 mm blood vessels at the depth of 7.5 cm with 0.4 mm depth resolution and 1 mm lateral resolution. Applications: Brain lesion detection, hemodynamics monitoring, breast cancer diagnosis.

In a simple case where a wide beam of light pulse heats a layered medium, the light energy deposition profile throughout the depth will be replicated by the detected PA signal, so, from the temporal PA signal, we can directly determined the depth-related information of the sample, such as the depth structure and properties (e.g., the absorption coefficient in a non-scattering medium). This PA depth profiling can be assumed as 1D PAT.

Safety Issue

EM radiation for human must be limited. One important safety parameter is maximum permissible exposure (MPE). It is defined as the level of EM radiation to which a person may be exposed without hazardous effects, tissue damage, or biological changes. MPE levels are determined as a function of EM frequency, exposure time, and pulse repetition.

The MPE unit is expressed in terms of either radiant exposure in J /cm², or irradiance in W/cm². In general, the longer the wavelength, the higher the MPE; and the longer the exposure time, the lower the MPE.

A Newly Developed PA Imaging Using an Ultrasonic Fresnel Zone Plate Transducer

A relatively new PA imaging system based on an ultrasonic Fresnel zone plate (FZP) transducer to image biological tissue has been developed by Hui Wang, Da Xing and Liangzhong Xiang at South China Normal University, Guangzhou.

A zone plate is used to focus light (here, to focus ultrasonic wave). Unlike lenses, zone plates use diffraction instead of refraction. It consists of a set of radially symmetric rings, known as Fresnel zones, which alternate between opaque and transparent. Ultrasonic wave hitting the zone plate will diffract around the opaque zones. Transparent part will transmit the ultrasonic wave while the opaque part will block it. The spaced zones enables the diffracted waves constructively interfere at the desired focus to create an image there. The radii of the zones are given by:

$$r_n^2 = n\lambda \left(z_0 + \frac{n\lambda}{4} \right) \quad (1)$$

To make acoustic FZP, a zone plate electrode pattern is deposited on one face of a piezoelectric transducer, and a full electrode is maintained on the opposite face. Sound-absorber material fills in between the zones to reduce the acoustic crosstalk. The electrodes on one face of the transducer are the divided same zone plate pattern. The opposite face is given a full-face gold electrode. The fourth and the second zone plates are used. Figure 2 (a) below shows the schematic diagram of the transducer.

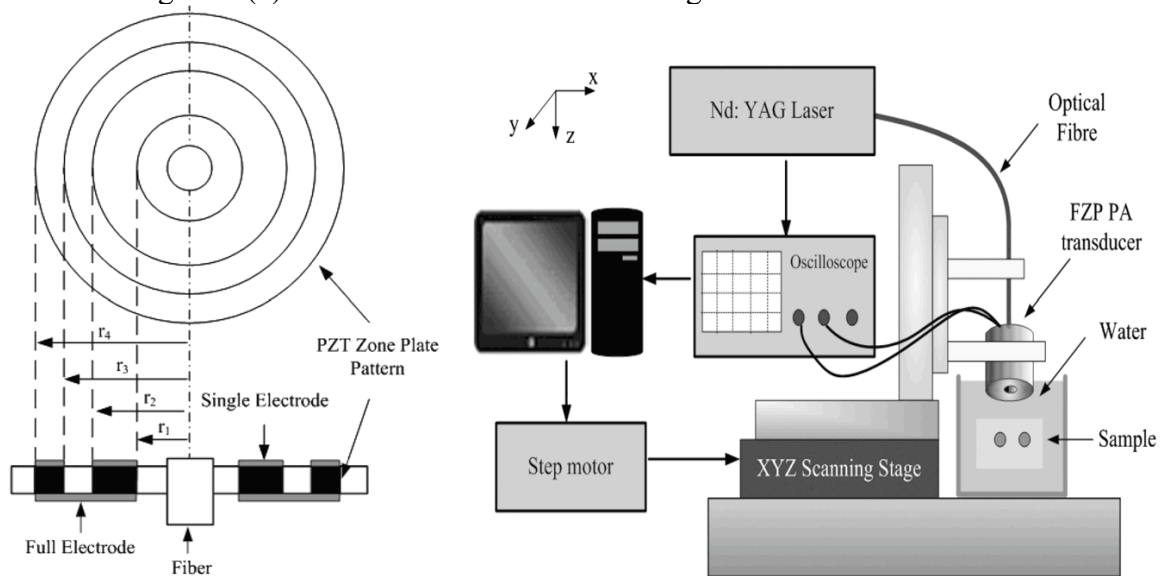


Figure 2. (a) The PA two-zone FZP transducer: cross-section along axis and the PZT zone plate pattern of the transducer. (b) The PA imaging system using the FZP PA transducer.

The ultrasonic two-zone FZP transducer consists of two concentric ring-shaped PZT. The focal length of 10 mm at the central frequency of 2 MHz is used so there are zone-boundary radii: $r_1 = 2.76$, $r_2 = 3.94$, $r_3 = 4.87$, $r_4 = 5.68$. The transducer is embedded in a brass housing to protect the electronics from electromagnetic noise. Figures 2(b) shows the experimental setup. To generate PA signals, a Q-switched Nd : YA Glaser with $\lambda =$

1064 nm, a pulse width of 6 ns at 40 mJ pulse⁻¹ and a repetition rate of 15 Hz was used. The light was coupled to an optical fiber (core diameter 600 μ m) placed in the centre of the transducer to send light pulses to the sample. The sample was placed in a container filled with water. The transducer was mounted in an X–Y–Z scanning system to scan over the sample, and immersed in water to ensure a good acoustical coupling. A dual-channel digital oscilloscope collected PA signals at a sampling rate of 250 Msamples s⁻¹. PA signal comes from a point source near the sample is measured by focusing the incident laser on an absorber surface to form a point source. To get the projections of optical absorption distribution, the recorded PA signal is deconvolved and the absorption distribution can be reconstructed.

The main parameters of an acoustic zone plate transducer include focal length, depth of focus and beam width. As applied to ultrasound imaging, the beam width determines the achievable resolution in the transverse direction, and the depth of focus determines the achievable imaging range. Quantitative assessments of the focal length and depth of focus can be obtained from the relative pressure distribution or beam profile on the axis of cylindrical symmetry for the zone plate. Quantitative assessments of beam width can be made from the focal plane beam profile. Figure 3(a) shows the calculated normalized axis acoustic pressure distribution. The acoustic field is focused at a distance of 10 mm on the axis of the FZP transducer with a depth of focus of 3 mm, so the imaging range is about 3 mm. Figure 3(b) shows the theoretical calculated focal plane profile. The FWHM of this profile is 0.94 mm. To assess the beam profiles, the transmit field acoustic pressure distribution of the FZP transducer is measured. Short 2 MHz sine wave excited the zones. The acoustic field measurements were done by scanning a commercial PVDF hydrophone with a diameter of 0.1mm element in a tank containing de-ionized water. To locate the focal plane for the FZP transducer, the hydrophone was scanned along the z axis to find the axial maximum and then in the x – y plane to find the true maximum in this plane.

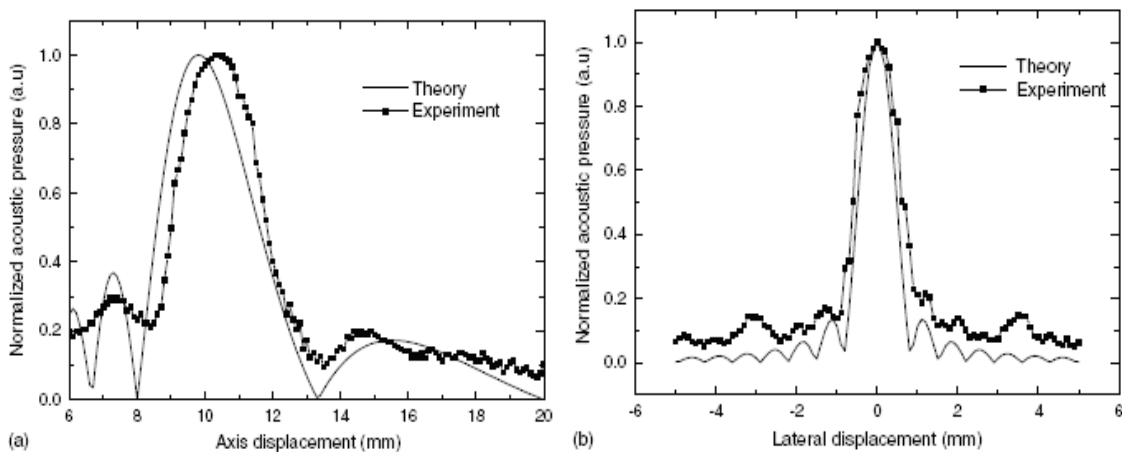


Figure 3. (a) Theoretical and experimental on-axis pressure profiles for the two-zone FZP transducer. (b) The theoretical and experimental focal plane profiles for the two-zone FZP transducer.

The actual focal length was determined to be 10.5 mm on the z axis for the zone plate transducer as shown in figure 3(a), and the actual depth of focus was 3 mm. Then, one-dimensional scans in the focal plane were performed. Figure 3(b) shows the measured focal plane profile.

The imaging resolution of the designed system is evaluated by imaging five graphite lines (0.1mm in diameter) fixed in turbid phantom made of 14.5% gelatin, and 85.5% water. Figure 4(a) shows the reconstructed PA image. Figure 4(b) shows the line profile of the reconstructed image shown in figure 4(a). The lateral resolution (the FWHM of the main lobe) is about $0.65 \pm 0.015\text{mm}$ (standard error). In figure 4 and the next images, the low limit of the grayscale was set to 15% of the maximum value, hence the grayscale below this value appear black in the image.

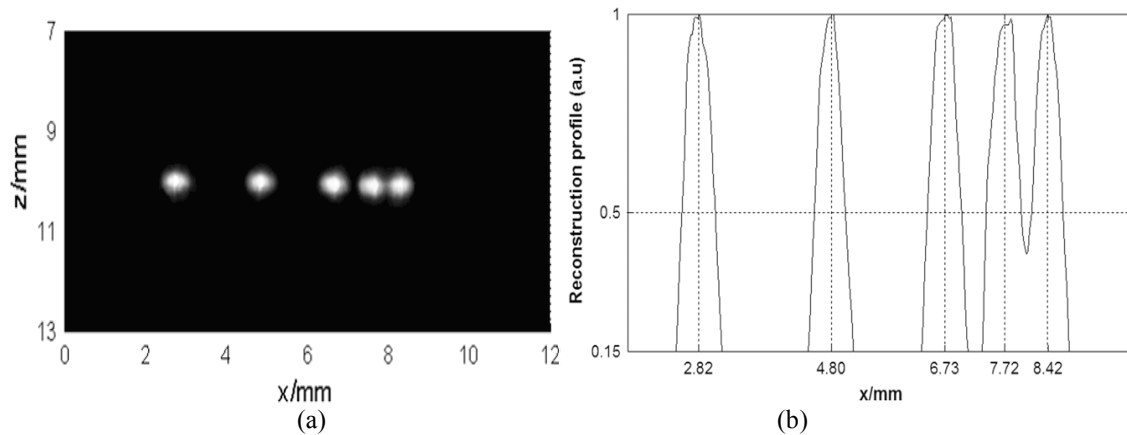


Figure 4. (a) The PA imaging for measuring the lateral resolution of this system. (b) The line profile of the reconstructed image shown in (a) with $z = 10.2$ mm.

Two-dimensional (2D) PA imaging

An experiment was performed with the two joining artificial blood vessels embedded in chicken breast tissues to show the ability of the FZP PA imaging system to image biological phantoms. Two silicone rubber tubes having different diameters was filled with undiluted human blood and acted as the artificial blood vessels. The depth position of the vessels with respect to the chicken breast tissue surface is 2.5 mm. Figure 5(a) shows the reconstruction PA imaging, and figure 5 (b) shows the photograph of the scanned area. The cross-section, even the joined location, of the blood vessels can be clearly imaged. The tissue surface is also visible due to the difference in optical absorption between the water and the tissue. The Monte Carlo simulation corrected the optical attenuation in depth and computed the dimensionless optical fluency in homogenized chicken breast tissue as a function of depth. The projection signal correction is based on the computed optical fluency along the depth.

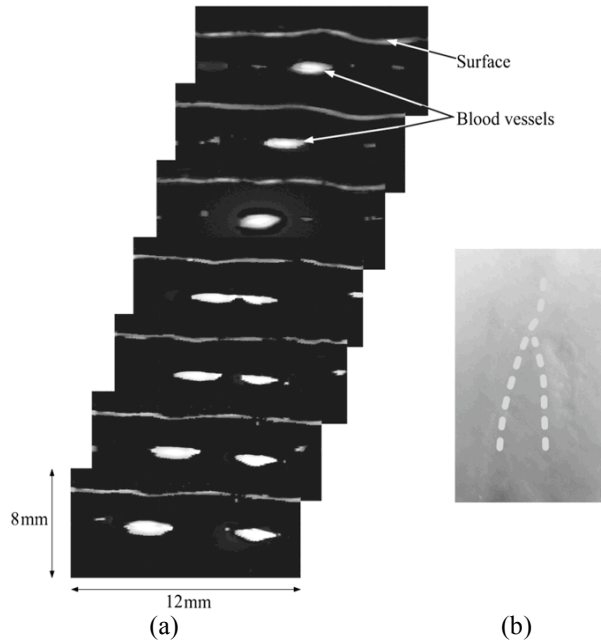


Figure 5. (a) A 2D (in depth and lateral) PA image of two joining artificial blood vessels embedded in chicken breast tissues, which consists of seven slices with 2 mm distance apart. Horizontal axis: scan direction (mm); vertical axis: depth (mm). Each slice consisted of 61 measurement positions, with a space of 0.2 mm. The PA signals were averaged 16 times to enhance the SNR. Because of the limitation of the lateral resolution of the imaging system, in the lateral direction, the shape of the cross-sectional images of the blood vessels is slightly broadened. (b) Photograph of measured area, the course of the vessels is indicated with dashed lines.

Another experiment was performed to show the ability of this imaging system in picturing the blood vessels network. The blood vessels of chicken embryo chorioallantoic membrane (CAM) (figure 6) were used. They were imaged by using the maximum amplitude projection (MAP) along the z axis to the imaging plane (x - y plane), so the MAP image was generated. A 2D scan over a $15 \text{ mm} \times 20 \text{ mm}$ area was done with a step of 0.2 mm by the FZP transducer with the distance of 10.5 mm to the blood vessels. Some microvessels are invisible because the limited frequency band response of the transducer is. If more zone plates and the high frequency wider bandwidth piezoelectric materials are used, this imaging system will be very potential for *in vivo* imaging.

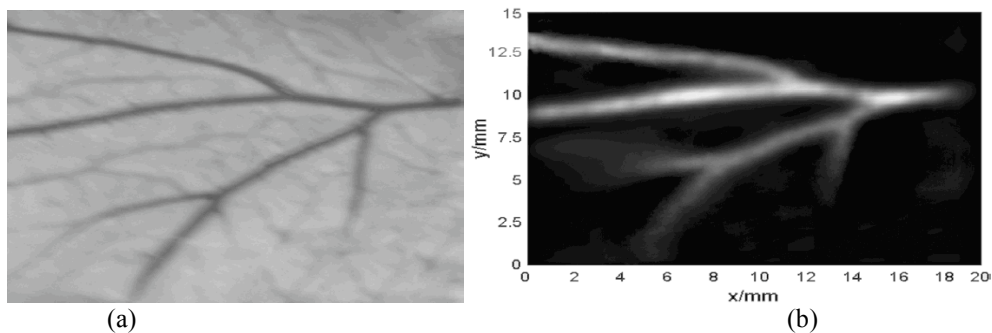


Figure 6. (a) Photograph of the imaged area of the blood vessels of chicken embryo CAM. (b) The MAP PA image of CAM *in vitro*. The main structure of the blood vessels is imaged with high contrast.

Conclusion

PAM imaging offers high optical-absorption contrast as well as high ultrasonic resolution due to the low scattering of ultrasound. PAM can clearly image structures with high optical absorption coefficients, such as blood vessels. Combining good acoustic resolution with optical or RF absorption contrast, PAT is suitable for biological tissues with inhomogeneous optical or RF absorption but relatively homogeneous acoustical properties, while ultrasound imaging mainly depends on acoustic heterogeneity.

PAT has better tolerance to sound speed variation than conventional pulse-echo ultrasound imaging which detects round-trip ultrasound. It can image animal or human organs, such as the breast and the brain, where the angiogenesis networks, blood vessels, and blood perfusion can be measured. PAT has limitations in both acoustic and EM radiations aspects. Hard tissues, such as human skull, would obstruct PAT's application to human brain imaging, for instance, since they generate strong ultrasonic wave-front aberrations.

The blood vessels of chicken embryo CAM can be imaged by the PA imaging system using ultrasonic FZP transducer with the MAP. Two-dimensional PA images of two joining artificial blood vessels embedded in chicken breast can be well reconstructed by the combination of limited-field back-projection deconvolution algorithm and appropriate signal processing technique. This system can be applied in supervising tumor angiogenesis. Nevertheless, its lateral resolution must be enhanced.

Even though many studies have demonstrated the possibilities to apply PA imaging in biomedical field, there have as yet been no large clinical trials. Impressive clinical applications of PA imaging technologies are greatly hoped to be seen in the near future.

References

Hui Wang, Da Xing and Liangzhong Xiang 2008, Photoacoustic imaging using an ultrasonic Fresnel zone plate transducer, *J. Phys. D: Appl. Phys.* **41** 095111

Minghua Xu and Lihong V. Wang 2006, Photoacoustic imaging in biomedicine, *Review of Scientific Instruments*, **77**, 041101

Yixiong Su, Fan Zhang, Kexin Xu, Jianquan Yao and Ruikang K Wang A 2005, A Photoacoustic tomography system for imaging of biological tissues, *J. Phys. D: Appl. Phys.* **38** 2640–2644

en.wikipedia.org/wiki/Photoacoustic_imaging_in_biomedicine