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PHOTOACOUSTIC IMAGING: AN ORCHESTRA OF LIGHT AND SOUND

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ABSTRACT: Photoacoustic imaging, also called optoacoustic imaging, is a new biomedical imaging modality based on the use of laser-generated ultrasound. It is a hybrid modality, combining the high-contrast and spectroscopy based specificity of optical imaging with the high spatial resolution of ultrasound imaging. In essence, a Photoacoustic image can be regarded as an ultrasound image in which the contrast depends not on the mechanical and elastic properties of the tissue, but its optical properties, specifically optical absorption. As a result, it offers greater specificity than conventional sonographic imaging with the ability to detect haemoglobin, lipids, water and other light-absorbing chromophores, but with greater penetration depth than purely optical imaging modalities that rely on ballistic photons. In addition to visualizing anatomical structures such as the microvasculature, it can also provide functional information such as blood oxygenation, blood flow and temperature. These attributes make photoacoustic imaging applicable in clinical medicine, preclinical research and early detection of cancer, cardiovascular disease and abnormalities of microcirculation. Photoacoustic microscopy is a promising tool for imaging both dental decay and dental pulp. Using photoacoustics, near-infrared optical contrast between sound and carious dental tissues can be detected relatively easily and accurately at ultrasound resolution and may ultimately allow for continuous monitoring of caries before and during treatment.

Photoacousting imaging compares favorably to other imaging modalities with its precise depth information, submillimeter resolution, and nanomolar sensitivity. With further improvement in background reduction, as well as the use of lasers with high-repetition rates, it is likely that Photoacoustic imaging will find wide use in the future in both basic research and clinical care. It is a highly vibrant research field in the years to come. This paper intends to discuss recent technical progress in photoacousting imaging and presents corresponding applications.

INTRODUCTION: Photoacoustic imaging, an emerging hybrid imaging modality that can provide strong endogenous and exogenous optical absorption contrasts with high ultrasonic spatial resolution using the photoacoustic (PA) effect, has overcome the fundamental depth limitation. The image resolution is scalable with the ultrasonic frequency. The imaging depth is limited to the reach of photons and up to a few centimeters deep in biological tissues. Possessing many attractive characteristics such as the use of nonionizing electromagnetic waves, good resolution and contrast, portable instrumentation, and the ability to partially quantitate the signal, photoacoustic techniques have been applied to the imaging of cancer, wound healing, disorders in the brain, and gene expression, among others. As a promising structural, functional, and molecular imaging modality for a wide range of biomedical applications, photoacoustic imaging can be categorized into two types of systems: photoacoustic computed tomography (PACT) and photoacoustic microscopy (PAM). The photoacoustic computed tomography (PACT), which uses reconstruction algorithms to generate an

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image .The second is photoacoustic microscopy (PAM) or macroscopy, which utilizes direct point by point detection and raster scanning over an object to render an image.[1]

PRINCIPLE OF PHOTOACOUSTIC EFFECT: Photoacoustic(PA) imaging is based on the principles of photoacoustic effect that were first explored by Alexander Graham Bell in1880.Typically, the PA effect starts from a target within tissue irradiated by a short laser pulse. The pulse energy is partially absorbed by the target and converted into heat, which generates a local transient temperature rise, followed by a local pressure rise through thermo-elastic expansion. The pressure propagates as ultrasonic waves, termed PA waves, and is detected by ultrasonic transducers placed outside the tissue.[1]

Fundamentally, the photoacoustic technique measures the conversion of electromagnetic energy into acoustic pressure waves. In biomedical PA imaging, the tissue is irradiated with a nanosecond pulsed laser, resulting in the generation of an ultrasound wave due to optical absorption and rapid thermal (or thermoelastic) expansion of tissue.. The initial pressure, p_0, generated by an optical absorber,is described as $p_0 = T\mu_a F$, where F is the laser fluence at the absorber, μ_a is the optical absorption coefficient, and T is the Grüneisen parameter of the tissue.By detecting the pressure waves using an ultrasound transducer, an image can be formed with the primary contrast related to the optical absorption of tissue.[2] This unique mechanism through which a PA image is generated provides distinct advantages compared to other in vivo imaging modalities.

First, the contrast mechanism in PA imaging is based on the differences in optical absorption properties of the tissue components. PA imaging is suited for imaging structures with high optical coefficient such as blood vessels. Second, PA imaging can be achieved using longer wavelengths in near-infrared (NIR) region, where tissue absorption is at a minimum. Light can penetrate up to several centimeters into biological tissues at wavelengths in the near-infrared range while remaining under the safe laser exposure limits for human skin. The photoacoustic technique enables imaging deeper into tissues than optical imaging methods that utilize ballistic or quasiballistic photons(e.g., optical coherence tomography or OCT) because photoacoustics does not rely on detection of photons instead, weakly scattering acoustic waves are detected in response to laser irradiation. Third, a PA imaging system can be easily combined with a ultrasound(US) system because both systems can share the same detector and electronics. The primary contrast in US imaging is derived from the mechanical properties of the tissue, which mostly describes anatomical information. Therefore, combined PA and ultrasound system can provide both anatomical and functional information.[3]

MULTISCALE PHOTOACOUSTIC TOMOGRAPHY SYSTEMS: From organelles to organs, currently, PAT is the only imaging modality spanning the microscopic and macroscopic worlds. The high scalability of PAT is achieved by trading off imaging resolutions and penetration depths. According to their imaging formation mechanisms, PAT systems can be classified into four categories: raster-scan based photoacoustic microscopy (PAM), inverse-reconstruction based photoacoustic computed tomography (PACT), rotation-scan based photoacoustic endoscopy (PAE), and hybrid PAT systems with other imaging modalities.[1]

a) Raster-scan based photoacoustic microscopy: By using a single focused ultrasonic transducer, usually placed confocally with the irradiation laser beam, PAM forms a 1D image at each position, where the flight time of the ultrasound signal provides depth information. A 3D image is then generated by piecing together the 1D images obtained from raster scanning, and thus no inverse reconstruction algorithm is needed. PAM has two forms, based on its focusing mechanism. In acoustic-resolution photoacoustic microscopy (AR-PAM), the optical focus is usually expanded wider than the acoustic focus, and thus acoustic focusing provides the system resolution. The other form of PAM, termed optical-resolution photoacoustic microscopy (OR-PAM), has an optical focus much tighter than the acoustic focus, and thus the system resolution is provided by optical focusing. Since the optical wavelength is much shorter than the acoustic wavelength, OR-PAM can easily achieve high spatial resolution, down to the micrometer or even sub-micrometer scale

b) Inverse-reconstruction based photoacoustic computed tomography: Despite its high spatial resolution and improved imaging speed, PAM usually has a limited focal depth and is not yet capable of video-rate imaging. In contrast, PACT is typically implemented using full-field illumination and a multi-element ultrasound array system to improve penetration depth and imaging speed though some PACT systems use a single-element transducer with circular scanning. The spatial distribution of acoustic sources needs to be inversely reconstructed.

c) Rotation-scan based photoacoustic endoscopy: Even though the penetration depth of PACT can reach several centimeters, internal organs such as the cardiovascular system and gastrointestinal tract are still not reachable. Non-invasive tomographic imaging of these internal organs is extremely useful in clinical practice. Besides pure optical and ultrasound endoscopy, photoacoustic endoscopy (PAE) is another promising solution for this clinical need. The key specifications of PAE are the probe dimensions and imaging speed. The first PAE was designed by Yang et al., and applied to animal studies. Here, the PAE probe has a diameter of 4.2 mm and the cross-sectional scanning speed is 2.6 Hz.[1]

d) Photoacoustic tomography integrated with other imaging modalities: Combining complementary contrasts can potentially improve diagnostic accuracy. Because of its excellent optical absorption contrast, PAT has been integrated into various imaging modalities, such as ultrasound (US) imaging (mechanical contrast), OCT (optical scattering contrast), confocal microscopy (scattering/fluorescence contrast), two-photon microscopy (fluorescence contrast), and MRI (magnetic contrast). Different modalities in hybrid systems usually share the same imaging area, thus their images are inherently co-registered.[1,2]

CONTRAST AGENTS FOR PHOTOACOUSTIC IMAGING: An ideal scenario for photoacoustic imaging would be that light absorption of normal tissue should be low for deeper signal penetration, whereas the absorption for the object of interest should be high for optimal image contrast. The contrast agents used for photoacoustic imaging can be categorized into two types: endogenous and exogenous contrast agents.

Theoretically, any intrinsic chromophore that has an optical absorption signature can potentially provide PAT contrast, as long as appropriate irradiation wavelengths are applied and the

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system sensitivity is sufficient.[1]Two of the biggest advantages of using endogenous contrast agents for imaging applications are safety and the possibility of revealing the true physiological condition, because the physiological parameters do not change during image acquisition if a relatively slow biological process is imaged.[4]

In many scenarios, such as the detection of early stage tumors, an endogenous contrast agent alone is insufficient to provide useful information. Because the intensity of a photoacoustic signal in biological tissue is proportional to optical energy absorption, which is proportional to the amount of the contrast agent, exogenous contrast agents are frequently needed to provide better signal/contrast for photoacoustic imaging.[4]

Anatomical and functional photoacoustic tomography using intrinsic contrasts: Biological tissues contain several kinds of endogenous chromophores that can generate PA signal. The main sources of endogenous contrast in PA imaging are hemoglobin, melanin, and lipids. Depending on the wavelength, these endogenous contrast agents may have strong absorption coefficients in comparison with other tissue constituents. Photoacoustic imaging has been used in various applications where endogenous chromophores are present, such as in the visualization of blood vasculature structure and melanoma.[2]

Photoacoustic tomography of hemoglobin: In the visible spectral range (450–600 nm), oxyhemoglobin (HbO2) and deoxyhemoglobin (HbR) account for most of the optical absorption in blood. The absorption coefficient ratio between blood and surrounding tissues is as high as six orders of magnitude; hence, PAT can image with nearly no background RBC-perfused vasculature, the functional vascular subset responsible for tissue oxygen supply. Furthermore, because PA signal amplitudes depend on the concentrations of HbO2 (C_{ox}) and HbR (C_{de}), spectroscopic measurements can be performed to quantify C_{ox} and C_{de} by solving linear equations. From C_{ox} and C_{de}, the total hemoglobin concentration (HbT) and oxygen saturation of hemoglobin (sO2) can be derived. Small animals, especially mice, are extensively used in preclinical research on human diseases.

Non-invasive whole-body imaging of small animals with high spatial resolution is extremely desirable for systemic studies such as tumor metastasis, drug delivery and embryonic development. This work may enable longitudinal studies of the effects of genetic knockouts on the development of vascular malformations.[1]

Photoacoustic tomography of human breast cancer: As the leading cause of cancer death among women, breast cancer can be diagnosed earlier by periodic screening. Currently, X-ray mammography is the only tool used for mass screening, and it has helped to increase the survival rate of breast cancer patients. However, in addition to the accumulation of ionizing radiation dose during lifetime screening, mammography also suffers from low sensitivity for early stage tumors in young women. Various non-ionizing-radiation based techniques have been investigated, such as ultrasound, MRI, and PAT. Among these techniques, PAT is superior in contrast, sensitivity, and cost effectiveness.The PAT contrast is contributed by the angiogenesis-associated microvasculature around and within the tumor.[1] Ermilov et al. have used PAT to image breast cancer in humans. They imaged single breast slices in craniocaudal or mediolateral projection with at least 0.5 mm resolution.[5]

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High-resolution functional photoacoustic tomography of microvasculature: Microvasculature, the distal portion of the cardiovascular system, delivers oxygen, humoral agents, and nutrients to the surrounding tissue and collects metabolic waste. Almost any microvasculature-associated parameter has important pathophysiological indications. PAT is highly desirable for microvasculature imaging because of its high spatial resolution and endogenous hemoglobin absorption contrast.

The strong capability of PAT for functional brain imaging will greatly advance neurological studies. First, a single-element unfocused ultrasound transducer based PACT was employed to assess the cerebral blood volume of small animal in vivo. Three physiological states (hyperoxia, normoxia, and hypoxia) were induced by changing oxygen concentration in the inhaled gases. Two PA images were acquired at two optical wavelengths (584 and 600 nm) for each physiological state.This neuroimaging modality holds promise for applications in neurophysiology, neuropathology and neurotherapy.[6]

Many eye diseases are associated with altered eye microvasculature. So far, PAT has been demonstrated to be safe for ocular and retinal microvasculature imaging in small animals. PAT offers significant promise for radiation-free monitoring of eye diseases.[7,8]

Anti-angiogenesis is an important cancer treatment strategy. PAT is an ideal tool for angiogenesis-associated studies and has been applied to various tumor models, such as melanoma, glioblastoma, adenocarcinoma, carcinoma, and gliosarcoma. PAT characterization of tumor vasculature will aid the development and refinement of new cancer therapies.[1,9]

Photoacoustic tomography of melanin: Although it is the foremost killer among skin cancers, melanoma can be cured if detected early. PAT has been investigated for non-invasive melanoma imaging using melanin, the light-absorbing molecules in melanosomes, as the contrast. The absorption of melanin is ~1000 times that of water at 700 nm, which can potentially enable PAT to detect early melanoma in deep tissue.[10]

Melanoma detection using photoacoustic microscopy: PAM can acquire (1) structural images measuring tumor burden and depth, (2) functional images of hemoglobin concentration measuring tumor angiogenesis—a hallmark of cancer, (3) functional images of hemoglobin oxygen saturation (SO_2) measuring tumor hypoxia or hypermetabolism—another hallmark of cancer, and (4) images of melanin concentration measuring tumor pigmentation—a hallmark of melanotic melanoma, consisting of >90% of melanomas.[11,12]

Photoacoustic tomography of lipid: Cardiovascular disease (CVD) has been the number one cause of death in the United States for over a century. The majority of CVD is due to atherosclerosis, characterized by plaques building up inside the arterial wall. Lipid is a common constituent in atherosclerotic plaques, the location and area of which are closely related to the progression of the disease. PAT is well suited for lipid imaging: compared with water-based tissue components, lipid has a distinct absorption spectrum between 1150 nm and 1250 nm. A recent advance in PAT lipid imaging was reported by Allen et al. A human aorta containing a raised lipid-rich plaque was imaged at 1200 nm. The plaque is clearly identified due to the strong absorption by lipid. The results demonstrate that spectroscopic PAT is a promising tool for lipid detection in atherosclerosis.[13]

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Photoacoustic tomography of cell nuclei: Cell nuclei are organelles where major cell activities take place. Compared with those of normal cells, nuclei of cancer cells have folded shapes and enlarged size. Imaging cell nuclei plays a critical role in cancer diagnosis. Traditional imaging of cell nuclei needs tissue sectioning and histological staining, which are not applicable for in vivo studies. Because nucleic acids, the major components of DNA and RNA in cell nuclei, have strong absorption in the ultraviolet range. PAT is a good choice for imaging of cell nuclei using nucleic acids as intrinsic contrast. By exciting DNA and RNA at 266 nm, Yao et al. have recently reported the first label-free PA ex vivo and in vivo images of cell nuclei termed UV-PAM.[14]

Chemical and molecular photoacoustic tomography using exogenous contrast agents: To image in deep tissues, the use of near-infrared (NIR) light is highly desirable for optical imaging. Exogenous contrast agents greatly enhance the sensitivity of PAT in the NIR spectral region. Additionally, some biological targets do not have intrinsic optical absorption contrast for PAT in the visible and near-infrared (NIR) regimes. One such important example is the lymphatic system. Through the use of contrast agents in PAT, imaging sensitivity and specificity are significantly improved just as in CT, PET, and MRI. Optically absorptive organic dyes, nanoparticles, reporter genes and fluorescence proteins have been successfully applied as PA contrast agents.[15]

Organic dyes: Dyes (or fluorophores) have been widely used for other medical imaging applications such as fluorescence imaging, Förster resonance energy transfer imaging (FRET), two photon microscopy and Raman spectroscopy. Recently, near infrared (NIR) absorbing dyes such as Alexa fluor 750, indocyanine green (ICG) have been utilized as contrast agents in PA imaging. These dyes possess high absorption coefficients and low quantum yield, making them effient contrast agents for PA imaging.[2]

Indocyanine green (ICG) is a nontoxic, water-soluble tricarbocyanine dye with a peak optical absorption at 790 nm. The penetration depth of PA imaging using ICG can be increased using near infra red (NIR) light. ICG is FDA-approved for determining human cardiac output, hepatic function and blood flow and ophthalmic angiography.

Methylene blue (MB) is used as a contrast agent on sentinel lymph node (SLN) mapping. Methylene blue (MB) is a heterocyclic aromatic chemical compound widely used in biology and chemistry. Sentinel lymph node biopsy (SLNB), i.e., the biopsy of the first lymph node receiving drainage from a cancer-containing area, has become the standard procedure for staging breast cancer patients to reduce the postoperative complications of axillary lymph node dissection (ALND). Although SLNB with blue dye (lymphazurin blue or methylene blue) and radioactive tracers has an identification rate of 90–95% and a sensitivity of 88–95%, these methods still require ionizing imaging tools and intraoperative procedures.[15,16]

PAT can identify whether a node is sentinel by detecting the accumulated dye because the dye has high optical absorption contrast. While PAT has broad potential applications, imaging the SLN is a perfect niche clinical application of PAT with anticipated high impact on breast axillary staging and management.

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Metallic Nanostructures: Metallic nanostructures made of noble metals such as gold or silver can be synthesized with tunable optical absorption and can significantly enhance the contrast in PA imaging. The mechanism of optical absorption in these nanostructures is based upon surface plasmon resonance (SPR) that can result in a significantly higher optical absorption compared to other optical absorbers such as dyes. Furthermore, the absorption spectrum of these SPR nanostructures can be tuned through controlling their sizes and geometries. Various different SPR nanostructures have been utilized for PA imaging and are reported in literature,including: gold nanospheres, gold nanorods , gold nanoshells , gold nanocages , gold nanoclusters, gold nanostars, gold nanoroses, gold nanowantons , and silver nanoplates with different ranges in size, optical absorption spectra and PA imaging applications.[17]

Single-walled carbon nanotubes: Single-walled carbon nanotubes (SWNTs) are essentially folded single layers of graphite, exhibiting strong optical absorption over a broad spectrum.The optical absorption of SWNTs is broad and covers the tissues optical window,thus making them a suitable contrast agent for PA imaging. Moreover, SWNTs can be synthesized as small as 1 nm diameter and with various aspect ratios to increase both absorption cross section and effective surface area for bioconjugation applications. Although the toxicity of carbon nanotubes is still an ongoing debate in biomedical applications,single-walled carbon nanotubes (SWNTs) were tested in PA imaging as a contrast agent for molecular specific tumor targeting and sentinel lymph node mapping in vivo. SWNTs were also investigated as agents for photothermal therapy.

Nanowontons: Composite-material nanoparticles, "nanowontons", were recently introduced at contrast agents for MRI and PAT. The nanowontons have a cobalt (Co) core for MRI and gold (Au) thin film coating. The nanowontons exhibit both ferromagnetic and optical responses, making them useful for dual-modality MRI and PAT studies.

Reporter genes: In gene expression imaging, an exogenous reporter gene can be incorporated into the genome of a tumor cell line and its expression can be controlled by a promoter. Eventually, the expression products of the reporter gene by the promoter can be used as contrast for imaging, either directly or indirectly via some assay. Since many diseases like cancer are related to genetic disorders, imaging of gene expression could potentially play an important role in molecular imaging.

Fluorescence proteins: Fluorescence protein imaging has become increasingly important in biological and medical research. However, due to the shallow imaging depth (~1mm) of fluorescence microscopy, the applicability of fluorescence proteins is quite limited. PA signals are proportional to the product of the molar extinction coefficient and the nonradiative quantum yield (fluorescence quantum yield) of a contrast agent. Thus, fluorescence proteins possessing less fluorescent quantum yields can be great candidates as contrast agents for PA imaging.[15]

Photoacoustic imaging in both soft and hard biological tissue: Recently photoacoustic (PA) imaging has been extended as a new modality for non-invasive medical diagnosis and visualization. PA imaging technique by using near-infrared laser pulses with nanosecond durations has been applied to obtain 2-D and 3-D images from both soft tissue and hard tissue to show the potential of

this technique for visualizing oral diseases. It therefore provides a unique visualization method with a depth resolution in the range of tens of micrometers, for exploring the internal properties of biotissues at a desired penetration depth within several centimeters. Effective techniques for diagnosis and visualization of early-stage human oral diseases such as the gingivitis and tooth decay are under development.[18]

Standard dental imaging instruments are limited to X-ray and CCD cameras. Subsurface optical dental imaging is difficult due to the highly-scattering enamel and dentin tissue. Thus, very few imaging methods can detect dental decay or diagnose dental pulp, which is the innermost part of the tooth, containing the nerves, blood vessels, and other cells. A study was conducted on imaging dental decay and dental pulp with PAM. The results showed that PAM is sensitive to the color change associated with dental decay. Although the relative PA signal distribution may be affected by surface contours and subsurface reflections from deeper dental tissue, monitoring changes in the PA signals (at the same site) over time is necessary to identify the progress of dental decay. The results also showed that deep-imaging, near-infrared (NIR) PAM can sensitively image blood in the dental pulp of an in vitro tooth. In conclusion, PAM is a promising tool for imaging both dental decay and dental pulp.[19]

Photoacoustic tomography of fluid dynamics: Flow, an important contrast for biomedical imaging, provides much useful pathophysiological information. PAT is receiving increased attention as a tool to measure flow, as in PAT flowmetry. Photoacoustic Doppler flowmetry, can potentially be used for detecting fluid flow in optically scattering media and especially low-speed blood flow of relatively deep microcirculation in biological tissue. With excellent scalability, Doppler PAT bridges the spatial gap between scattering-based optical and ultrasonic technologies. More importantly, the high optical absorption contrast between the intravascular blood and extravascular background greatly increases detection sensitivity.[20,21]

CHALLENGES FOR PA IMAGING:
Laser Safety: During PA imaging, skin is irradiated with the laser light. For safety reasons, laser radiation should be kept below the maximum permissible exposure (MPE), which is the level of laser radiation to which a human can be exposed without hazardous effects or biological changes. MPE for human skin to a pulsed laser defined by the American National Standards Institute (ANSI) is 20-100 mJ/cm2 at the wavelengths ranging from 400 to 1500 nm. Higher laser radiation provides higher signal-to-noise ratio (SNR) in PA imaging. However, using a fluence greater than the MPE limits leads to a temperature rise in the irradiated tissue, with the potential for causing pain and burning the patient's skin.[2]

Safety of Photoacoustic Exogenous Contrast Agents: Photoacoustic imaging with exogenous contrast agents is rapidly emerging field because of the advantages described earlier. However, the long-term toxicity and accumulation of nanoparticles remains a concern. These toxicity and accumulation risks are highly variable based on differences between sizes, geometries and surface characteristics of nanoparticles. For the nanoparticles to move into the clinic, it is important that more toxicity studies are conducted for each type of nanoparticle. Most of these studies are aimed to study the long term safety issues in living subjects as the nanostructures larger than a certain size

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(~5-6 nm) cannot be cleared through renal clearance and will accumulate in biologically important organs such as the liver and spleen. Biodegradable clusters of nanoparticles were recently introduced as a promising tool to address the clearance time and long term side effects issues of metallic nanoparticles.[2]

Temporal Resolution: Temporal resolution of current existing PA imaging systems is one of the most important limiting issues. PA system utilized with optical parametric oscillator (OPO) lasers are mostly operating at low frame rates due to the low pulse repetition rates (PRF) (often less than 50 Hz) of the laser sources. Recently, efforts have been made to increase the temporal resolution of PA imaging with the goal of developing real-time PA imaging systems.[2]

Cost and Portability of Pulsed Lasers: The major cost associated with a PA imaging system is due to the need for expensive Q-switched lasers. The use of low-cost compact laser diodes with wide emission wavelength availability instead of conventional Q-switched pulsed systems opens the possibility of creating portable imaging instrumentation suitable for clinical applications.[2]

PROSPECTS AND SUMMARY: From organelles to whole bodies, from superficial microvasculature to internal organs, from anatomy to functions, PAT is playing an increasingly important role in basic physiological research and pre-clinical studies. Exciting events are happening in this fast growing field.

Integration of the state-of-the-art techniques in system implementation will eventually lead PAT to commercialization for clinical practice. For PAM, a fast scanning mechanism and a high repetition rate laser with a wide tuning range of wavelengths are necessary for real-time functional imaging without compromising the spatial resolution. Also, a better optical and acoustic focusing method is needed to maintain the resolution in the depth dimension. For PACT, new techniques for assembling ultrasound arrays help to increase the imaging sensitivity and improve the spatial resolution. More homogeneous beam expansion over the sample surface is necessary for whole-field illumination. Parallel, real-time data acquisition is also important for further improving the imaging speed.

PAT is safe for clinical applications as it generally delivers optical fluence well within the American National Standards Institute (ANSI) safety standards. However, technical improvement is required to facilitate an effective clinical translation. For internal organ (such as gastrointestinal tract and prostate) imaging, PAE is an ideal tool. Recent progress in PAE is exciting; nevertheless, its size must be further reduced to be compatible with generic endoscopes, and its spatial and temporal resolutions require improvements. For cutaneous applications, such as skin cancer detection and cutaneous vascular lesion diagnosis, a multiscale, handheld photoacoustic probe is required, which would enable users to select an optimal trade-off between the spatial resolution and the penetration depth for different clinical applications.

Multimodality imaging, providing complementary information for more accurate diagnosis, is always favorable. PAT combined with confocal microscopy,OCT(Optical coherence tomography), ultrasound imaging,or MRI will provide fruitful anatomical, functional, and molecular information.[9] In summary, photoacoustic tomography perfectly complements other biomedical imaging modalities by providing unique optical absorption contrast with highly scalable spatial resolution, penetration

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depth, and imaging speed. In light of its capabilities and flexibilities, PAT is expected to play a more essential role in biomedical studies and clinical practice.[1]

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