Simultaneous photoacoustic and ultrasound imaging: A review

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ABSTRACT

Photoacoustic imaging (PAI) is an emerging biomedical imaging technique that combines the advantages of optical and ultrasound imaging, enabling the generation of images with both optical resolution and acoustic penetration depth. By leveraging similar signal acquisition and processing methods, the integration of photoacoustic and ultrasound imaging has introduced a novel hybrid imaging modality suitable for clinical applications. Photoacoustic-ultrasound imaging allows for non-invasive, high-resolution, and deep-penetrating imaging, providing a wealth of image information. In recent years, with the deepening research and the expanding biomedical application scenarios of photoacoustic-ultrasound bimodal systems, the immense potential of photoacoustic-ultrasound bimodal imaging in basic research and clinical applications has been demonstrated, with some research achievements already commercialized. In this review, we introduce the principles, technical advantages, and biomedical applications of photoacoustic-ultrasound bimodal imaging techniques, specifically focusing on tomographic, microscopic, and endoscopic imaging modalities. Furthermore, we discuss the future directions of photoacoustic-ultrasound bimodal imaging technology.

1. Introduction

Biomedical imaging technology is an indispensable tool in modern medicine. It provides rich biological information, assists in accurate disease diagnosis, guides treatment planning, and enables early detection of potential health issues, thereby improving overall health and treatment outcomes [1–7]. Currently, commonly used clinical imaging techniques include computed tomography (CT), magnetic resonance imaging (MRI), positron emission tomography (PET), optical imaging, and ultrasound imaging (US). CT offers high resolution, rapid scanning, and multi-level imaging capabilities. However, it has the drawback of radiation exposure and relatively limited ability to differentiate certain tissues and types of lesions. MRI excels in its radiation-free nature, multiparametric imaging, excellent soft tissue contrast, and high spatial resolution. It provides detailed anatomical and functional information. However, MRI requires longer scanning and image data processing times, and its imaging sensitivity is not always high. It sometimes

requires a large number of exogenous contrast agents, resulting in higher equipment manufacturing and operating costs [8]. PET excels in providing molecular-level metabolic information and is used for early disease detection, treatment response evaluation, and tumor diagnosis. Its disadvantages include the use of radioactive tracers during the imaging process, which carries radiation exposure risks and higher equipment costs [9]. Optical imaging provides high contrast and high-resolution images. It is widely used in research and clinical practice in the fields of cell biology, molecular biology, neuroscience, oncology, cardiovascular medicine, and drug development. However, its imaging depth is still limited by the photon propagation limit [10–13]. Ultrasound imaging operates by utilizing the echo signals from tissue interfaces with varying impedance, enabling the non-destructive visualization of deeper tissue structures. However, visualizing tissue structures smaller than 100 μm in diameter can be challenging without ultrasound contrast agents (microbubbles). These agents, while enhancing imaging capabilities, may diminish sensitivity to

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pathological, physiological, inflammatory, and vascular changes associated with diseases. Ultrasound also faces difficulties in directly extracting functional information like blood oxygenation. Despite its drawbacks, such as lower resolution and reduced effectiveness in differentiating targets with minimal acoustic impedance contrasts, ultrasound offers notable benefits over other medical imaging technologies, including its non-invasive nature. It is important to note that the 'deep penetration' attribute of ultrasound imaging is influenced by the central frequency of the ultrasound waves. Lower frequencies allow for deeper penetration but at the expense of image resolution, whereas higher frequencies provide better resolution but with shallower penetration. This balance between penetration depth and resolution is a key consideration in ultrasound imaging applications.

Given these considerations, the integration of ultrasound with novel imaging technologies is gaining momentum, aiming to achieve non-destructive imaging with both high resolution and deep penetration (compared with pure optical imaging). In this context, photoacoustic imaging is emerging as a promising technique in the realm of new imaging technologies."

In photoacoustic imaging, short laser pulses are directed into the tissue. These pulses are absorbed by specific components within the tissue, such as hemoglobin in blood vessels, causing a slight and rapid temperature increase. This temperature rise leads to thermoelastic expansion, which in turn generates ultrasound waves (the photoacoustic effect). These ultrasound waves, which carry information about the tissue's structure and composition, are then detected by ultrasound sensors. Due to the strong scattering nature of light when it irradiates biological tissues [5–7], optical imaging usually can only provide high-quality images of tissue surfaces within a depth of 1 mm, which is insufficient for imaging deeper tissues. The scattering intensity of sound waves in tissue is 2 to 3 orders of magnitude less than that of light waves [8–10], allowing them to propagate over long distances, especially in soft biological tissues [11,12]. Photoacoustic imaging technology uses ultrasound waves generated by the thermal expansion of heated biological tissues to capture the tissue's optical absorption information. By replacing photon detection in traditional optical imaging with ultrasound detection, this technique avoids the limitations in penetration depth caused by optical scattering during the information reception (detection) process. This breakthrough surpasses the soft limit (about 1 mm) of traditional optical imaging, enabling photoacoustic imaging of deep tissues up to a depth of 7 cm [13–15].

In principle, photoacoustic imaging technology utilizes the biological component fingerprint characteristics of laser light and tissue absorption differences. Photoacoustic imaging can reflect both structural and functional information of the tissue. It enables quantitative analysis of various components within biological tissues, finely depicting extremely subtle tissue abnormalities, as well as important physiological parameters such as hemoglobin concentration [16–19], blood oxygenation [20–23], oxygen metabolism rate [24–26], blood glucose content [27], and degree of vascular calcification [28–30]. This allows for dynamic functional imaging. Therefore, photoacoustic imaging technology has great potential for achieving cross-scale, multi-functional, non-destructive, and high-resolution biomedical imaging monitoring (see Fig. 1).

Currently, photoacoustic imaging technology can be broadly classified into three categories: photoacoustic computed tomography (PACT), which employs full-field illumination using a larger diameter pulsed laser beam to irradiate the tissue surface. PACT offers a greater imaging depth, reaching several centimeters, and is suitable for whole-body and deep tissue imaging while simultaneously acquiring both structural and functional information [34–36]. Photoacoustic microscopy (PAM) utilizes mechanical scanning and either a focused ultrasound detector or a focused laser beam to obtain photoacoustic images. PAM provides high spatial resolution, enabling cellular-level imaging, and is suitable for observing microscopic structures in superficial tissues and surface organs [10,37,38]. Photoacoustic endoscopy (PAE) enables endoscopic imaging of organs within the body cavities, including clinical evaluations of coronary artery diseases, gastrointestinal lesions, and prostate cancer [39–41]. These three photoacoustic imaging techniques have been successfully combined with ultrasound imaging in practical
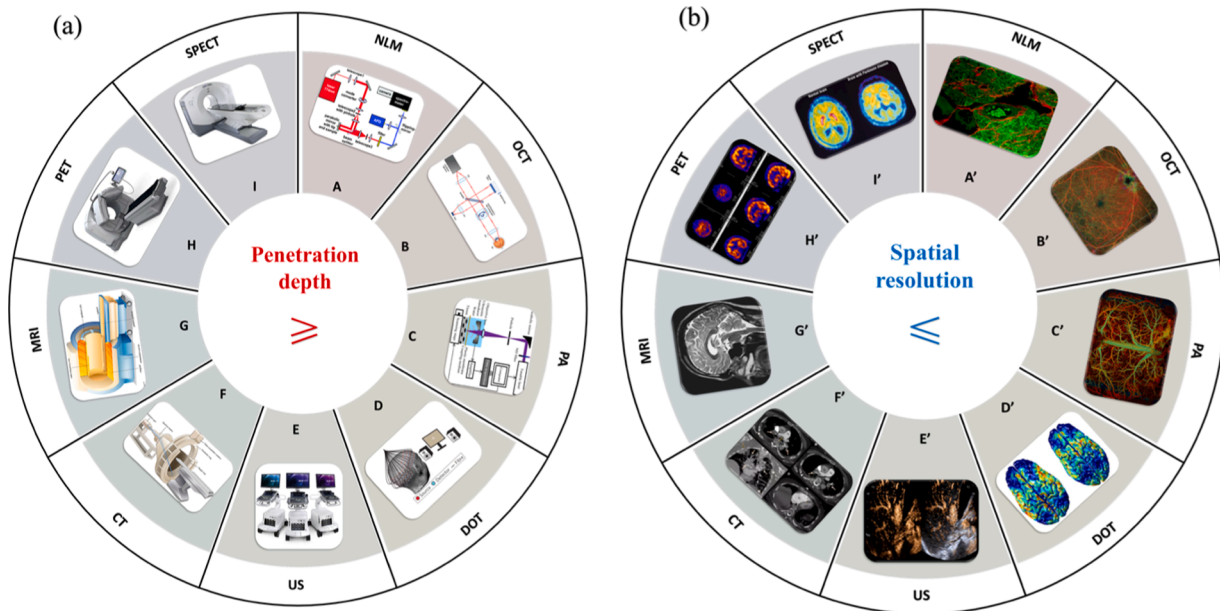

Fig. 1. Comparison of Imaging Depth and Resolution in Common Imaging Techniques. (a) shows the imaging depth comparison of several imaging modes, ranking from A to I represents the increase of imaging depth, and is shown from A to I, NLM , Nonlinear Microscopy ; OCT , Optical Coherence tomography ; PA, Photoacoustic ; DOT , Diffuse Optical tomography ; US , Ultrasound ; CT , Computed Tomography ; MRI , Magnetic Resonance Imaging ; SPECT , Single Photon Emission Computed Tomography ; PET , Positron Emission Tomography. Figure b shows the comparison of imaging resolution of several imaging modes, ranking from I' to A' represents the improvement of imaging resolution, PET normal brain and brain with Parkinson disease, Brain SPECT with Acetazolamide Slices, brain and knee MRI, US noninvasive assessment of liver disease, DOT normalized cortical sensitivity [1], PA the oxygen saturation of hemoglobin (sO2) map of mouse brain [2], OCT right eye of a person [3], NLM ovary tissue [4].

applications, resulting in excellent imaging outcomes. The schematic diagrams and imaging results of typical systems are shown in Fig. 2 a, b, and c. The bimodal imaging technique that combines ultrasound imaging and photoacoustic imaging overcomes the physical limitations of the aforementioned imaging modalities, enabling high-resolution, high-contrast, deep-penetration, real-time and non-invasive imaging (see Fig. 3).

This article primarily introduces the combination of three mainstream forms of photoacoustic imaging (PACT, PAM, PAE) with ultrasound imaging (US). It elaborates on the basic imaging principles and configurations, imaging characteristics and advantages, current development status, and biomedical applications of each combination. Furthermore, it discusses and explores potential future directions for each approach.

2. Photoacoustic-ultrasound Computed Tomography (PACT-US)

The goal of PACT is to image deep tissues by illuminating the entire region of interest (ROI) with high-pulse energy and subsequently detecting the photoacoustic (PA) signals from the entire area using sensors [36,42–44]. Due to its capability of imaging deep tissues, PACT is well-suited for the study of large organ systems and has been widely applied in both basic research and clinical settings [45,46]. According to the imaging principles of PACT, its integration with existing ultrasound imaging systems is relatively straightforward. Some research studies have already been conducted on the development of PACT-US multimodal systems. The notable advantage of this combined modality is the ability to achieve real-time, dynamic imaging over a wide field of view, enabling the observation of target tissues at significant depths within the biological body. It allows for simultaneous imaging of both the overall structural features and functional information of organ tissues.

Over the past 20 years, extensive research efforts have been devoted to the development of PACT-US imaging techniques [47–57]. In the PACT-US system, the array-based ultrasound transducer is one of the key components and has a significant impact on image quality. Linear array transducers can be easily integrated into clinical ultrasound platforms [58–65]. However, linear array transducers have limitations in terms of their aperture and bandwidth. Due to the finite field of view of each element, this can result in radial artifacts and morphological distortion.

To overcome these limitations, circular array transducers [66–70] and hemispherical array transducers [71–73] (as shown in figures b and c below) have been developed. Circular array transducers are highly suitable for PACT (Fig. 4b). However, due to the limited reception angle of each element, the use of a ring array does not capture vertically oriented PA waves. To cover PA waves on a spherical surface in three dimensions, hemispherical array transducers have been developed (Fig. 4c). They can receive three-dimensional omnidirectional PA signals, enabling real-time generation of high-quality three-dimensional PACT volumetric images throughout the illuminated target. However, limited by strong scattering of light in biological tissue, the penetration depth of PACT remains limited. The combination of ultrasound imaging and photoacoustic computed tomography (PACT) addresses this limitation. By leveraging the penetration depth of ultrasound imaging and the high contrast provided by PACT, it is possible to simultaneously acquire comprehensive structural and functional information of organs such as the breast and thyroid, providing more accurate information for diagnosis and treatment.

The application of PACT-US imaging has been widely explored in existing research studies [34,67,74–79]. In this paper, we will focus on providing a brief overview of selected application studies in PACT-US imaging. PACT-US imaging provides valuable insights into the study of the brain, particularly in animal disease models.

2.1. PACT-US applications of brain

Fig. 5a demonstrates that PACT is capable of imaging the microvasculature across the entire brain region, allowing observation of neuroactivity and drug treatment processes through hemoglobin concentration mapping. Researchers have utilized a custom-built PACT system to image the mouse brain, achieving high spatiotemporal resolution for cerebral hemodynamics and oxygen consumption imaging. They have successfully visualized functional responses of the brain to sensory stimulation, demonstrating the potential of PACT in functional brain imaging [80]. Additionally, as shown in Fig. 5b, the use of the photoacoustic-ultrasound dual-modal system allows for the simultaneous visualization of structural information, cerebral hemodynamics, and blood oxygenation in specific brain regions, making it a powerful tool for non-invasive three-dimensional brain imaging [81]. Researchers

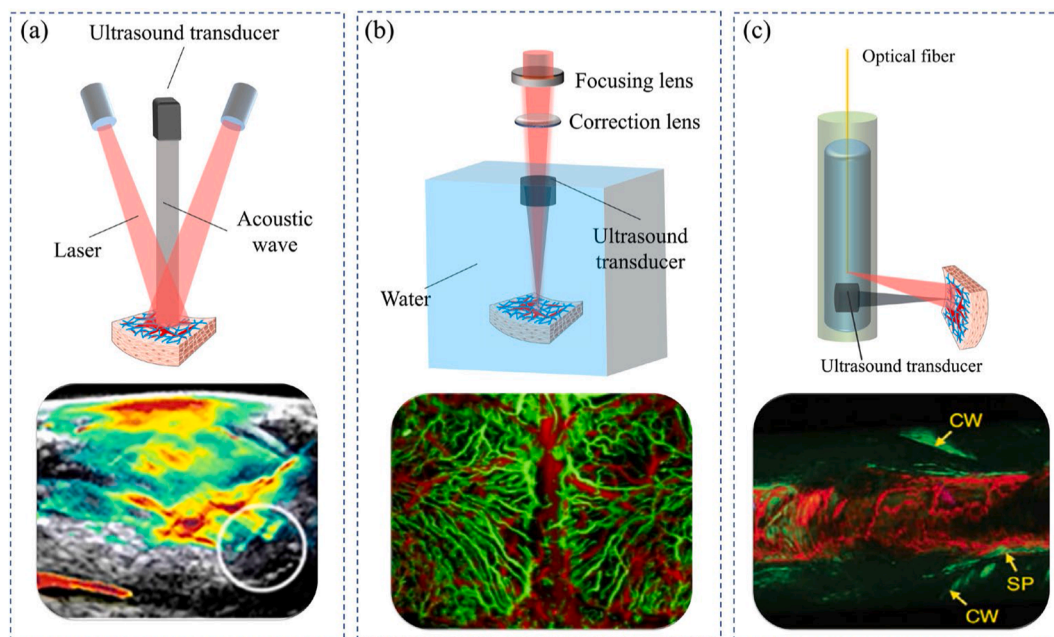

Fig. 2. Typical system diagram and imaging results of PAI-US (a)PACT-US imaging(results from PAI with breast cancer) [31] ; (b)PAM-US imaging(results from human brain) [32] ; (c)PAE-US imaging(results from a rat colon acquired in vivo) [33].
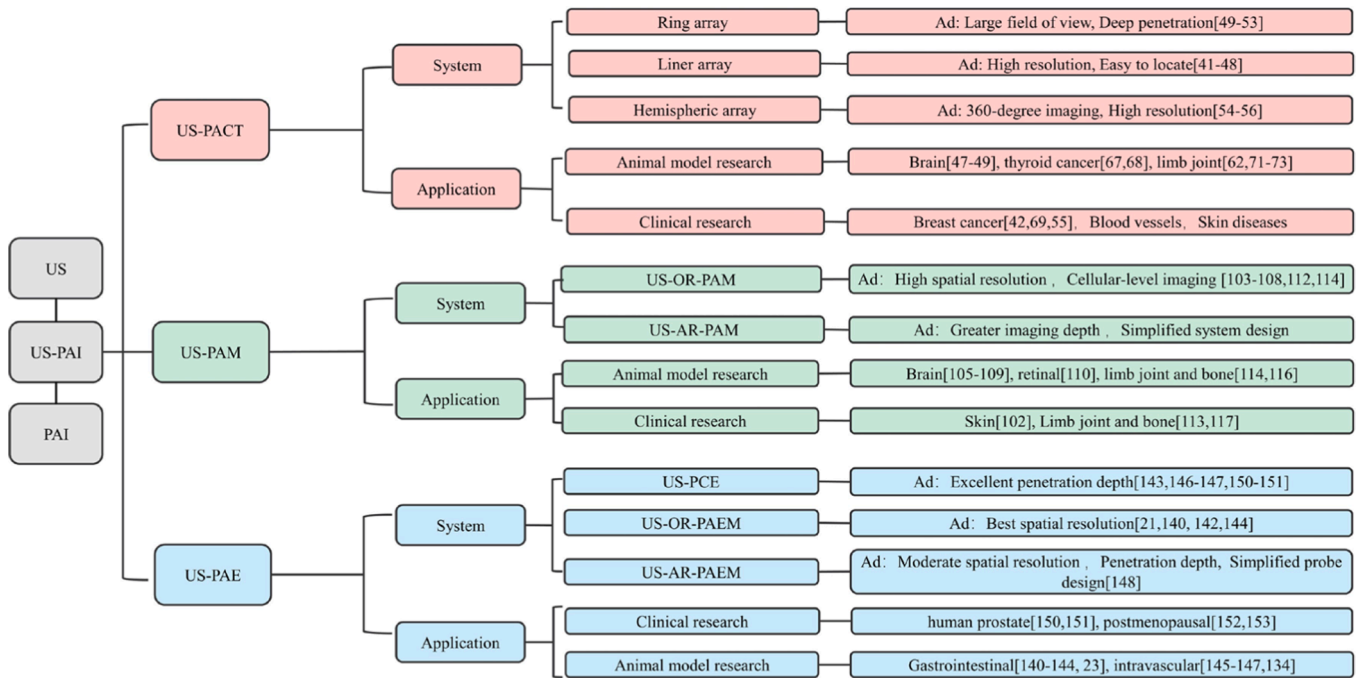
Fig. 3. The structure of this text diagram(US, Ultrasound ; PAI , Photoacoustic Imaging ; PACT , Photoacoustic Computed Tomography ; PAM , Photoacoustic Microscopy ; OR-PAM, Optical-Resolution Photoacoustic Microscopy ; AR-PAM, Acoustic-Resolution Photoacoustic Microscopy ; PAE , Photoacoustic Endoscopy ; PCE , Photoacoustic Computed Endoscopy ; PAEM , Photoacoustic Endoscopic Microscopy.
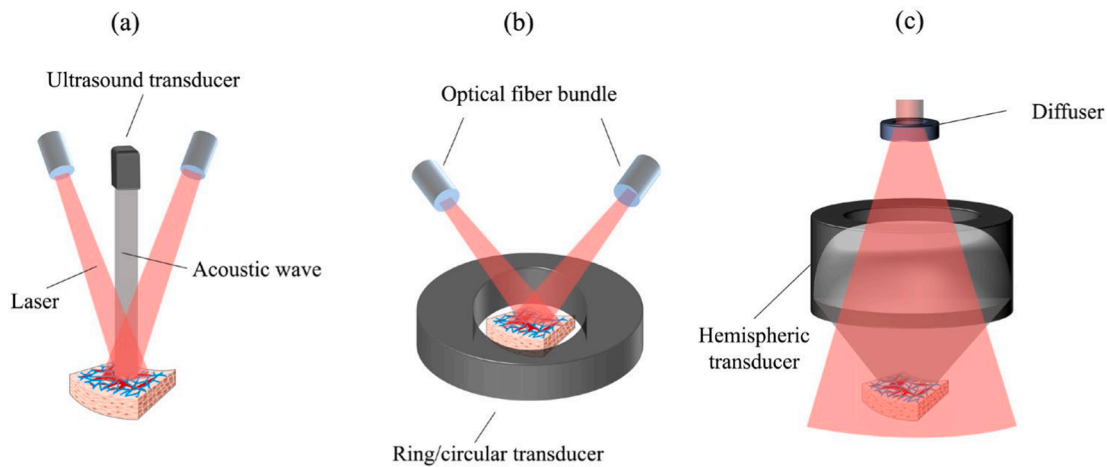

Fig. 4. The three implementations of the PACT system employ (a) linear array sensors, (b) ring array sensors, and (c) hemispherical array sensors.

tested this approach in a mouse model of ischemic stroke and were able to real-time visualize changes in cerebral blood flow, oxygen saturation, and tissue morphology. This study demonstrated the potential of the PACT-US imaging system in investigating the pathophysiology of ischemic stroke and monitoring therapeutic interventions. Overall, this system could become a powerful tool for future longitudinal studies on ischemic stroke treatment.

In addition to detecting stroke-related information, the PACT-US dual-mode system also exhibits significant advantages in detecting brain tumor. In Fig. 5c, researchers conducted imaging of mice before and after inducing ischemic stroke, enabling the observation of changes in blood volume, oxygen saturation, and tissue morphology [82]. This study demonstrated that PACT can provide early detection of ischemic stroke and real-time monitoring of its progression. Furthermore, ultrasound-guided photoacoustic imaging techniques have been utilized for tumor recurrence prediction and treatment monitoring, as shown in

Fig. 5d. Researchers employed this method to monitor the growth of breast tumor in a mouse model and predict tumor recurrence after treatment. This study demonstrates the potential of ultrasound-guided photoacoustic imaging technique in non-invasive monitoring of tumor growth and treatment response. In the field of brain tumor treatment, photothermal therapy (PTT) and photodynamic therapy (PDT) are currently hot research topics. The combination of photoacoustic imaging with PTT/PDT enables precise localization of tumor size and position, as well as monitoring of treatment efficacy. Additionally, PAM-US can be used to evaluate tissue recovery after treatment. This combined imaging technique holds significant importance for tumor diagnosis and treatment and is expected to be a crucial direction in the field of biomedical research. The use of PACT-US dual-modal systems also allows for the observation of the PTT process. Researchers have utilized highly crystalline multi-color carbon nanodots (CNDs) for dual-modal imaging-guided PTT. This provides necessary multi-color and deep
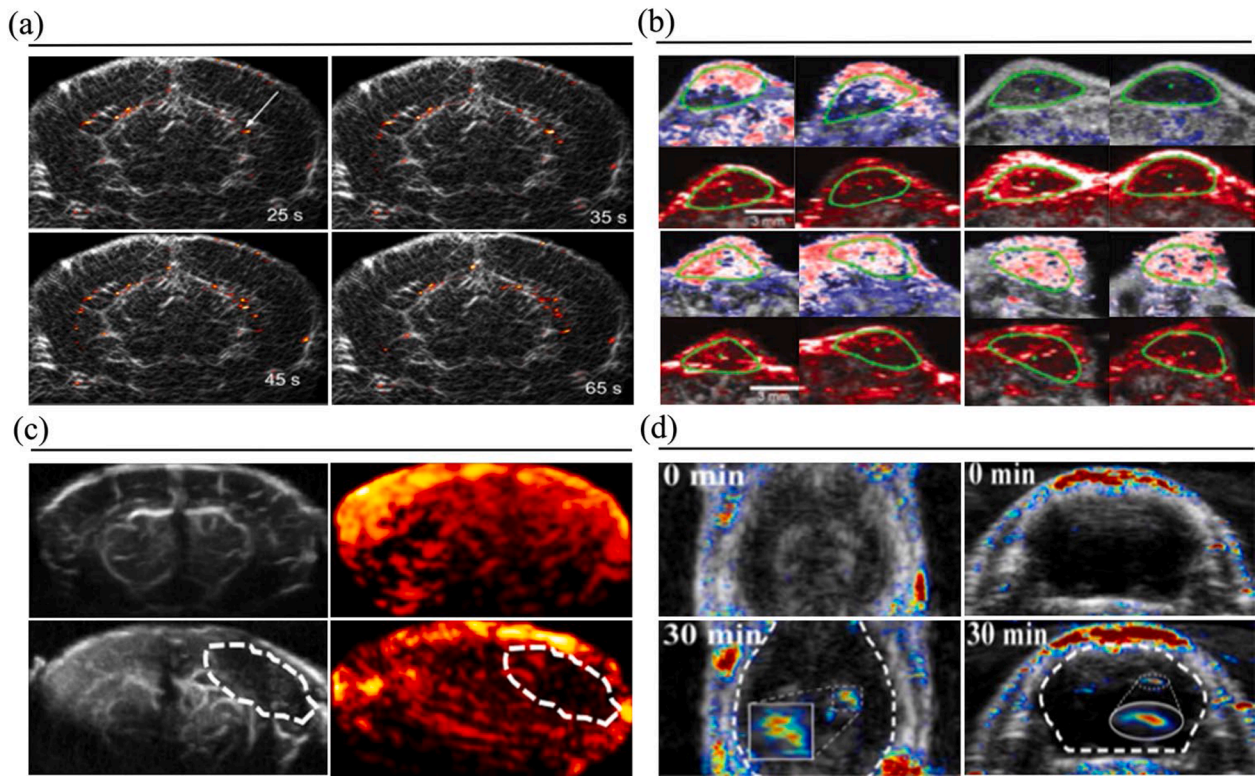
Fig. 5. PACT-US brain imaging applications.(a) Epileptiform activities of a mouse brain during a seizure, as imaged by PACT [80]. (b) Combined photoacoustic and ultrasound images of responders in 1-hr DLI group and non-responder from 3-hr DLI group [81]. (c) Mouse induced before and after ischemic stroke, as imaged by PACT-US [82]. (d) Real-time photoacoustic images of glioma in mice at different time points after intravenous administration of HCCDs [83].

Fig. 6. PACT-US for thyroid imaging applications. (a) photoacoustic and ultrasound cross-sections of the left thyroid lobe of a volunteer [84]. (b) photoacoustic and ultrasound results for a left lobe papillary thyroid cancer [85].

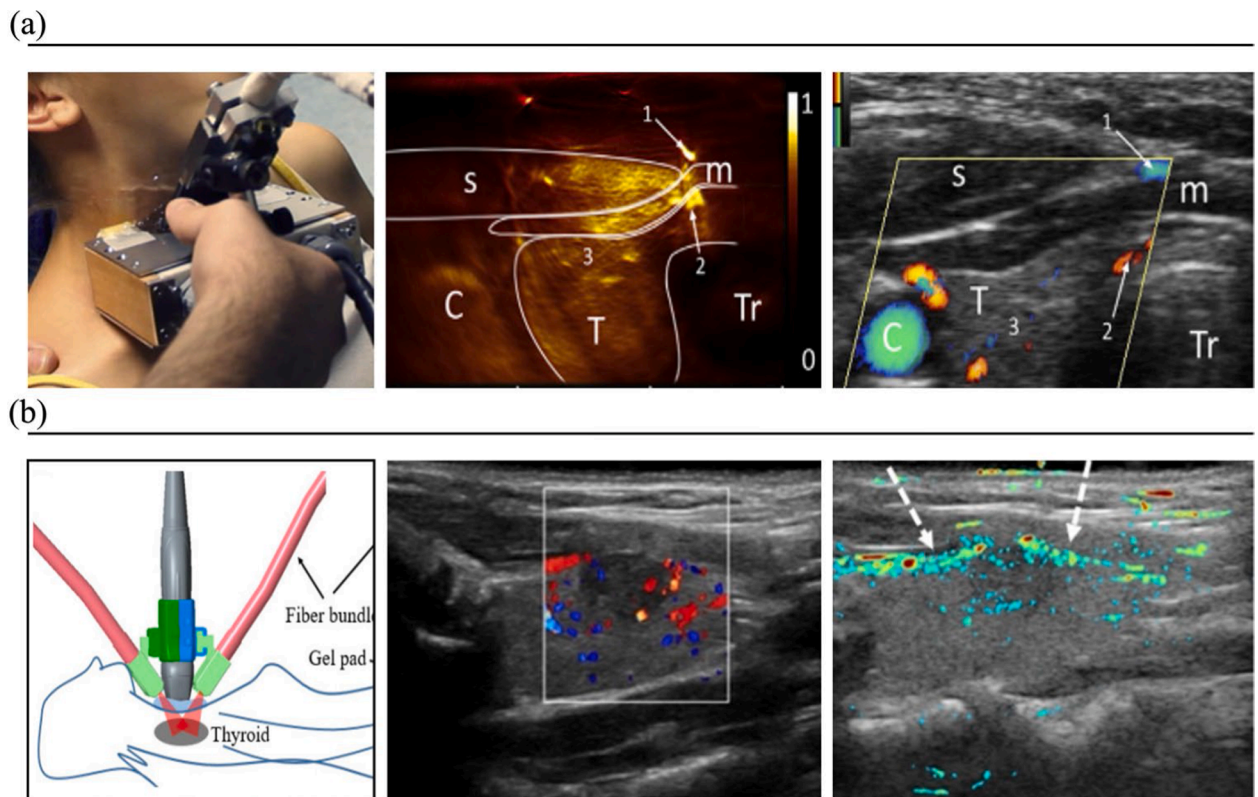spatial resolution for the unique characteristics of therapeutic nanoparticles to achieve optimal treatment outcomes. With guidance from this dual-modal imaging system, the distribution of drugs in mice at different time points after administration can be observed. Armed with this information, researchers can ensure that drugs accumulate directly in the optimal treatment areas, avoiding side effects on normal biological tissues [83].

2.2. PACT-US applications of thyroid

Thyroid tumor are common neoplasms in the head and neck region. With advancements in diagnostic imaging techniques such as ultrasound, X-ray, and magnetic resonance imaging (MRI), there has been an increase in newly diagnosed cases of thyroid cancer. While the occurrence rate of malignancy is approximately 10 % among all detected thyroid nodules, not all nodules require immediate treatment. However, traditional color Doppler ultrasound has limited capability in distinguishing atypical benign and malignant nodules. Reliable vascular information is crucial for accurate diagnosis of thyroid diseases. In recent years, contrast-enhanced ultrasound (CEUS) has been applied in the clinical evaluation of thyroid nodules. However, CEUS requires the administration of contrast agents via intravenous injection, which is invasive. Therefore, a non-invasive functional imaging modality that

can simultaneously assess morphological and functional information would be beneficial for early diagnosis and clinical management of thyroid tumors. Utilizing PACT-US for diagnosing thyroid diseases can provide reliable vascular information and offer important clues for diagnosing thyroid diseases. Some studies focusing on thyroid nodules have employed customized PACT-US systems. Both curved and linear ultrasound detector arrays have achieved promising experimental imaging results in the human thyroid (as shown in Fig. 6a, b) [84,85]. Both of these studies demonstrate the feasibility of detecting the contour of the thyroid and identifying vascular features. Furthermore, the research findings suggest that PACT-US is more effective in detecting blood vessels compared to color Doppler ultrasound.

2.3. PACT-US applications of breast

Breast cancer is one of the most common cancers in women. Compared to other parts of the body, the breast has lower vascular density, and dense breast tissue has little effect on the PA signal. Additionally, changes in angiogenesis, blood oxygen saturation (sO$_2$), and hemoglobin concentration are indicators of malignant breast tumor. PACT-US enables imaging of blood vessels and quantitative assessment of angiogenesis, blood oxygenation, and total hemoglobin concentration, making it an ideal method for breast cancer detection [69,86,87].
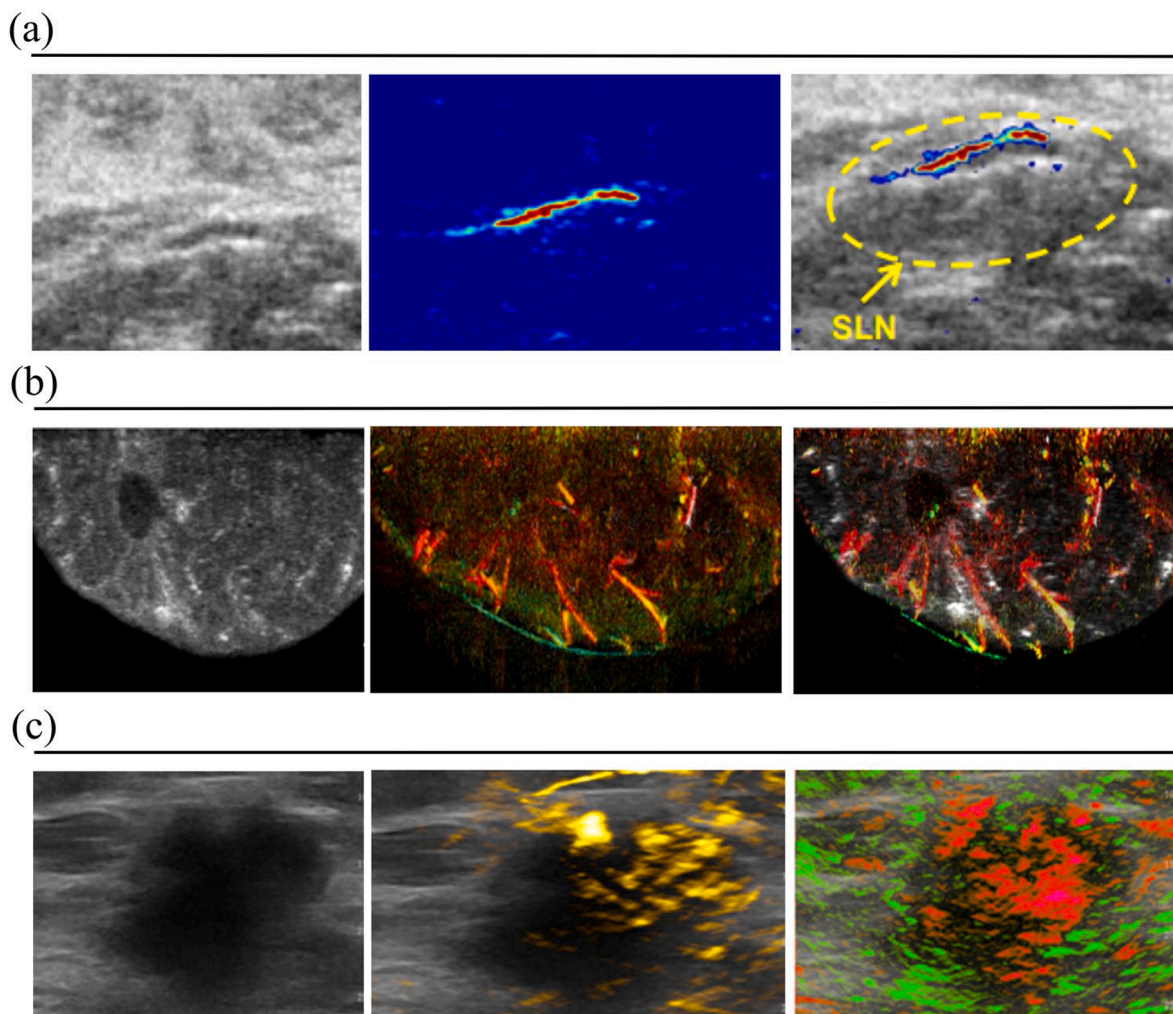
Fig. 7. PACT-US breast imaging applications. (a) In vivo US mage of a lymph node, in vivo PACT image of methylene blue dye and co-registered PACT-US image of the SLN [59]. (b) S-factor distribution image, US C-mode image and S-factor distribution image overlaid on the US C-mode image [88]. (c) Upper row shows a 2.6 cm malignant mass on gray scale ultrasound with increased internal total hemoglobin due to high density of angiogenesis in more than half of the tumor and diffuse internal blood deoxygenation [89]. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

In recent years, the clinical feasibility of PACT-US dual-modal imaging technology in the diagnosis of human breast cancer has been demonstrated. Advanced systems have been designed in research settings for simultaneous PACT-US breast imaging. In Fig. 7a, b, and c, a photoacoustic breast imaging system is both presented that allows for the simultaneous acquisition of photoacoustic and ultrasound images [59,88,89]. Studies have shown that the combination of photoacoustic imaging and ultrasound imaging can improve the detection rate and accuracy of breast tumor. Photoacoustic imaging provides comprehensive biomarker information, while ultrasound imaging provides detailed anatomical structural information. Therefore, this combined imaging technique can effectively assess the size, location, and morphology of breast lesions, assisting physicians in better diagnosing breast cancer. Compared to the previously described two-dimensional (2D) functional PACT-US imaging, three-dimensional (3D) functional PACT-US imaging has several advantages. 3D PACT-US imaging provides quantitative results on top of 2D PACT imaging, better representing the overall functional imaging characteristics of breast tumor. To validate this, Yang et al. explored a method for quantitative analysis of breast tumor features using 3D volume data obtained from a 3D PACT-US functional imaging system. Three-dimensional analysis of vascular distribution can describe the tumor vascular system more comprehensively than 2D analysis. Additionally, quantifying the functional information of PACT in three dimensions may reduce inter-observer variability compared to previous 2D PACT-US imaging studies. Limitations of this study include the issue of "limited field of view," which results in a tendency for most reconstructed vessels to be parallel to the scanning direction. It is noteworthy that PACT-US is accelerating its clinical translation in macroscopic and microscopic imaging for breast cancer patients. Further research is needed to clarify the role of PACT-US in clinical practice, including feature analysis and interpretation strategies.

Furthermore, further technological advancements in this technique will focus on achieving quantitatively accurate PACT-US images and developing large-field-of-view 3D PACT-US systems.

2.4. PACT-US applications of joints and limbs

The PACT-US system has also been applied in the research of diseases such as synovitis and tenosynovitis in the joints of the limbs. For common rheumatoid arthritis (RA), ultrasound power Doppler imaging (US-PD) and magnetic resonance imaging (MRI) can predict disease progression and bone erosion. However, US-PD is limited by its dependence on the angle between blood flow vectors and the ultrasound beam, as well as the interference of probe pressure on blood flow. MRI is expensive, moderately specific, and requires contrast agents for more accurate observations. In recent years, optical imaging methods have been investigated as potential alternative approaches. For example, optical spectral transmission (OST) has shown good performance and relatively low cost in detecting synovitis. However, its sensitivity and specificity are moderate, and the low spatial resolution limits the differentiation between synovitis and tenosynovitis. In the study of rheumatoid arthritis (RA), photoacoustic imaging can clearly visualize the affected area (as shown in the yellow region in Fig. 8a). By combining the structural imaging capability of ultrasound imaging, the inflammatory areas in finger joints can be precisely localized, leading to more accurate disease classification [90]. In addition, PACT-US imaging can provide vascular and molecular imaging information, offering a more comprehensive assessment for early diagnosis and treatment of conditions such as synovitis. Research has demonstrated the feasibility of photoacoustic-ultrasound (PACT-US) dual-modality imaging in the imaging of human joint regions. For instance, a comparison of photoacoustic (PA) and ultrasound (US) images was conducted on the
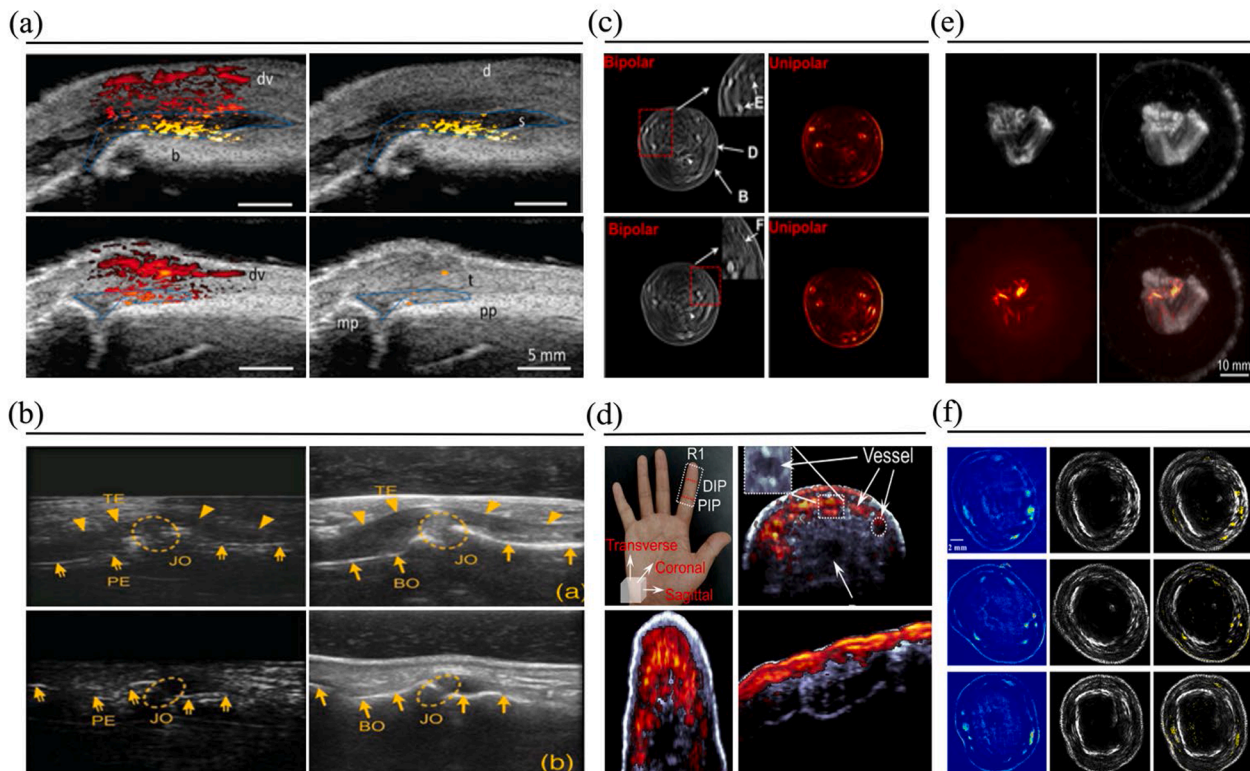
Fig. 8. PACT-US Human limb joint imaging applications. (a) PACT-US images show a difference in color between inflamed and non-inflamed corresponding to an increase in amplitude levels [90]. (b) A comparison of PACT and US images of the proximal interphalangeal (PIP) joint was shown in normal volunteers. (c) In vivo PACT-US imaging of Human finger joint [91]. (d) Photography of the finger and representative co-registered harmonic US and PA images in the coronal, sagittal, and transverse planes [78]. (e) Photoacoustic ultrasound image of finger joint cross-section. (f) In vivo PA (upper row) and US (middle row) reconstructed images of typical joint slices [92].

proximal interphalangeal (PIP) joint of healthy volunteers, as shown in Fig. 8b. PACT and US exhibited noticeable similarities in depicting bone structures, tendons, and cartilage. However, due to the fundamental differences in image contrast between the two imaging modalities, the US image reflected the acoustic reflection of bone structures, while the PA image represented the optical absorption of the vascular system in the bone surface periosteum. Integration of PACT with commercial US imaging enables better identification of functional characteristics within joint tissues, thereby enhancing the diagnostic capabilities for inflammatory joint diseases.

As shown in Fig. 8c, cross-sectional imaging of the human finger was performed using photoacoustic (PA) and ultrasound (US). From the ultrasound image, we can clearly distinguish the bone structure (indicated by the white arrow A in Fig. 8c). From the photoacoustic image, we can observe the vascular component (rightmost column in Fig. 8c). With the assistance of this image, we can determine the diameter of the blood vessels, and the boundary between the epidermis and dermis can be visualized in the photoacoustic image (indicated by the white arrow in the middle column of Fig. 8c) [91]. In the context of real-time dynamic imaging for arthritis, a video-rate dual-mode wide-beam harmonic photoacoustic and ultrasound computed tomography (PACT) technique was proposed, as depicted in Fig. 8d. This technique enables real-time video-rate imaging and combines harmonic photoacoustic and ultrasound imaging modes to provide more detailed tissue information. Researchers have also conducted multi-parametric photoacoustic and ultrasound imaging for arthritis using the PACT-US system [78]. Fig. 8f presents a multi-parametric photoacoustic and ultrasound imaging technique for assessing the development and treatment of rheumatoid arthritis. This technique enables simultaneous acquisition of multiple parameters, including hemodynamics, oxygenation status, and tissue acoustic properties, to provide a more comprehensive assessment of arthritis information [92].

2.5. Brief summary of PACT-US

Despite its significant strides in biomedical imaging, PACT-US still encounters several challenges. Regarding depth imaging limitations, the photoacoustic signals are compromised by light scattering and absorption in tissues, which affects the resolution at greater depths. To advance this area, future developments could focus on enhancing light sources and detector designs. These improvements, along with the implementation of sophisticated imaging algorithms and exploration of novel optical technologies, are poised to significantly enhance depth imaging capabilities. Another promising direction is the integration of new imaging modes, such as multispectral or multimodal imaging, to provide richer tissue characterization and better depth penetration. In terms of imaging speed, the current pace of PACT-US systems is not conducive to real-time imaging and dynamic monitoring applications. To accelerate this, advancements in imaging algorithms are crucial, along with the development of faster laser and detector systems. Employing parallel imaging and multi-channel approaches could revolutionize the imaging speed, making PACT-US more suitable for rapid diagnostics and real-time tissue monitoring.

As for clinical feasibility, the integration of PACT-US into regular clinical practice faces challenges including equipment stability, standardization, and validation of clinical efficacy. Future efforts should involve close collaboration with clinical professionals, extensive multi-center trials, and development of comprehensive training programs for practitioners. These efforts are essential for establishing reliable operational procedures and ensuring robust clinical data validation. In terms of large-scale application scenarios, PACT-US has the potential to revolutionize areas such as oncology, cardiology, and neurology. In oncology, PACT-US can be utilized for early tumor detection and monitoring treatment responses. In cardiology, it could be pivotal in imaging vascular structures and assessing plaque vulnerability. For neurology, PACT-US can offer insights into cerebral hemodynamics and

brain disorders. The combination of molecular imaging agents with PACT-US could open new vistas in personalized medicine, allowing for targeted imaging and therapy. Furthermore, its application in portable devices can transform emergency medicine and remote healthcare, providing high-quality imaging in diverse settings.

3. Photoacoustic-ultrasound microscopy (PAM-US)

Unlike photoacoustic computed tomography (PACT) based on image signal reconstruction, another major implementation of photoacoustic imaging is photoacoustic microscopy (PAM) [93,94]. PAM utilizes optical and acoustic focusing scanning to directly form images using the acquired signals, which provide depth-resolved information [10,95,96]. PAM maximizes its detection sensitivity through co-alignment of optical illumination and acoustic detection [97–99]. The axial resolution of PAM is primarily determined by the imaging depth and the frequency response of the ultrasound transducer, while the lateral resolution is determined by the combination of the point spread functions of the dual focal points [97,98,100]. Based on this, PAM can be further classified into optical-resolution PAM (OR-PAM), where the optical focus is tighter than the acoustic focus, and acoustic-resolution PAM (AR-PAM), where the acoustic focus is tighter [101–103]. The schematic diagrams of the imaging principles of OR-PAM and AR-PAM are shown in Fig. 9a, b, and c.

For photoacoustic microscopy (PAM), it enables spatial resolution at the μm level for imaging of small tissue structures [38,104,105]. PAM offers several advantages compared to conventional optical microscopes such as confocal, two-photon microscopy, or optical coherence tomography (OCT) [106,107]. Firstly, photoacoustic microscopy (PAM) has an optical diffusion limit of over 1 mm, allowing it to operate at greater imaging depths. By utilizing ultrasound for imaging, the photoacoustic signals are 2–3 orders of magnitude weaker than light scattering in biological tissue [108]. Secondly, PAM provides high sensitivity to offer structural and functional information of microvasculature in each region [109,110]. This means it can provide detailed anatomical and hemodynamic data about the vascular network, providing a comprehensive understanding of the blood supply and metabolic activity of biological tissue [111]. Additionally, PAM does not require optical slicing of the biological tissue to obtain three-dimensional volumetric images [112,113]. This non-invasive imaging technique can acquire high-resolution three-dimensional structural information without damaging the sample.

Over the years, PAM systems have been developed in various forms and applied in numerous fields including vascular biology, histology, oncology, neuroscience, and ophthalmology, among others [114]. Its high-resolution and functional imaging capabilities have made PAM a powerful tool in both research and clinical applications [115,116]. As an ultrasound-based technique, ultrasound microscopy (USM) offers sufficient imaging depth in biological tissue [117,118]. Importantly, PAM and USM exhibit good integration and complementarity [119]. In recent years, excellent work has been reported on dual-modal imaging systems combining US and PAM. Benefiting from the advancements in resolution and image contrast over the years, photoacoustic microscopy (PAM) has demonstrated its valuable applications in the field of basic research [109,120]. Building upon this foundation, PAM's high-resolution and high-contrast imaging capabilities in biological tissue [121], combined with the volumetric imaging capability of ultrasound imaging, give PAM-US imaging a strong competitive advantage in assisting disease diagnosis, assessing disease conditions, and monitoring drug treatment processes. In the following sections, we will introduce representative applications of PAM-US imaging. In current research, PAM-US has demonstrated promising applications in various areas including the brain, eyes, human limbs, joints, and skin.
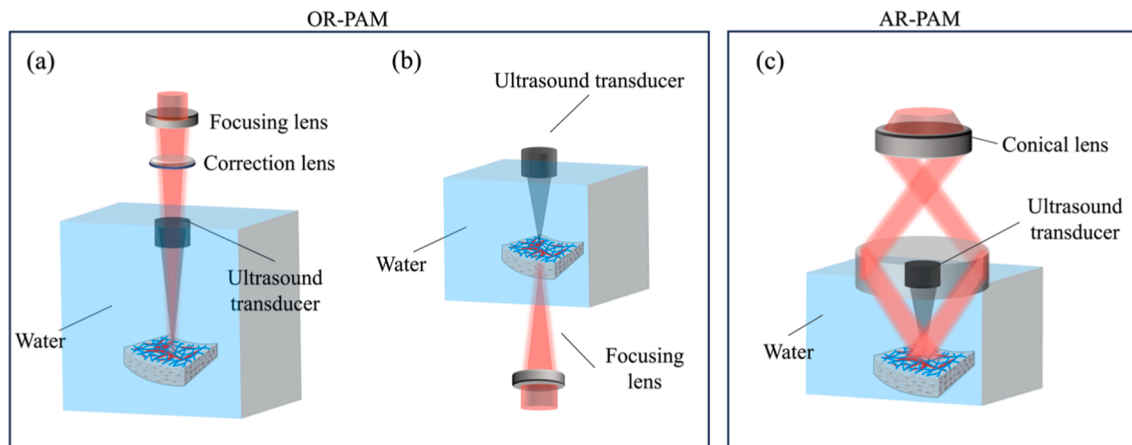
Fig. 9. Main forms of PAM. (a) Transmission-type optical-resolution photoacoustic microscopy. (b) Reflection-type optical-resolution photoacoustic microscopy. (c) Acoustic-resolution photoacoustic microscopy.

3.1. PAM-US applications of brain

The brain is one of the most complex and vital organs in the human body. Studying the structure and function of the brain is of great significance for understanding the workings of the nervous system, the mechanisms of diseases, and the development of relevant treatment methods and drugs. In a study depicted in Fig. 10a, researchers introduced a virtual cranial opening technique known as high-resolution optoacoustic brain microscopy. By accurately simulating the shape and optical properties of the skull, they successfully achieved high-resolution imaging of the brain [122]. This innovative approach provides researchers with a powerful tool to explore the intricacies of the brain at the microscopic level. By using a dual-modality imaging system combining ultrasound and optoacoustic imaging, researchers are able to simultaneously acquire geometric and spectral information from the skull's pulse-echo ultrasound images and optoacoustic images. This enables them to obtain accurately co-registered volumetric images of the skull and brain and obtain crucial information about vascular details and distribution. In the study shown in Fig. 10b, researchers employed a large-scale optoacoustic and ultrasound microscopy system to investigate strain-specific morphogenesis and vascular development in the mouse skull [123]. By combining optoacoustic and ultrasound imaging techniques, they were able to dynamically observe and analysis the processes of skeletal development and vascular formation in different mouse strains. This comprehensive approach provides a large-scale, high-resolution imaging capability, enabling researchers to gain valuable insights into the processes of bone morphogenesis and vascular genesis. These findings have the potential to significantly contribute to a deeper understanding of skeletal biology and the study of skeletal development and related diseases. In a study depicted in Fig. 10c, Ning et al. proposed an ultrasound-assisted multi-parameter optoacoustic microscopy technique for imaging the mouse brain. By combining ultrasound and optoacoustic imaging modes, they were able to obtain detailed information about the structure and functional parameters of
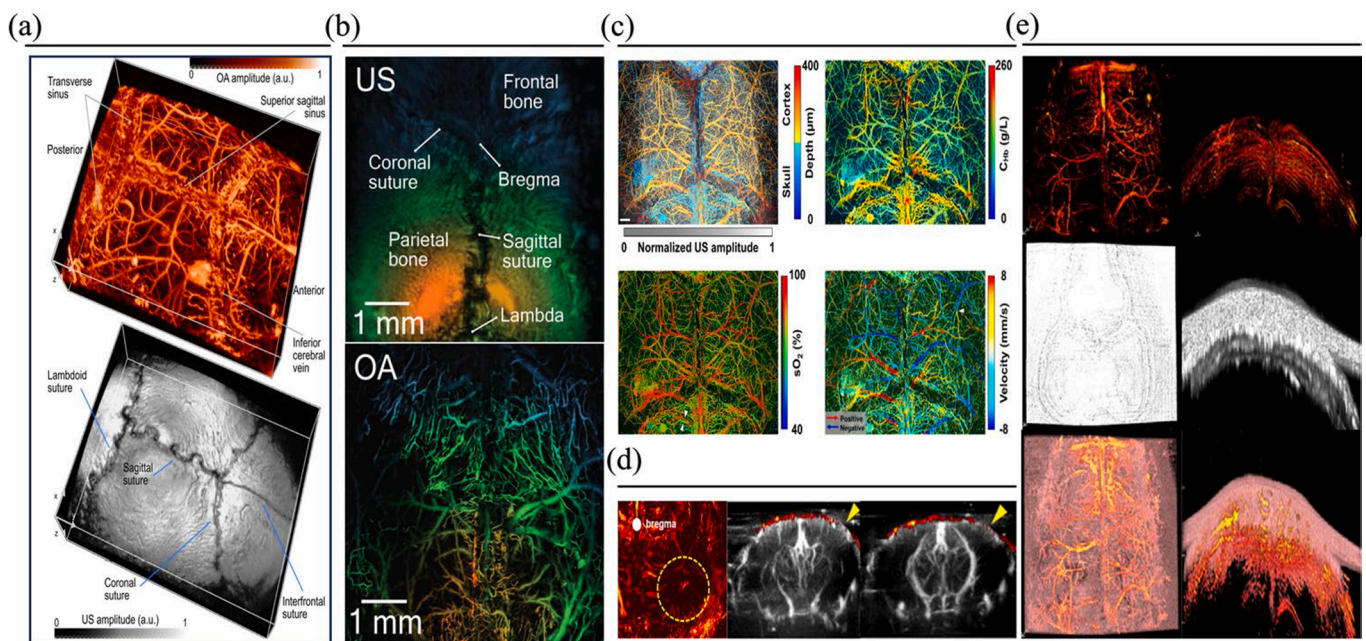
Fig. 10. PAM-US brain imaging applications. (a) Dual mode optoacoustic and ultrasonic microscopy of a mouse brain [122]. (b) The co-registered US and PAM datasets shown as depth-encoded MIPs. Anatomical landmarks are shown in the US image, including frontal bones, coronal sutures intersecting at Bregma, parietal bones, suture connecting Bregma and Lambda [123]. (c) Ultrasound-aided multi-parametric PAM of the mouse brain through the intact skull [124]. (d) Imaging results of the transplanted glioma [125]. (e) The corresponding photoacoustic, ultrasonic, and merged 3D images in the dashed boxes [126].

the mouse brain [124]. This approach combines spatial information of anatomical structures obtained through ultrasound imaging with functional information of tissues obtained through optoacoustic imaging. This comprehensive imaging technique provides a comprehensive and non-invasive method for studying the mouse brain, facilitating neuroscience research and enhancing our understanding of brain function. In a study depicted in Fig. 10d, Pang et al. proposed a multimodal optoacoustic/ultrasound imaging technique based on a commercial ultrasound platform [125]. By harnessing the capabilities of existing ultrasound systems, they successfully integrated optoacoustic imaging, enabling simultaneous acquisition of optoacoustic and ultrasound images. This integrated approach combines the complementary advantages of optoacoustic and ultrasound imaging, providing a convenient and practical solution that enhances the diagnostic capabilities for various biomedical applications. Researchers conducted imaging experiments using this technology and achieved satisfactory results, offering a practical and feasible option for non-invasive imaging in preclinical research.

Lastly, in the study depicted in Fig. 10e, the authors proposed a commercialization strategy for utilizing optoacoustic and ultrasound dual-scanning microscopy for in vivo imaging of small animals [126]. By combining optoacoustic (532 and 1064 nm) and ultrasound imaging, they successfully achieved real-time high-resolution imaging of small animals. By utilizing two different wavelengths of light sources, researchers were able to capture complementary information about tissue structure and molecular composition. This strategy provides a practical and versatile solution for non-invasive imaging in preclinical research, with the potential to drive the development of new diagnostic and therapeutic approaches in biomedical applications. This study is of significant importance in advancing imaging technologies in the field of biomedicine.

3.2. PAM-US applications of eyes

PAM-US has shown extensive applications not only in brain research but also in the field of ocular imaging, demonstrating tremendous potential. Through optoacoustic imaging, high-resolution structural and functional information of ocular tissues can be non-invasively obtained, providing strong support for research and clinical applications in ophthalmology. By combining optoacoustic and ultrasound imaging, multimodal imaging of ocular tissues can be achieved, including structures such as the retina, vitreous body, sclera, and anterior chamber (as shown in Fig. 11)[127]. This multimodal imaging approach can provide detailed anatomical information of ocular tissues, allowing for the observation of vascular networks, blood flow dynamics, and other important biological parameters. This is of significant importance for early diagnosis of ocular diseases, monitoring treatment efficacy, and

investigating the mechanisms underlying ocular conditions.

3.3. PAM-US applications of limbs

PAM-US technology has also demonstrated potential and promising applications in limb imaging. By combining photoacoustic imaging with ultrasound imaging, high-resolution imaging of limb tissues can be achieved, opening up new possibilities for evaluating structures such as muscles, bones, and blood vessels. In limb research, photoacoustic imaging can be used to observe the anatomical structure and function of muscle tissue [115,128]. By acquiring photoacoustic images, we can non-invasively obtain information about the layered structure, fiber distribution, and tendon connections of muscles [72]. This is of great significance for studying muscle diseases, sports injuries, and muscle changes during rehabilitation processes. Additionally, photoacoustic imaging can provide information about muscle hemodynamics, including vascular density, blood flow velocity, and oxygenation status, aiding in the assessment of muscle tissue function [129]. The application of PAM-US technology in human limbs holds important clinical and research value. By harnessing the advantages of photoacoustic and ultrasound imaging, this technique can provide high-resolution, real-time, and multi-parameter information, offering a comprehensive tool for the structural and functional assessment of limb tissues, as shown in Fig. 12a and b below [130,131].

In the field of sports medicine, PAM-US can be used to assess changes in muscle and skeletal structures, helping doctors understand conditions such as muscle injuries, skeletal deformities, and arthritis. Through real-time imaging and functional monitoring, this technology can assist athletes in rehabilitation training, injury prevention, and performance optimization. PAM-US can also be applied to the evaluation and diagnosis of limb blood vessels. By monitoring vascular structure and hemodynamics, the presence and severity of vascular diseases such as arterial stenosis, thrombosis, and varicose veins can be detected. This provides crucial information for doctors to develop appropriate treatment plans, such as surgery, endovascular interventions, or medication-based therapies. Furthermore, PAM-US contributes to the study of changes in limb blood perfusion and tissue metabolism. By assessing photoacoustic signals of biomarkers such as oxygenated hemoglobin and lipids, the tissue's oxygenation level and metabolic activity can be understood. This is significant for investigating limb hemodynamics, inflammatory responses, tissue regeneration, and other related aspects. PAM-US has also achieved success in the application to human limb joints. For example, it can be used to image articular cartilage to detect cartilage injuries or degradation [132]. Different wavelengths and imaging modes can provide imaging information at different levels of the cartilage. By utilizing PAM-US for imaging synovium, synovitis or other lesions can be detected. It can also be employed to image joint capsules
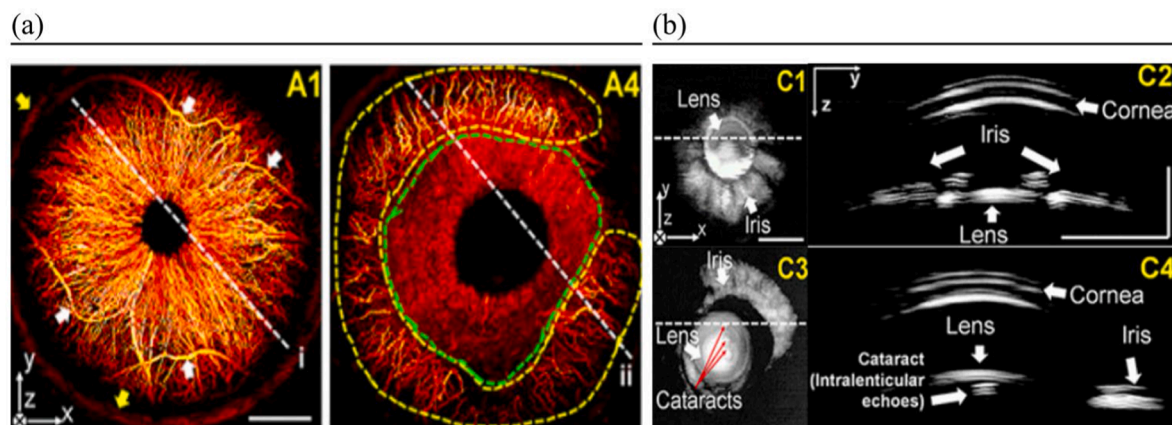

Fig. 11. PAM-US retinal imaging application. (a)PA MAP, depth-encoded PA MAP, B-scan, and (b) enlarged B-scan images and US MIP and B-scan images [127].
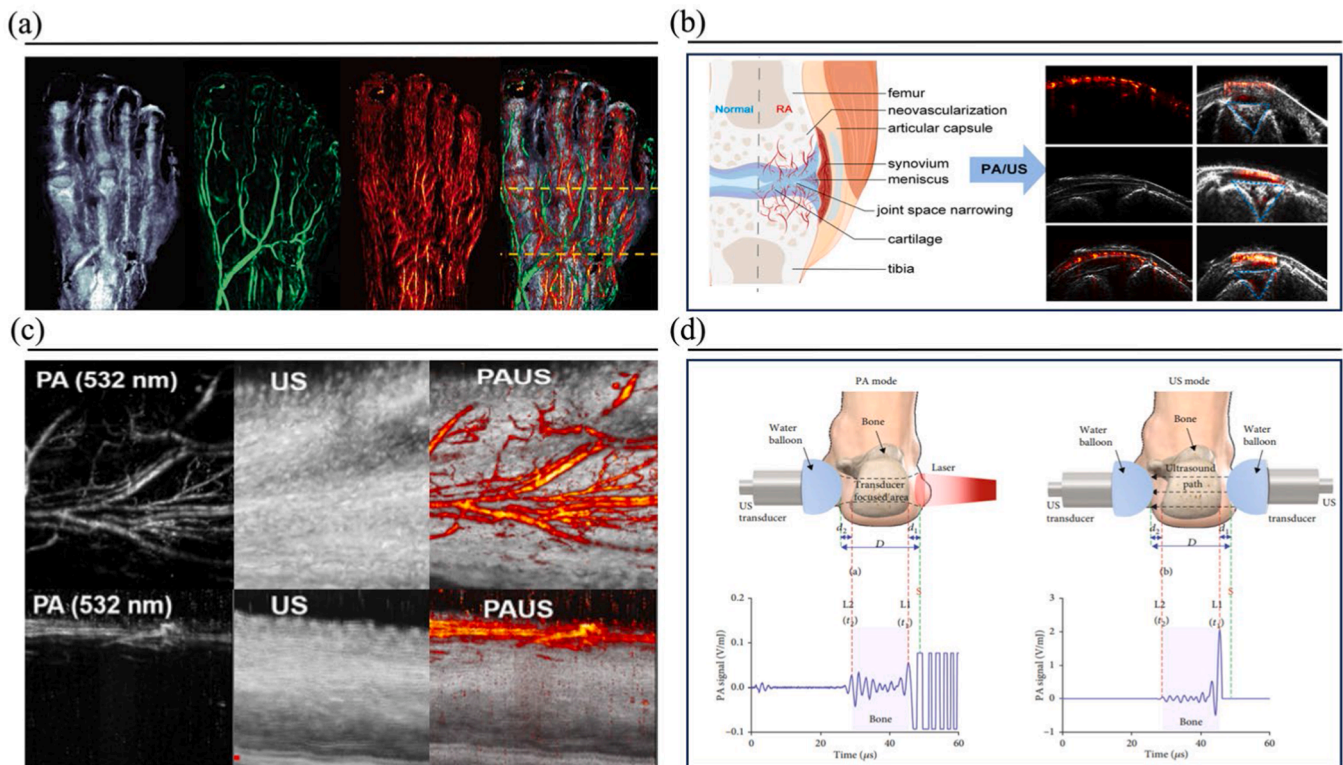
Fig. 12. PAM-US limb joint imaging applications. (a) US MIP vessel image, and PA maximum amplitude projection (MAP) vessel image [130]. (b) Concurrent PA-US of a mouse hind paw. In vivo PAM-US results of a mouse's hind paw, showing the XY and XZ projections for US [131]. (c) Images of the PAM-US dual-modality system on the knee joint of an RA mouse are also shown, with PA images, US images and PAM-US coupled images [133]. (d) Detection of the PA signal from the human calcaneus bone in vivo [134]. The signal marked between the two red dashed lines is from the calcaneus bone, where the right and the left boundaries are marked by L1 and L2, respectively. The large and saturated signal at the right side of the green dashed line marked with "S" is from the soft tissue covering the bone. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

to detect conditions like cysts.

Rheumatoid arthritis (RA) is a chronic autoimmune disease characterized by neovascularization, synovial hyperplasia, and articular cartilage destruction. However, targeted methods for early diagnosis and treatment monitoring are still lacking. As depicted in Fig. 12c, a study utilizing photoacoustic-ultrasound microscopy (PAM-US), a dual-modal imaging technique, was introduced to observe RA disease [133]. By establishing the collagen-induced arthritis (CIA) mouse model and utilizing a subjective grading system for disease classification, PAM-US imaging enables real-time assessment of synovial erosion and vascular turbidity within the knee joint at high spatial resolution. This system also quantitatively monitors the vascular physiology and morphology in the subcutaneous vessels of the hind paw, measuring the area of neo-vascularization and the intensity of the photoacoustic signal, which correlates positively with disease grading. Compared to traditional subjective scoring of arthritis severity, PAM-US imaging is more sensitive, allowing the observation of vascular signals and synovial erosion at early stages of arthritis progression. Members of this research group have also explored bone and joint detection and developed a non-invasive imaging technique that provides functional and structural information of bone tissue (Fig. 12d) [134]. Functional photoacoustic imaging allows visualization of bone microvasculature and measurement of blood oxygen levels, providing insights into the metabolic activity of bone tissue. On the other hand, ultrasound imaging provides information about bone density and structural integrity. In a clinical feasibility study, we recruited a group of patients known to have osteoporosis and a control group without osteoporosis. The successful demonstration of functional photoacoustic and ultrasound imaging techniques showed the ability to differentiate between healthy bone and osteoporotic bone. Imaging results revealed significant differences between the two patient groups in terms of vascular patterns and

oxygenation levels, as well as changes in bone density and structure. These findings confirm the potential of PAM-US in early detection and monitoring of osteoporosis.

3.4. PAM-US applications of skin

In the field of dermatology, photoacoustic-ultrasound imaging can be used to assess and monitor various skin lesions, such as warts, eczema, and skin cancer. By observing the photoacoustic and ultrasound reflection signals from the skin, physicians can obtain information about the skin's structure, vascular distribution, and depth of lesions, aiding in diagnosis and treatment planning [135], as shown in Fig. 13b, 13c, and 13d [136,137]. Our research group has also conducted studies on PAM-US for skin imaging, as depicted in Fig. 13a [119]. The designed PAM-US skin probe combines the principles of photoacoustic imaging and ultrasound, providing a more comprehensive approach to skin assessment. This technique utilizes a dual-crystal transducer with high sensitivity and better penetration depth, enabling imaging of both superficial and deep skin layers. By integrating photoacoustic and ultrasound modes, the PAM-US skin probe provides information about skin morphology, blood vessels, and intravascular components. The high sensitivity of the PAM-US skin probe allows for the detection of subtle changes in the skin, enabling observation and diagnosis of melanoma or other skin cancers at an early stage. Furthermore, its penetration capability visualizes structures such as blood vessels and subcutaneous tissues, providing valuable insights into microvascular networks and tissue structures. This technology has the potential to revolutionize the field of dermatology by improving the accuracy and efficiency of skin lesion diagnosis. By achieving high-resolution and deep non-invasive imaging, the PAM-US skin probe offers a promising tool for dermatologists to assess skin conditions, guide biopsy procedures, and monitor treatment responses.
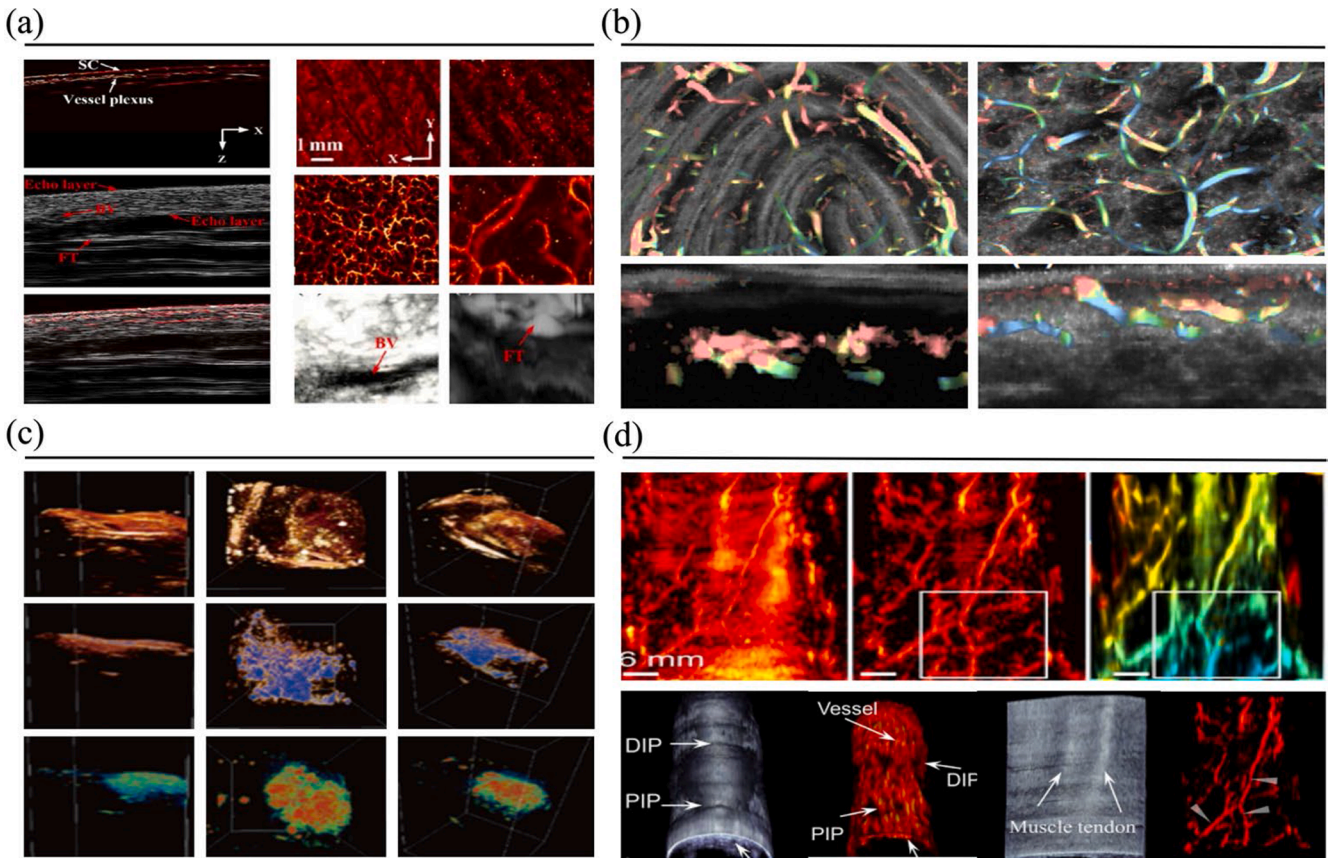
Fig. 13. PAM-US skin imaging applications. (a) In vivo imaging of the human palm. The hybrid PA and US image of the human palm. PA lateral MAP image of epidermal (0–90 μm), epidermal-dermal junction (90–210 μm), dermis (210–350 μm) and vessel plexus (350–1500 μm). US volume projection image of big vessel at a depth of 1.5–2.6 mm. US volume projection image of fibrous tissue at a depth of 2.6–5 mm. SC, stratum corneum. BV, blood vessel. FT, fibrous tissue [100]. (b) Examples of PAM-US images of bird's eye [117]. (c) Reconstructed 3D images with the visible light and NIR light AR-PAM data and the US data from different perspectives. First line, US imaging results. Second line, photoacoustic imaging results with visible light excitation, and third line, photoacoustic imaging results with NIR light excitation [118]. (d) Photoacoustic and ultrasonic imaging of finger region skin.

In addition, PAM-US can be used to assess changes in skin hemodynamics and tissue metabolism. By monitoring the morphology and blood flow velocity of skin micro vessels, the perfusion status and oxygenation level of the skin can be understood. This is of significant importance in studying skin vascular function, inflammatory responses, and wound healing. The photoacoustic-ultrasound imaging technology also holds potential applications in dermatological aesthetics and plastic surgery. Through real-time imaging and in-depth observation, physicians can

evaluate skin elasticity, wrinkles, pigmentation, and other features, providing a basis for personalized cosmetic treatment plans. Furthermore, this technology can be used to monitor the effects of plastic surgery and postoperative recovery (see Fig. 14).

3.5. Brief summary of PAM-US

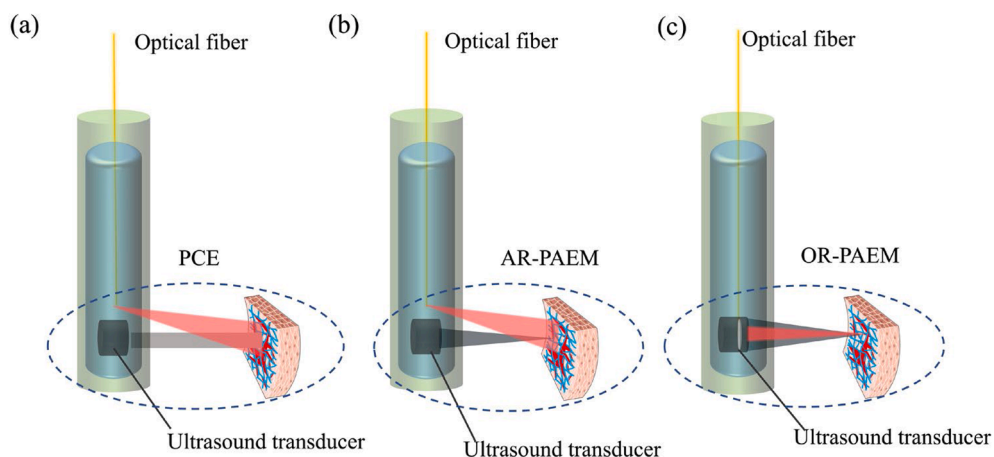In the years of its development, PAM-US imaging has made

Fig. 14. PAE system main form schematic diagram. (a) PCE , Photoacoustic Computed Endoscopy. (b) AR-PAEM , acoustic-resolution photoacoustic endoscopic microscopy. (c) OR-PAEM , optical-resolution photoacoustic endoscopic microscopy.

significant progress in terms of resolution and contrast, thanks to continuous advancements in hardware technology. However, as the exploration of microscopic imaging applications continues, the demand for higher lateral resolution is increasing. Although the lateral resolution of the photoacoustic imaging system can be improved by using high numerical aperture objectives, it is still limited by the optical diffraction limit [138,139]. It is foreseeable that in the future direction of PAM-US, further exploration of cellular and subcellular targets will be a research focus. Furthermore, the limited imaging depth remains a major drawback of PAM-US imaging, greatly restricting its biomedical applications [132]. Currently, most PAM-US systems can only observe targets in superficial skin tissue [140] or utilize techniques such as tissue clearing and cranial windows to assist in improving imaging depth. Additionally, the imaging quality in non-focal regions often falls far behind that in the focal region, highlighting the need to enhance the image quality in non-focal areas. To achieve widespread adoption in biomedical applications, the improvement of imaging speed is also crucial for PAM-US technology. Although imaging speed has been greatly enhanced through the use of technologies such as MEMS, GM, polygonal scanners, and micro lens array-based scanning methods, further improvements are still needed for daily application scenarios [141]. In terms of ultrasound imaging, as it delves into the microscale domain, it can accurately reflect the interactions between mechanical waves and small elastic media. With the aid of ultrasound contrast agents, ultrasound imaging has already achieved observations of certain microstructures [142,143].

In terms of future development directions, several key areas that could enhance the application potential of PAM-US technology. The future development of PAM-US technology will benefit from innovations in several key areas. Firstly, the integration of nanotechnology, especially in probe design and the development of imaging agents, is expected to significantly enhance imaging depth and resolution. Secondly, the optimization of data processing and image reconstruction algorithms will improve image quality, particularly in non-focal areas, and will help speed up the imaging process. Additionally, the development of multimodal imaging techniques, by combining PAM-US with other imaging technologies such as Magnetic Resonance Imaging or Optical Coherence Tomography, will enable more comprehensive biomedical analysis. Lastly, the development of precise biomarkers and probes for various biomedical applications will enhance the capability of target-specific imaging. These advancements will not only improve the performance of PAM-US technology but will also expand its applications and depth in the field of biomedicine.

It is foreseeable that with the continuous advancement of photoacoustic and ultrasound microscopy technologies [144–146], photoacoustic-ultrasound microscopy will reveal more microscopic stories to us.

4. Photoacoustic-ultrasound endoscopic imaging (PAE-US)

In the context of internal tissues and organs in living organisms, such as the digestive system and vascular walls, the advantages of PACT (Photoacoustic Computed Tomography) and PAM (Photoacoustic Microscopy) techniques are not evident. Therefore, researchers have turned to the integration of well-established optical endoscopy methods with the photoacoustic effect to image deeper internal tissues and organs [147,148]. The concept of Photoacoustic Endoscopy (PAE) was first reported in 2009 by WANG L V et al [39]. In this work, a rotary mechanical scanning system with integrated optical excitation and micromotor-based acoustic detection was proposed, establishing the concept of PAE (Photoacoustic Endoscopy). PAE offers three main imaging modalities [40,41,149]: the first is Photoacoustic Computed Endoscopy (PCE), which is similar to PACT and utilizes planar ultrasound sensors or sensor arrays for regional acoustic signal reception, requiring corresponding reconstruction algorithms to form images. The second modality is Acoustic Resolution Photoacoustic Endomicroscopy (AR-PAEM), which typically images by focusing the received acoustic

signals from a focused ultrasound transducer and the laser beam at the same point. The third modality is Optical Resolution Photoacoustic Endomicroscopy (OR-PAEM), which uses a highly focused laser beam for illumination instead of regional illumination in AR-PAEM. PCE achieves a penetration depth of up to 5.5 mm but has lower spatial resolution, while PAEM achieves a maximum spatial resolution of 3.0 μm [150].

To obtain high-quality PA images, the optimal design of a PAE imaging probe should include fiber optics for delivering the excitation light and US detectors for signal detection [151,152]. Various probes using different types of light delivery, US detection, and scanning mechanisms have been studied, each with its own advantages and limitations. Based on clinical applications, these designs can be divided into two groups: gastrointestinal and intravascular imaging probes [153,154]. Although PAE has made significant progress in technology and applications in recent years, its clinical application is not yet mature. This is due to higher requirements compared to PACT and PAM [114,155]. Firstly, the endoscopic approach imposes strict limitations on sensor size and requires high stability during the scanning process [156,157]. However, most current PAE systems that employ external mechanical scanning methods struggle to meet the requirements of stability and compactness. Additionally, the complex internal environments of the gastrointestinal tract and other organs highlight the issue of defocusing [158], which significantly affects image quality. Secondly, endoscopic imaging often requires capturing more information beyond optical absorption, posing greater challenges for sensor design.

Endoscopic ultrasound (EUS) provides detailed structural information of various tissues based on their different acoustic impedances [159–161]. Although EUS offers greater penetration depth, the contrast is often low. The combination of PAE and EUS can provide complementary contrasts, allowing simultaneous acquisition of both functional and anatomical information of tissues. Furthermore, the integration of both modalities is facilitated as PAE and EUS share the same sensor. Currently, gastrointestinal visualization examinations in clinical practice typically involve the use of endoscopy. However, in order to further diagnose and ensure the accuracy of the diagnosis, doctors often need to perform a biopsy by removing a small portion of the suspicious lesion during endoscopy. Although this is a standard diagnostic method, endoscopic examinations only provide surface morphological information of the gastrointestinal wall [162]. These findings do not reveal the layered architectural and functional information. Additionally, the diagnostic accuracy is limited by the number and size of the samples available. To overcome the limitations of traditional gastrointestinal endoscopy, various techniques such as endoscopic ultrasound (EUS), optical coherence tomography (OCT) [163–166], near-infrared fluorescence (NIRF) [167–169], and multiphoton imaging have been applied in the gastrointestinal tract. These techniques visualize layered structures and microvasculature, detect early-stage diseases, and assess the therapeutic response of exogenous optical contrast agents. This represents an important step towards non-invasive comprehensive characterization of gastrointestinal diseases. However, a key parameter, the oxygen saturation ($_sO_2$) level, still lacks imaging capability. Additionally, the use of contrast agents during NIRF imaging increases invasiveness and may pose safety concerns. Endoscopic photoacoustic (PA) imaging provides molecular contrast with depth information, allowing simultaneous visualization of structural and functional information. It has attracted significant research interest and has been applied for the characterization of gastrointestinal diseases, including vascular mapping, measurement of $_sO_2$ saturation, and evaluation of elasticity.

4.1. PAE-US applications of gastrointestinal tract

Researchers have made significant advances in the field of endoscopic imaging of the gastrointestinal tract. In a study depicted in Fig. 15a, they developed a disposable endoscopic photoacoustic-
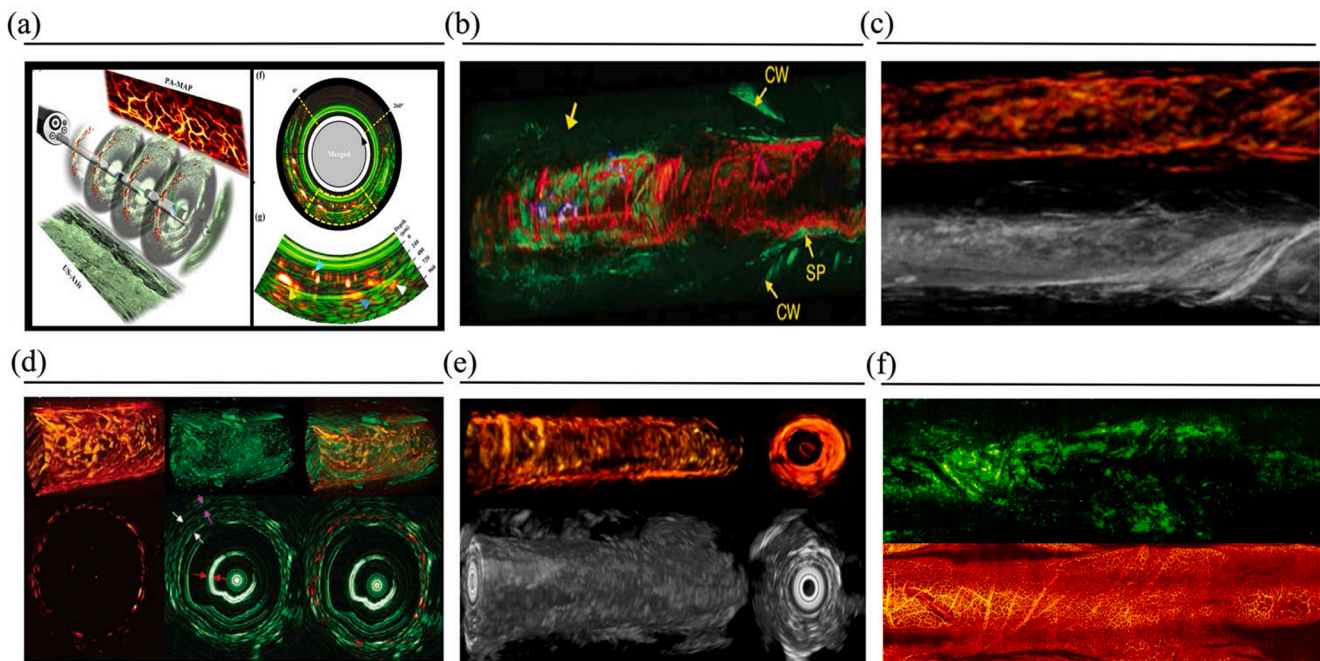
Fig. 15. PAE-US gastrointestinal imaging applications. (a)Schematic diagram of intra-instrument channel workable, PA, and US dual-mode imaging [170]. (b)Three-dimensionally rendered photoacoustic-ultrasonic structural image [33]. The right side of this image is closer to the anus, and the negativey axis corresponds to the ventral direction of the animal. The red and green colors correspond to photoacoustic and ultrasonic signals respectively. (c) Three-dimensional photoacoustic/ultrasound endoscopic imaging of a healthy rat rectum in vivo [171]. (d) Imaging results of a healthy rat rectum. 3D PAE-US images of the rectum, and fused photoacoustic and ultrasound images [172]. (e) 3D endoscopic PA and US images of the rat rectum [173]. (f) Three-dimensionally rendered, merged US (green)-PAE (red) pseudo color image acquired from a rat colorectum in vivo over a ~ 6.4 cm range with a ~ 5.3 mm image diameter [174]. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

ultrasound probe system for in vivo imaging of the gastrointestinal tract [170]. The system combines photoacoustic and ultrasound modes to provide detailed anatomical images of the gastrointestinal tract. The researchers improved signal detection and imaging depth by utilizing a high-throughput relay-based design, enhancing the capabilities of endoscopic imaging. Additionally, the disposable nature of the system reduces the risk of infection, making it a safe choice for clinical applications. In a study depicted in Fig. 15b, the researchers developed a dual-mode endoscopic probe capable of simultaneously acquiring photoacoustic and ultrasound signals, enabling comprehensive imaging and functional assessment [33]. The integrated photoacoustic and ultrasound endoscopic system enables real-time imaging of tissue morphology, blood flow, and oxygen saturation, providing valuable functional information for clinical applications. In a study depicted in Fig. 15c, researchers developed a dual-mode endoscopic system that combines both photoacoustic and ultrasound imaging modes for in vivo imaging. This system integrates photoacoustic and ultrasound imaging, enabling comprehensive visualization and characterization of tissues and organs [171]. By combining the structural imaging capability of ultrasound with the functional imaging capability of photoacoustic imaging, researchers have obtained complementary information about tissue composition and physiology. This study demonstrates the feasibility and potential applications of the dual-mode photoacoustic-ultrasound endoscope, providing valuable insights for disease diagnosis, treatment monitoring, and minimally invasive interventions.

Partial research has also been conducted on the miniaturization of PAE-US systems. For example, in Fig. 15d, researchers have developed a miniaturized catheter probe for obtaining high-resolution images of biological tissues [172]. The catheter probe utilizes a hybrid optoacoustic lens and a ring-shaped transducer array to achieve both optoacoustic and ultrasound imaging. This probe effectively overcomes the field-of-view and depth-of-field limitations of traditional endoscopic imaging techniques. Experimental results demonstrate that the probe is highly effective in visualizing anatomical structures and detecting

functional information within the body. The miniaturized catheter design offers advantages of compatibility with standard endoscopic procedures and access to hard-to-reach areas, presenting potential for clinical translation. Additionally, targeted developments have been made in improving the hardware performance of PAE-US systems. Researchers have utilized PMN-PT/epoxy resin 1–3 composite structures to fabricate high-performance optoacoustic and ultrasound transducers [173]. For endoscopic applications (Fig. 15e), a composite transducer has been developed, exhibiting excellent performance in both optoacoustic and ultrasound imaging, including sensitivity, bandwidth, and imaging depth. In vitro and in vivo experiments have validated the superior performance of the transducer, demonstrating its potential for high-resolution and high-contrast imaging of biological tissues. The development of this composite transducer offers a promising solution for optoacoustic and ultrasound imaging in endoscopic surgeries, providing a new avenue to improve diagnostic accuracy and guide clinical interventions. In the study depicted in Fig. 15f, researchers have designed and fabricated a compact microprobe system that integrates OR-PAM and ultrasound imaging into a standard endoscope [174]. The microprobe system utilizes fiber-optic-based optical transmission and an array of ultrasound transducers to achieve real-time imaging. Experimental results have demonstrated the excellent performance of the microprobe system in high-resolution imaging of gastrointestinal tissues, allowing visualization of microvascular networks and tissue structures. The introduction of the microprobe system has enhanced the diagnostic capabilities of gastrointestinal endoscopy and provided new possibilities for improving the detection and personalized treatment of gastrointestinal diseases.

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validated the superior performance of the transducer, demonstrating its potential for high-resolution and high-contrast imaging of biological tissues. The development of this composite transducer offers a promising solution for optoacoustic and ultrasound imaging in endoscopic surgeries, providing a new avenue to improve diagnostic accuracy and guide clinical interventions. In the study depicted in Fig. 15f, researchers have designed and fabricated a compact microprobe system that integrates OR-PAM and ultrasound imaging into a standard endoscope [174]. The microprobe system utilizes fiber-optic-based optical transmission and an array of ultrasound transducers to achieve real-time imaging. Experimental results have demonstrated the excellent performance of the microprobe system in high-resolution imaging of gastrointestinal tissues, allowing visualization of microvascular networks and tissue structures. The introduction of the microprobe system has enhanced the diagnostic capabilities of gastrointestinal endoscopy and provided new possibilities for improving the detection and personalized treatment of gastrointestinal diseases.

In clinical practice, conventional coronary angiography is commonly used to identify stenotic areas caused by plaque formation through two-dimensional visualization of the coronary arteries. However, it lacks the necessary spatial resolution to resolve tissue-level information of the arterial wall, thus limiting its effectiveness in studying vulnerable plaques. The development of modern intravascular imaging techniques aims to address this limitation. Intravascular ultrasound (IVUS) and intravascular optical coherence tomography (IVOCT) are currently the most important clinical modalities. IVUS, with its penetration depth, enables full-depth visualization of the coronary artery lumen, vessel wall, and atherosclerotic plaque formation, and has been routinely used

in clinical practice since the early 21st century. IVOCT offers high resolution ranging from 1 to 15 μm and can measure fibrous cap thickness. However, IVOCT has limited penetration depth and practicality in larger plaques, while IVUS lacks the resolution needed for visualizing microstructures. Additionally, IVUS and IVOCT have limited sensitivity in studying chemical composition and quantifying tissue mechanical properties, which are crucial indicators of plaque vulnerability. Intravascular near-infrared fluorescence (NIRF) and near-infrared spectroscopy (NIRS) are capable of providing molecular contrast with high sensitivity for characterizing lipid content within lesions but lack depth information. In contrast, intravascular photoacoustic (IVPA) imaging can provide highly sensitive molecular contrast while maintaining superior imaging depth of ultrasound, allowing simultaneous mapping of the vessel wall and lipid content. Research teams have developed various intravascular photoacoustic imaging systems and conducted relevant validations and evaluations, resulting in a series of significant research achievements. Below, we will briefly introduce selected research contents of intravascular PAE-US.

4.2. PAE-US applications of intravascular

Fig. 16a illustrates an intravascular photoacoustic imaging system capable of acquiring intravascular images in two different frequency ranges: 35 MHz and 80 MHz. The research results demonstrate that intravascular photoacoustic imaging at both frequencies can provide clear vascular images. The imaging results obtained at these two frequencies can be compared to analyze the imaging capabilities of different frequencies on intravascular structures and tissues [175]. In
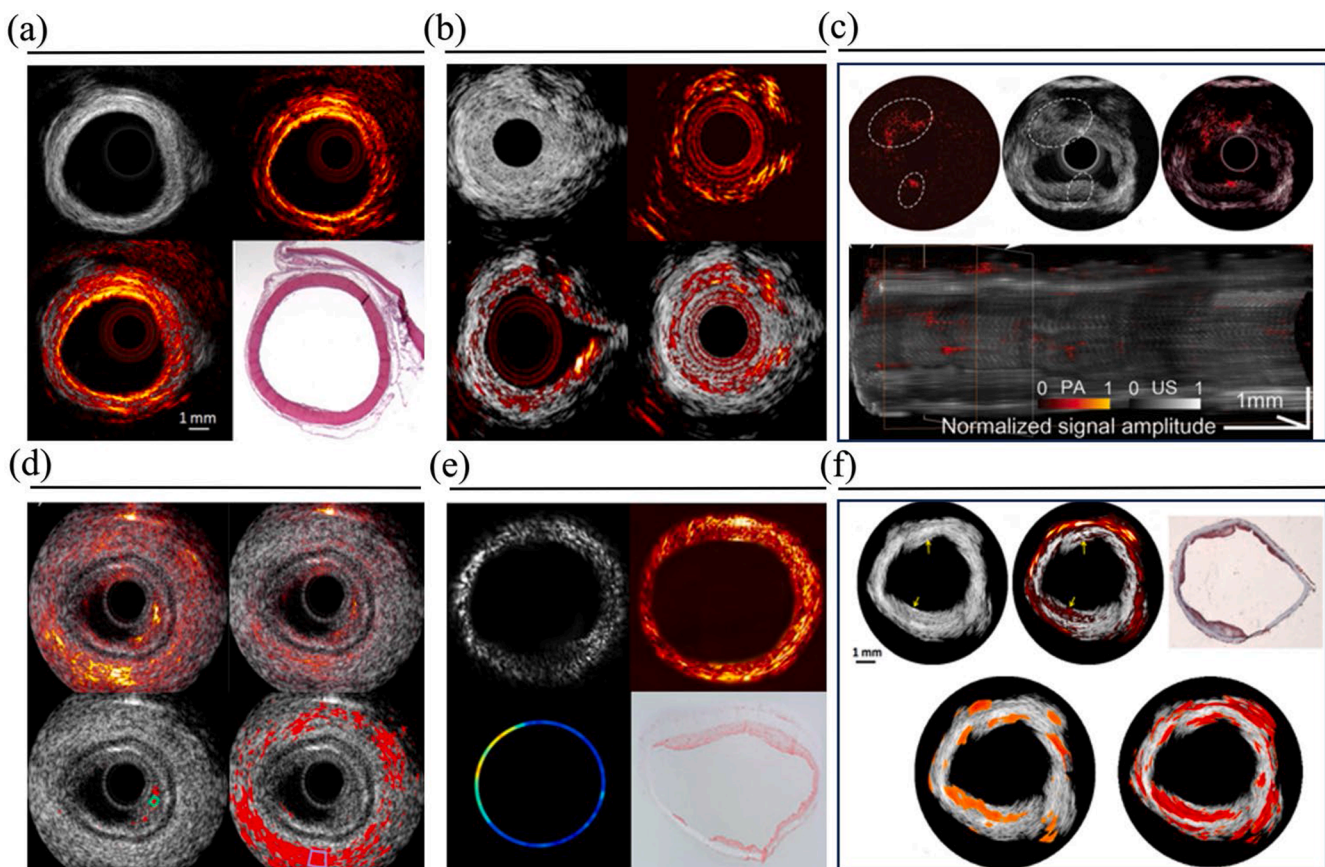
Fig. 16. PAE-US intravascular imaging applications. (a) Cross-sectional IVUS, IVPA, and fused images of a healthy rabbit aorta at 35 MHz, and hematoxylin-eosin (H&E)-stained histology image [175]. (b) PAE-US images of an atherosclerotic rabbit aorta acquiredin the presence of blood [176]. (c) Ex vivo PAE-US image of the atherosclerotic rabbit abdominal aorta [150]. (d) Lipid detection in an early stage atherosclerotic human coronary artery [177]. (e) Cross-sectional and histological images of the normal vessel, the lipid-less plaque, and the lipid-rich plaque, respectively [178].(f) US and combined PAE-US(1210 nm wavelength) images of the atherosclerotic vessel [179].

Fig. 16b, another intravascular photoacoustic imaging system developed by the research team is presented. This system utilizes the photoacoustic effect to detect the lipid components within atherosclerotic plaques and introduces blood during the imaging process to simulate a realistic vascular environment. The research results demonstrate that, even in the presence of blood, intravascular photoacoustic imaging can effectively detect and image the lipid components within atherosclerotic plaques, indicating its potential for plaque composition imaging in a physiological blood environment [176]. To achieve faster intravascular PAE-US imaging, the research team also developed an intravascular photoacoustic imaging system based on a rapid optical parametric oscillator laser (Fig. 16c). This system enables high-frame-rate intravascular photoacoustic imaging. Within the wavelength range of 1.7 μm, they observed vascular structures and plaque characteristics, demonstrating that using a rapid optical parametric oscillator laser for intravascular photoacoustic imaging enables high-speed imaging and provides clear intravascular structural and plaque images [150]. In addition, to obtain more comprehensive intravascular information using the PAE-US system, researchers developed a spectroscopic-based intravascular photoacoustic imaging system for detecting lipid components in atherosclerotic plaques (Fig. 16d). By analyzing the photoacoustic signals at different wavelengths, they were able to quantitatively identify lipid components within the arterial wall and obtain information about the lipid content and distribution within the plaque tissue [177]. The system depicted in Fig. 16e is an integrated intravascular imaging probe that combines an ultrasound transducer, a photoacoustic probe, and an elastography device. This probe enables simultaneous acquisition of ultrasound, photoacoustic, and elastography data, allowing for a comprehensive assessment of vascular structure, tissue optical properties, and tissue mechanical properties. The research findings demonstrate that the intravascular three-modal imaging system can provide high-resolution vascular structural images, photoacoustic images of intravascular lipid components, and tissue elastography, thereby offering more accurate vascular information for the diagnosis and evaluation of arterial diseases [178].

In addition to the aforementioned studies, a thermomechanical-based intravascular photoacoustic imaging system has been developed, leading to the successful acquisition of high-resolution intravascular images. Through the thermomechanical effect, researchers were able to observe the fine structures of blood vessel walls and the distribution of plaques, providing valuable information about the vascular tissue and plaque characteristics. This thermodynamic intravascular photoacoustic imaging technology holds great potential for clinical applications, offering a new approach for early diagnosis and treatment of vascular diseases such as atherosclerosis [179]. These research findings are of significant importance for understanding and diagnosing the composition and characteristics of atherosclerotic plaques. They also provide strong support for the clinical investigation of intravascular photoacoustic imaging technology in diseases such as atherosclerosis. The emergence of these achievements has marked important progress in the development of intravascular photoacoustic imaging technology, particularly in the areas of high-speed imaging, spectroscopic analysis, multimodal imaging, and thermodynamic imaging. These advancements provide a solid foundation for further research and application of intravascular photoacoustic imaging technology and offer new possibilities for the early diagnosis and treatment of diseases like atherosclerosis.

In addition to the applications of PAE-US in the gastrointestinal tract and blood vessels, the scope of endoscopic applications in the human body is continuously expanding. Relevant studies have been conducted
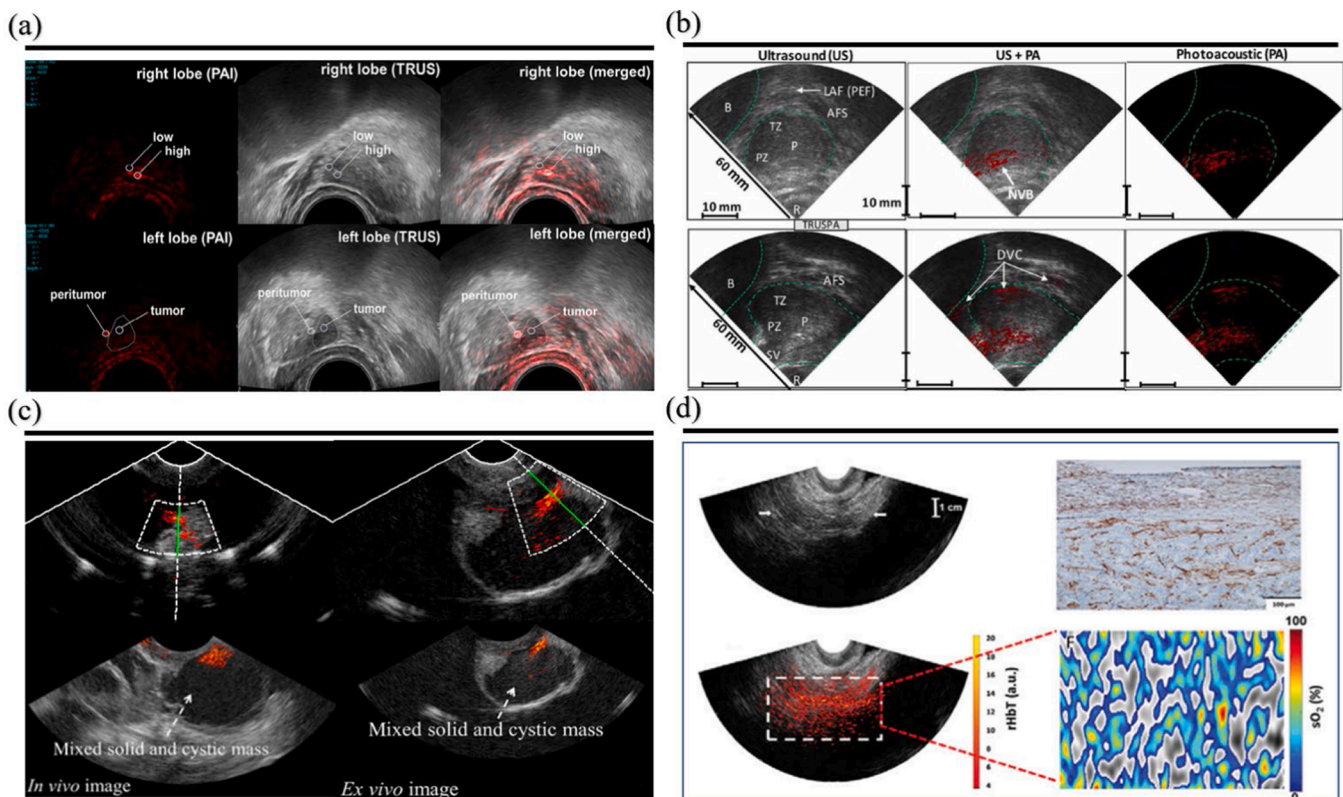
Fig. 17. PAE-US Other duct and organ region imaging applications.(a)PAI images (left), TRUS images (mid), and their merged images (right) of normal prostatic tissues (upper panels) and the index tumors (lower panels) [180].(b) Contrast-enhanced PAE-US imaging of human prostate using intravenous ICG [181]. (c) In vivo coregistered PAE-US image of a postmenopausal ovarian mass and ex vivo coregistered PAE-US image of the same ovary after oophorectomy [182].(d) US image (EC-12R; Alpinion Medical Systems) of the right adnexa (arrows) [183]. The coregistered US and photoacoustic tomography relative total hemoglobin (rHbT) map shown in color, with extensive diffused vascular distribution covering a large area of the region of interest in the depth range of 1–4 cm.

on organ tissues such as the prostate, ovaries, and uterus.

4.3. PAE-US applications of reproductive system organs

In the study depicted in Fig. 17a, researchers conducted experiments using a PAE-US system on tumor-bearing mice and prostate cancer patients [180]. This study assessed the potential of photoacoustic imaging in visualizing angiogenesis in prostate cancer. The researchers compared the photoacoustic images with histological analysis to validate the imaging results. The results of the study demonstrated successful identification of blood vessels associated with prostate tumors using photoacoustic imaging, highlighting its potential for clinical and preclinical applications. Similarly, in a study involving a PAE-US system focused on the prostate (Fig. 17b), researchers obtained images of the human prostate using transrectal photoacoustic and ultrasound imaging systems [181]. Transrectal ultrasound provides real-time structural imaging of the prostate, while photoacoustic imaging provides functional information based on tissue optical absorption characteristics. The authors conducted experiments on healthy volunteers and prostate cancer patients, demonstrating the feasibility of simultaneous transrectal photoacoustic and ultrasound imaging. The imaging results were compared with histopathological analysis to validate the research findings. The results showed that the combined imaging technique provided detailed anatomical and functional information of the prostate. It enabled visualization of structural features and functional parameters related to prostate cancer, such as blood flow and oxygen saturation. In the context of intravaginal imaging of the ovaries, researchers performed in vitro and in vivo experiments using a PAE-US system (Fig. 17c). They obtained images of excised ovarian tissue samples and live animals with induced ovarian tumors [182]. The researchers obtained comprehensive imaging data of ovarian cancer by combining photoacoustic imaging (providing functional and molecular information based on tissue absorption characteristics) and ultrasound imaging (providing structural information). The authors utilized various image analysis techniques to extract quantitative features from the combined photoacoustic and ultrasound images, which were then used to develop classification algorithms for distinguishing healthy ovarian tissue from malignant ovarian tumors.

The results demonstrated that the PAE-US method improved the accuracy of ovarian cancer detection and classification compared to individual imaging modalities. The combined imaging technique enhanced the visualization of tumor vasculature and functional features, thereby improving the ability to differentiate between benign and malignant lesions. Similar experimental results can also be observed in Fig. 17d [183].

4.4. Brief summary of PAE-US

PAE-US imaging has emerged as a comprehensive modality, delivering structural, functional, and molecular insights. This approach effectively addresses the gaps in conventional endoscopy, offering a broader spectrum of diagnostic information, as substantiated by studies in ex vivo tissues and animal models [184]. Leveraging the advancements in intravascular ultrasound (IVUS) technology [185–187], PAE-US imaging systems have undergone significant evolution. When integrated with IVUS, PAE-US enables detailed assessments of arterial wall structures and compositions, heralding a new era in cardiovascular diagnostics. Looking forward, refined PAE-US techniques are poised to become indispensable in clinical settings for the identification of vulnerable plaques, monitoring of plaque progression, and appraisal of interventional therapies.

As technological enhancements continue, PAE-US's role in clinical diagnostics is set to expand. It's particularly effective in evaluating key gastrointestinal disease parameters such as sub-surface structures, vascular system morphology, and SO2 saturation levels. This capability positions PAE-US as a pivotal tool for early detection and staging of gastrointestinal cancers, alongside providing critical guidance in surgical procedures like tumor margin identification. The application of exogenous optical contrast agents in PAE-US enables dynamic monitoring of therapeutic responses in real-time.

In vascular imaging, the acquisition of molecular and elasticity data through PAE-US significantly boosts the precision in identifying vulnerable plaques [188,189]. Despite these advancements, PAE-US is predominantly in the preclinical research phase, necessitating focused efforts towards its clinical application. Presently, PAE-US imaging systems grapple with challenges such as slow imaging speeds, prolonged data acquisition times, bulky sensor sizes, suboptimal sensitivity, and restricted imaging depths. For clinical adoption, pivotal improvements are needed. Paramount among these is overcoming the technical bottleneck related to the speed of PAE-US imaging, primarily due to the lack of suitable laser sources. The development of a high-repetition-rate, high-pulse-energy nanosecond laser, tailored for lipid imaging at optimal wavelengths, is critical for enabling swift and efficient multimodal PAE-US imaging suitable for clinical use. Additionally, enhancing imaging sensors—focusing on reducing their size and advancing miniaturization in photoacoustic endoscopic sensors—is vital for improving portability and facilitating intricate and deeper internal explorations. Equally crucial is the advancement of rapid scanning modules and heightened imaging sensitivity within PAE-US systems."

5. Summary and outlook

Photoacoustic-ultrasound imaging (PAI-US) is an emerging imaging modality that combines the advantages of photoacoustic and ultrasound imaging [190–192]. With advancements in laser and ultrasound detection technologies, there have been many new designs aimed at improving the imaging performance of PAI-US, including spatial resolution, temporal resolution, sensitivity, and imaging depth [193–195]. Despite exciting progress, there are still limitations to be addressed for the clinical translation of PAI-US. In this section, we will discuss the future directions for the development of PAI-US systems, focusing on system hardware and applications [194]. In terms of system hardware, there are several aspects to consider for the future development of PAI-US. An important area of improvement is the integration of photoacoustic and ultrasound imaging systems into a single platform. Traditionally, photoacoustic and ultrasound imaging have been performed independently, requiring separate devices and operational procedures. However, integrating them into a single platform offers several advantages. The integrated platform provides convenience in operation and higher efficiency. By using a single platform for photoacoustic and ultrasound imaging, operators only need to familiarize themselves with one device and one user interface, simplifying the operational workflow, reducing the cost of learning and training, and making it more suitable for the clinical translation of PAI-US systems. Real-time imaging capability is crucial for clinical applications, particularly during surgical procedures. Researchers are striving to develop fast imaging techniques and hardware to achieve real-time photoacoustic-ultrasound imaging (PAI-US) for immediate visualization and assessment during surgery. To achieve real-time PAI-US imaging, improvements in imaging speed and frame rate are required. Researchers are focusing on enhancing the laser pulse emission rate in photoacoustic imaging systems and the data acquisition speed of ultrasound probes to achieve faster image acquisition. Additionally, the use of fast data processing algorithms can expedite image reconstruction and display, enabling real-time image updates. On the other hand, hardware design is also crucial for achieving real-time PAI-US imaging. Researchers are developing smaller and portable devices to meet the demands of surgical settings. These devices require highly integrated photoacoustic and ultrasound modules, as well as real-time data processing and display capabilities [196]. Furthermore, optimizing probe design, optical fiber coupling, and signal isolation are also necessary to reduce surgical interference and improve image quality. Improving image quality and resolution is a focal point in

photoacoustic-ultrasound imaging (PAI-US) [193]. Researchers are actively exploring various methods to enhance transducer technology, laser systems, and data acquisition systems to achieve higher spatial resolution and better image fidelity. In terms of transducer technology, researchers are developing advanced transducer designs and manufacturing methods. This includes improving the material properties, geometric shapes, and construction of ultrasound probes to enhance their sensitivity and frequency response [197]. By optimizing transducer design, signal reception and transmission efficiency can be enhanced, leading to improved signal-to-noise ratio and resolution of the images [198]. Regarding laser systems, researchers are seeking more stable and high-power laser sources. Stable laser output is crucial for obtaining high-quality photoacoustic signals. Additionally, using multi-wavelength laser systems can expand [199] the optical window of imaging and improve the imaging capabilities for different tissue types. Improvements in data acquisition methods are also critical for enhancing image quality and resolution [144,200]. Researchers are developing new signal processing algorithms and image reconstruction techniques to optimize the extraction and processing of photoacoustic signals [201]. These algorithms can reduce noise, enhance image contrast, and improve edge detection and detail preservation. Furthermore, utilizing higher-speed data acquisition systems and parallel imaging techniques can enable faster data acquisition and image reconstruction, thereby improving temporal resolution. In addition to technological and hardware improvements, physiological and tissue factors that affect image quality need to be considered. Researchers are studying the influence of tissue optical properties, sound velocity distribution, and ultrasound attenuation parameters, and developing calibration methods to correct these effects and obtain more accurate image information [202].

Overcoming the limited penetration depth of photoacoustic imaging is a significant challenge. Researchers are exploring various strategies, such as advanced signal processing algorithms, multi-wavelength imaging, and novel photoacoustic contrast agents, to improve deep tissue imaging capabilities [203]. To facilitate the clinical translation of photoacoustic-ultrasound imaging (PAI-US), extensive clinical research is essential to validate its imaging performance and diagnostic accuracy [204]. Such studies can provide quantitative data on the performance, sensitivity, and specificity of PAI-US under various disease conditions [205]. Establishing standardized protocols and benchmarks is critical during clinical research to ensure consistency and comparability of imaging results in different clinical environments. Standardization also enables researchers to compare different study outcomes and drive advancements in the field. Moreover, comparative studies with traditional imaging techniques such as ultrasound and radiology are necessary. By comparing PAI-US with existing imaging methods, the advantages and limitations of PAI-US in diagnosis and monitoring can be assessed. These comparative studies contribute to establishing the clinical significance of PAI-US and provide support for its wider adoption in specific clinical applications. Large-scale prospective studies covering multiple clinical centers and patient populations are also needed. Such studies can evaluate the application of PAI-US in different populations and disease types, providing more compelling evidence to support its clinical use. Additionally, collecting a substantial amount of clinical data and case control information can establish associations between PAI-US imaging parameters and disease diagnosis, prognosis, and treatment response. Finally, ethical considerations and risk assessments need to be taken into account during clinical research. Ensuring the safety and compliance of the study is essential. Researchers should adhere to appropriate ethical review processes and obtain informed consent from patients. Additionally, conducting risk assessments on patients ensures that their participation does not have adverse effects on their health and well-being. By addressing these limitations and focusing on these improvements, the future development of PAI-US imaging holds great potential for clinical applications, including early disease detection, improved characterization of pathological conditions, and guidance for minimally invasive interventions.

In the field of biomedical applications, the future development directions of PAI-US can be discussed and elaborated from the following perspectives. Firstly, PAI-US can provide high resolution and rich tissue information, facilitating the detection and diagnosis of early-stage diseases. For example, in the early diagnosis of tumors such as breast cancer, skin cancer, and liver cancer, PAI-US can offer more accurate imaging information, assisting physicians in early treatment interventions, thus intervening and mitigating severe diseases at an early stage. Secondly, in tumor treatment monitoring and evaluation of therapeutic efficacy, PAI-US can be utilized to real-time monitor the biological behavior of tumors and treatment effects [206]. By observing and assessing tumor vasculature, the effectiveness of treatment can be evaluated, allowing timely adjustments of treatment strategies. For instance, employing PAI-US systems for preoperative lesion localization and postoperative outcome observation in photothermal/photodynamic therapy can significantly enhance the efficiency and efficacy of the treatment. In the field of neuroscience research, PAI-US can offer non-invasive imaging of the structure and function of the nervous system [207]. It can be used to observe changes in brain neural activity, vascular supply, and neurodegenerative diseases, aiding in the understanding of the functionality and disease mechanisms of the nervous system [208]. There have been some studies focusing on Alzheimer's disease, and the results suggest that PAI-US can serve as a powerful tool to understand the pathogenesis of Alzheimer's disease [209–213]. Combined with ultrasound imaging, it enables precise localization of the affected brain regions, allowing comprehensive observation and understanding of the disease's progression, and the formulation of precise treatment plans [214]. Furthermore, in the assessment of cardiovascular diseases, PAI-US can be employed to evaluate the structure and function of the cardiovascular system. It can provide high-resolution imaging of the heart, vessels, and blood flow, aiding in the diagnosis and treatment of diseases such as heart disease and atherosclerosis. As a biomedical imaging technique with tremendous potential, PAI-US has vast opportunities for future development. Through continuous technological innovation and clinical research, PAI-US is expected to play a significant role in early disease detection, treatment monitoring [215], and personalized medicine, bringing forth more innovation and breakthroughs in the field of medical healthcare [216].

CRediT authorship contribution statement

Yinshi Yu: Investigation, Visualization, Writing – original draft. **Ting Feng:** Investigation, Methodology, Supervision. **Haixia Qiu:** Investigation, Methodology, Resources. **Ying Gu:** Investigation, Methodology, Validation. **Qian Chen:** Conceptualization, Formal analysis, Funding acquisition, Investigation, Resources, Supervision. **Chao Zuo:** Formal analysis, Funding acquisition, Investigation, Methodology, Project administration, Resources, Visualization, Writing – original draft. **Haigang Ma:** .

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

No data was used for the research described in the article.

Acknowledgements

Appendix A. An example appendix

Authors including an appendix section should do so after References section. Multiple appendices should all have headings in the style used above. They will automatically be ordered A, B, C etc.

A.1. Example of a sub-heading within an appendix.

There is also the option to include a subheading within the Appendix if you wish.

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