From bench to market: commercialization of photoacoustic imaging

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Abstract: Photoacoustic imaging (PAI) or optoacoustic imaging, the modern application of an ancient physical discovery to biomedical imaging, is without doubt one of the most exciting imaging technologies that has drawn increasing attention from biomedical specialists. In PAI, the rich contrast of optical excitation is seamlessly combined with the high spatial resolution and large penetration depth of ultrasonic detection to produce clear images of optically scattering biological tissues. As a complementary imaging modality that surpasses the territory of traditional microscopic optical imaging, PAI has been explored for numerous biomedical studies, and hence enthusiastically embraced by researchers around the globe who have attested to its unique imaging capabilities, namely the deep penetration and functional sensitivity. Not surprisingly, as the market clearly sees the promise, the commercial production of PAI systems has grown apace with the technological advancements and clinical applications. The adoption of commercial PAI in research and clinical settings has however seen difficulties, majorly due to costs, regulatory blocks, and competition with mainstream technologies. Here, from a practical standpoint, a wide range of commercial PAI systems currently available in the market were introduced, their advantages and disadvantages were analyzed, and the design considerations for targeted applications were emphasized. The key technological, logistical, and clinical issues were also discussed that need to be solved to accelerate the technology translations. By doing so, it is hoped that a clearer picture of the future commercialization of PAI for clinicians, researchers, and industrial entrepreneurs will be presented.

Key words: photoacoustic imaging; commercialization; oxygenation saturation of hemoglobin; tumor imaging; breast cancer imaging; endoscopy

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0 Introduction

In the 1880s, Alexander Bell discovered an interesting physical phenomenon later termed the photoacoustic effect in his pursuit of the photophone[1]. The photoacoustic effect describes the formation of sound waves after light absorption in a medium. Even with his admirable ingenious and insight, he might never have envisioned that his discovery of the photoacoustic effect would one day become one of the most exciting imaging technologies in the 21st century. Although Bell′s original ´photophone´ failed to gather sufficient momentum to see the final commercialization, photoacoustic imaging (PAI) is quickly gaining its share in the world of biomedical imaging, a highly competitive field currently dominated by mainstream techniques such as magnetic resonance imaging (MRI), X-ray computed tomography (X-ray CT), and ultrasound imaging (UI)[2]. MRI is used as a diagnostic tool for its high-resolution imaging of soft tissues, but is disadvantaged by its slow imaging speed and high cost. X-ray CT is another example of electromagnetic waves used in biomedical imaging, and has been highly successful in delineating the skeleton structures. However, the radiation exposure of ionizing X-ray waves is a persisting concern that prevents its applications in interventional procedures or on sensitive patient populations. UI is cost effective and can provide real-time imaging and blood flow information using the Doppler effect. However, UI lacks the contrast sensitivity in soft tissue required to image early-stage tumors and small lesions. PAI, on the other hand, can effectively bridge the gaps of other mainstream imaging modalities.

PAI is based on the photoacoustic effect discovered by Bell, where ultrasonic waves induced by optical excitation into biological tissue are detected outside the tissue and used to reconstruct the original local optical energy (or heat) distribution[3-8]. Because PAI naturally combines biological tissue′s two important properties, namely, rich optical absorption contrast and weak acoustic scattering, it has shown clear advantages in retrieving anatomical, functional, molecular, metabolic, and histologic information at depths not achievable by traditional optical imaging. In this sense, compared with other imaging modalities, nature is extremely generous to PAI, which happens to exploit three optical, mechanical and physical properties of the biological tissue.

(1) Although 99% of the mass of the human body is made up of six elements (oxygen, carbon, hydrogen, nitrogen, calcium, and phosphorus), the combination of these elements has produced thousands of different molecules with their own optical absorption features. Such a high diversity in optical absorption has provided sufficient ´fingerprints´ for PAI to identify different tissue components. More importantly, many molecules′ optical properties are closely correlated with their microenvironment and can faithfully reflect the functional status of the tissue, which allows PAI to probe many physiological functions with only endogenous contrasts. In addition to the endogenous molecules in the tissue, most exogenous molecules developed for biomedical imaging also have distinctive optical absorption features, which provided PAI with intrinsic molecular sensitivity.

(2) While biological tissue is generally unsuitable for the propagation of photons in the visible and near infrared regimes by imposing high scattering and thus attenuation, it is significantly more ´straightforward′ for acoustic waves. The acoustic scattering in tissue is roughly 1 000 times weaker than the optical scattering. In other words, tissue is opaque to photons but transparent to sound. The strong optical scattering limits traditional microscopic optical imaging to 1 mm or so in tissue due to microscopy′s reliance on unscattered photons. By contrast, the weak acoustic scattering has provided ultrasound imaging with high spatial resolutions at depths up to tens of centimeters,

and this exact property also gives PAI the privilege to harness the scattered photons and explore the tissue′s optical features at depths far beyond traditional optical imaging.

(3) Photons and ultrasound are entirely different waves, but the energy conversion between the two different formats via the photoacoustic effect, governed by a composite parameter called Grunesien coefficient, is just efficient enough to allow generation of detectable ultrasound waves without causing photothermal damage to the tissue. More specifically, at body temperature, every degree of local temperature rise induced by the optical excitation results in about an 800 Pa rise of pressure. Fortunately, such a pressure rise is readily detectable for commercial ultrasound transducers.

These tissue properties have collectively enabled the translation of the physical phenomenon to a powerful biomedical imaging tool. With the above unique imaging capabilities, PAI has seen a vast market for clinical and research opportunities, and thus strong commercial potentials. Biomedical imaging manufactures around the globe are clearly tracking this potential market and accelerating their development of commercial PAI products. So far, there are around ten commercial PAI devices currently available in the market. They fall within three major imaging device categories: computational tomography, microscopy, and endoscopy. The implementations of these devices differ based on this categorization and the specific clinical and research needs determined by their manufacturers. Most devices are currently being used for the imaging of small animals and waiting for the approval by the FDA for clinical use. Although the future is promising, the commercialization of PAI technologies faces several key hurdles that need to be overcome before they can be widely adopted in biomedical research and clinical settings. Three pressing hurdles are (1) the cost and safety concerns for the use of high-power pulsed lasers, (2) the limited penetration depths for many internal organs, and (3) the lacking of matched clinical applications where PAI has clear advantages over other imaging modalities.

In this review, we start with a recollection of the history of PAI technologies, and then provide an overview of the commercial PAI ecosystem to date. We describe the available devices, discuss their key features, and summarize their relevant applications. We continue with a more practical look at the current technological, logistical, and clinical hurdles faced by commercial PAI devices and their potential solutions. At last, we conclude with a discussion on future considerations for researchers and technologists with regards to design and engineering specifications that PAI technology can look forward to.

1 A brief history of PAI

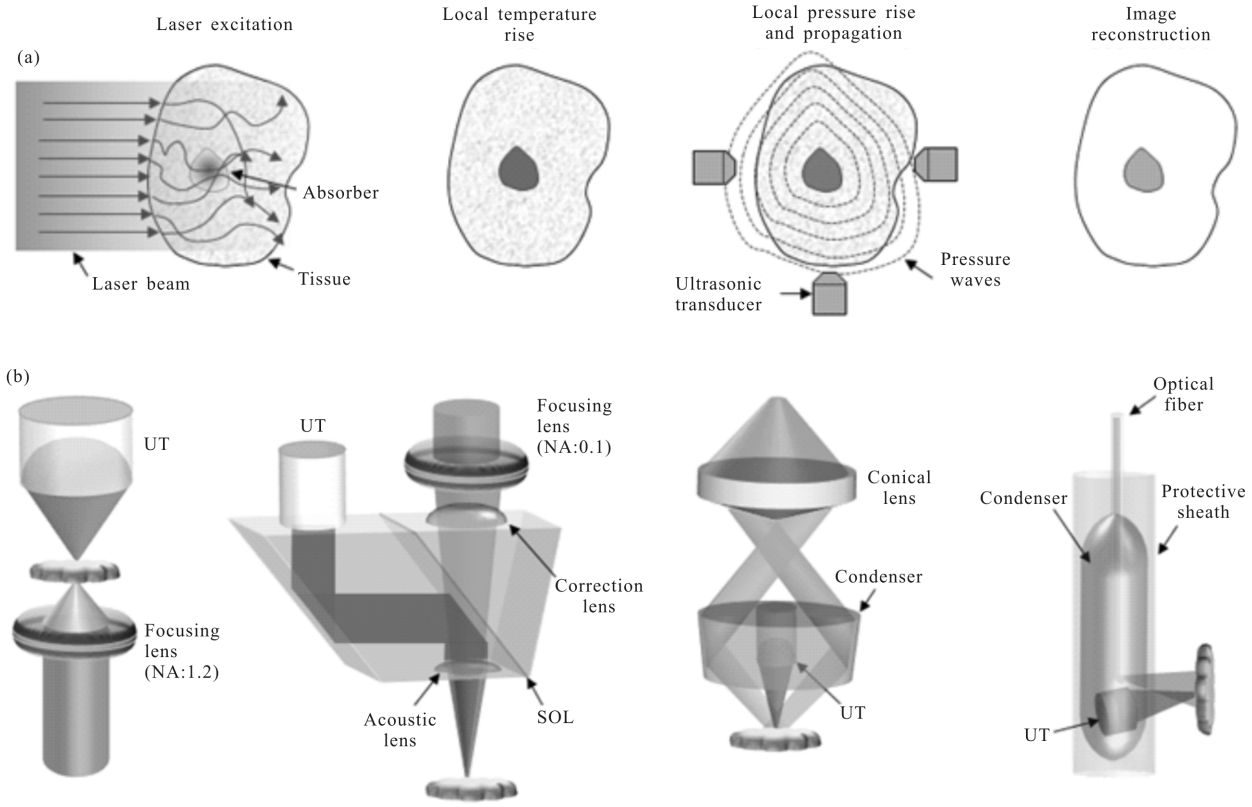
PAI and its many other sister technologies based on the photoacoustic effect have a lengthy history [9]. The photoacoustic effect was discovered by Alexander Graham Bell in 1880, with the first intention for a wireless communication device ‘photophone’. This invention was overshadowed by the then much more efficient Marconi′s radio, but set the important conceptual foundation for modern high-bandwidth telecommunication using optical fibers. During the following 100 years, while the fundamental mechanisms of photoacoustics had been substantially clarified, the research interest in applying the photoacoustic effect had experienced several revivals with long interval dormant times. Important works included optico-acoustic spectroscopy of gases by Veingerov[10], pulsed radiation-induced elastic waves by Michaels and White [11-12], short laser pulse induced stress waves by Amar[13], and ultra-sensitive gas optoacoustic spectroscopy by Kreuzer[14].

It was not until 1980s that Bowen demonstrated the first depth-resolved photoacoustic imaging by radio-wave excitation [15]. Around the same time, Rosencwaig reported the first photoacoustic spectroscopy of biological materials by using optical

excitation[16-17], a precursor of photoacoustic imaging. In the 1990s, with the advent of high-power pulsed lasers, laser-induced photoacoustic imaging was successfully demonstrated as a promising biomedical imaging modality by Oraevsky and Kruger[18-23], although early photoacoustic imaging had little lateral resolution(~6 mm). Since 2000, with coherent advances in laser and ultrasound technologies as well as image reconstruction, cross-sectional and volumetric photoacoustic imaging developed with substantially improved lateral and axial resolutions[5,24-39]. Within this period of time, several milestones were reached in anatomical, functional, and molecular photoacoustic imaging [40-49]. For a comprehensive history of photoacoustics, readers are referred to a comprehensive review article by Manohar and Razansky[50].

2 General schematics of a PAI system

In Fig.1, Figure 1 (a) is imaging principle of PAT. When a short laser pulse is fired at the biological tissue, some photons are absorbed by biomolecules, and their energy is converted into heat through nonradiative relaxation of excited molecules. The local temperature rise induces a local pressure rise, which propagates as an acoustic wave through the tissue and reaches an ultrasonic transducer or transducer array. The received signals are used to form an image that maps the original optical energy deposition inside the tissue. Figure 2(b) representatives PAM systems, where the ultrasonic transducer (UT) and the light beam are confocally aligned to achieve optimal detection sensitivity. We also show a side-viewing intravascular PA catheter with an outer diameter of 1.25 mm, including the protective sheath in which the catheter rotates[51]. Figure 2(c) representatives PACT systems with ultrasonic transducer arrays (UTA)[52]. The laser beam is usually expanded and homogenized by a diffuser to provide wide-field illumination. We also show a PACT system with a 2D Fabry-Perot interferometer as the acoustic sensor [47]. The PA waves are recorded by raster scanning a probing laser beam over the surface of the interferometer. Note that the acoustic coupling



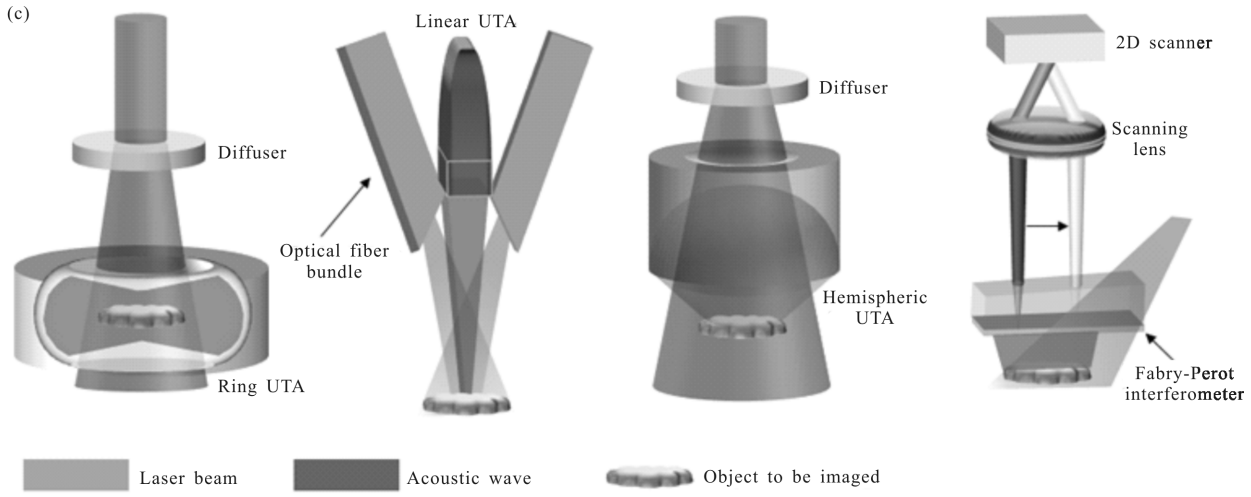


Fig.1 Principle and representative implementations of photoacoustic imaging

medium (typically water or ultrasound gel) is not shown in the schematics. Adapted with permission from reference[9].

A PAI system usually consists of a pulsed light source, an ultrasonic detection system, and a data acquisition system. The light source is typically a short laser pulse from a solid-state laser that activates the biological tissue. Biomolecules, such as hemoglobin, nucleic acids, lipids and water act as optical agents. They absorb photons propagating through the optically excited tissue from the laser excitation. The absorption dynamics vary depending on the light source wavelength and pulse rate of the light source. Through non-radiative relaxation, a significant amount of the energy absorbed is converted into heat. The generated heat produces pressure that propagates in the tissue as an ultrasonic wave (Fig.1(a)).

The transducer component of the device detects these ultrasonic waves outside of the tissue. Ideally, the bandwidth of the transducer array should fall into alignment with the bandwidth of the signals originating from the biological optical absorbers at the desired imaging depth. The data acquisition system amplifies and digitizes the signals. PAI systems also typically include a computer for system synchronization, data collection, and image formation. The schematics of the device also vary depending on the requirements of the specific imaging modality. The modalities of photoacoustic tomography are further broken down into photoacoustic microscopy(PAM) and photoacoustic computational tomography (PACT). In PAM, image capture is based on focused-scanning image construction(Fig.1(b)). This is executed through repeated scanning of a focused excitation light beam and/or a focused single-element ultrasonic transducer. Photoacoustic endoscopy (PAE) is a special type of PAM. In PACT, the emphasis is on inverse reconstruction of images through widefield illumination and multi-element transducer arrays to detect acoustic waves at multiple locations (Fig.1(c)).

3 Commercial devices

The advantages provided by PAI systems have inspired the production of several commercial PACT systems, including a PAM device from Microphotoacoustics and a PAE device from Vibronix. The systems differ systematically across laser pulse rates, wavelengths, transducer array element number, and ultrasound frequency. On the front end, some devices have programmable user interfaces. Most devices are only being used for small animal research and have not achieved FDA approval, and those that are, only have approval for the ultrasound components.

3.1 Commercial PACT devices

PACT devices are distinguished by multi-element ultrasound transducer arrays to reconstruct 2D and 3D images by merging data from all transducer elements. They have the largest representation among commercial PAI devices with the Endra Nexus 128, Thera Medical MSOT, Tomowave Laboratories LOIS 3D, PA Canon, Twente PA Mammoscope, and Imagio.

3.1.1 Endra Nexus 128

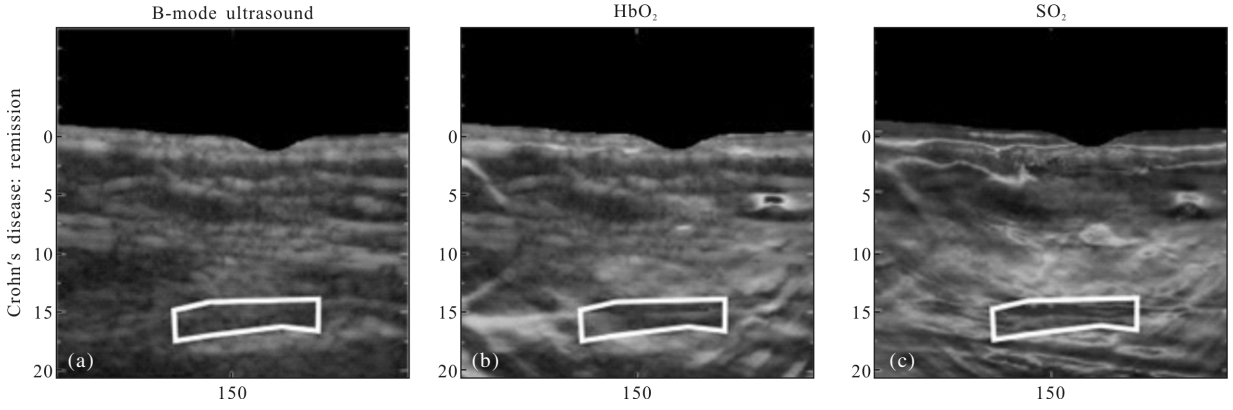
The Nexus 128 from Endra Life Sciences is considered to be the first commercially available photoacoustic device of its kind[53]. An early innovation, the manufacturer directly recognized Robert Kruger′s 2003 research on thermoacoustic imaging of small animals as inspiration for its technology. It was built to image in vivo mouse models of cancer and quantify tumor development and responses to therapy. The advantages of the Nexus 128 over prior PACT systems are its minimal animal preparation and short scanning time. With the Nexus 128, the ultrasonic medium is a built-in feature. The transducer array is water-filled, so the animal being imaged is placed on a disposable animal tray above the detector array and does not have to be submerged in water as an additional preparation step. The acquisition sequence of the Nexus 128 synchronizes the recording of the photoacoustic signals with the laser pulses as the detector array is rotated around the animal.

3.1.2 Fujifilm and visualsonics VEVO LAZR

The VEVO LAZR PACT system is marketed for applications in tumor analysis. Its 256 −element transducer array captures high frequency ultrasound from 13−55 MHz, much higher than the range of its competitors such as Nexus 128. Therefore, it can provide greater spatial resolution and detect multiple contrast agents in vivo simultaneously. Typically, PAM devices have a higher ultrasound frequency to the order of 50 MHz, and PACT devices have ultrasound frequencies to the order 5 MHz. VEVO LAZR comes as an exception to this convention with both a 256 −element transducer array and high frequency ultrasound detection. The VEVO LAZR system also emphasizes its programmable software interface. Massachusetts General Hospital utilized VEVO LAZR for photoacoustic imaging and data analysis, including a "split screen" feature where a previously acquired image can be compared side-by-side to the real-time image[54]. The particular therapy the researchers were tracking was photodynamic therapy (PDT).

3.1.3 Thera medical MSOT

MSOT provides the option of 64, 128, or 256 transducer elements. A distinguishing feature of the technology is the FastPK analysis of kinetic processes, using a laser-integrated pulse energy meter to measure the kinetics of a molecular probe. The MSOT Acuity is a clinical device with a handheld detector. It was FDA approved for a gastroenterology study at the Erlangen Department of Medicine in Germany to evaluate the device′s ability to noninvasively track the inflammation of the gastrointestinal tract in patients with Crohn′s disease (Fig.2). MSOT technology was



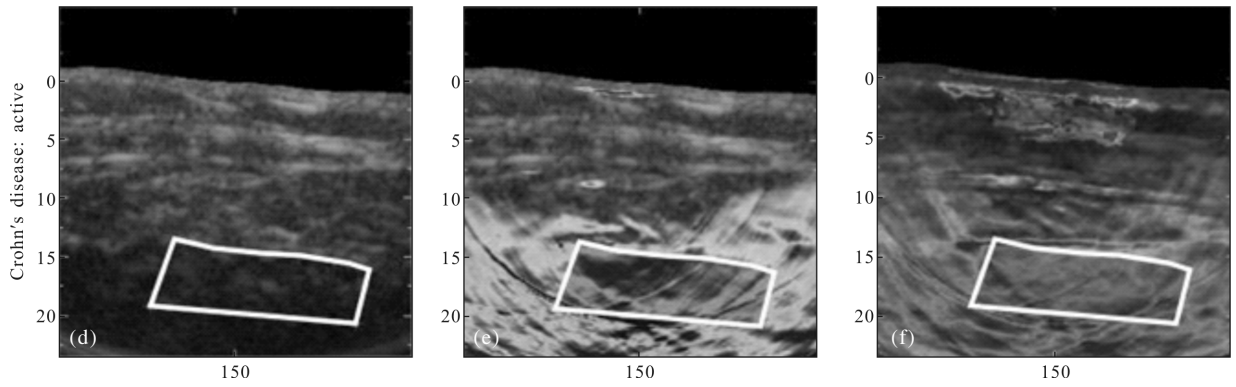


Fig.2 Hemoglobin tracking with MSOT in patients with Crohn′s disease, showing increased oxygenation in Crohn′s disease patients. Adapted with permission from[24]

combined with B-mode ultrasound imaging to locate parts of the intestine where photoacoustic detection of hemoglobin oxygenation was taking place. The study found MSOT to be an effective method for monitoring Crohn′s disease symptoms[24].

3.1.4 Tomowave laboratories LOIS-3D

LOIS -3D is Tomowave Laboratory′s laser optoacoustic imaging system. With its illumination by 4 optical fiber bundles, it achieves over 300 microns of resolution throughout the field of view allowing it to image microvessels down to 50 microns in size. This degree of resolution allows it to couple with chemical contrast agents like nanoparticles, molecular dyes, or fluorescent proteins. Tomowave used the LOIS-3D to track optical activity in mice before and after insertion of gold nanorods (GNRs) and map the distribution of the GNRs in the mice′s circulatory system after observed accumulation in the liver, spleen, and kidneys (http://www.tomowave.com/uploads/1/4/0/5/14059460/19_2011_spie_oat_mouse_gnr.pdf).

3.1.5 Canon PA mammography system

The emphasized application of Canon′s photoacoustic mammography system developed in conjunction with Kyoto University is the early detection of breast cancer (http://www.canon.com/technology/approach/special/md_image.html). The laser system has a tunable wavelength in the range of 700-900 nm and acoustic waves are captured by a 354-element transducer array. The image reconstruction algorithm applies the unique peak absorption of HbR and HbO_2 at 756 and 797 nm to calculate and project saturated oxygen concentration values in the region of interest[55]. It specifically visualizes angiogenesis in cancerous tissue by assessing the concentration of oxygen and can further characterize the cancer as benign or malignant due to the growing cancerous region having a lower oxygen concentration than the surrounding tissues (Fig.3). Forty female patients with primary breast lesions participated in a breast scanning study with the Canon device. Of these patient scans, 29 showed lesion-associated PAI signaling, and the oxygenation levels in the lesions had a lower oxygen concentration than the normal breast regions.

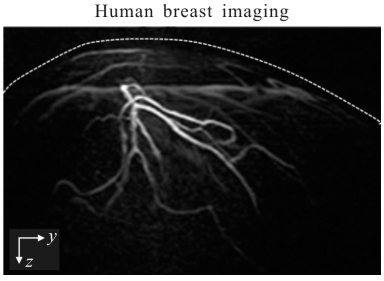


Fig.3 Human breast imaging using hemispherical-array based PACT system. Adapted with permission from[56]

3.1.6 Twente PA mammoscope

The Twente PA mammoscope is also built for breast cancer detection. In this system, the

mammoscope is integrated into a hospital bed on which the patient lies for the breast scan. The signal processing and image reconstruction algorithm removes signal noise from the breast surface tissue. It also back projects the signals over spherical geometries and acknowledges the angular position of the transducer elements with respect to the physiological tissue to ascertain possible points of origin in the tissue. Imaging was done on patients with breast malignancies to evaluate the performance of the Twente PA mammoscope, and the results showed high contrast for breast malignancies irrespective of breast density. The contrast also excluded cysts in the high contrast regions. Some of the limitations of the mammoscope were its inability to determine accuracy with tumor size and shape and some signaling overlaps between the skin and interior tissue[57].

3.1.7 Imagio Seno Medical

In Imagio, Seno Medical has another PACT device applied towards breast cancer imaging also operating on angiogenesis and oxygenation to identify tumors (http://senomedical.com/content/view/10/12/). The device applies two laser colors to provide excitation in the ranges appropriate for oxy-and deoxy-hemoglobin, water, and lipids. Absorption spectra from these four endogenous agents provides qualitative differentiation in imaging results. The imaging probe sits underneath the patient bed and the 64-element transducer array is arranged in a hemicylindrical configuration for data acquisition. Fifteen patients were observed on the Imagio at the University of Texas Medical Branch. Photoacoustic images obtained at two wavelengths showed enough qualitative differentiation to distinguish between benign and malignant tumors.

3.2 Commercial PAM devices

Unlike PACT, PAM applies a focused, single-element transducer to construct an image directly[7]. Because its optical illumination and acoustic detection are confocally aligned, PAM optimizes detection sensitivity. It reaches spatial resolutions ranging from sub-micrometer to sub-millimeter, and imaging depths from a few hundred micrometers to a few millimeters.

3.2.1 Microphotoacoustics OR-PAM/AR-PAM

Microphotoacoustics, Inc. is the manufacturer of commercial PAM devices. The device name references the functionality of switching from optical resolution modes (OR-PAM) at 5 Hz B-scan rates to acoustic resolution modes (AR-PAM) at 50 Hz B-scan rates. The system also switches from a single-mode fiber laser to a multimode fiber laser through a configurable lens. The single-mode laser provides more lateral resolution in the optical setting, and the multi-mode laser allows for more acoustic energy in the acoustic setting[58]. The flexibility between the two modes allows for both high-resolution images of shallow features and functional, lower resolution images of deeper structures. The Microphotoacoustics system was applied to assess vascular differences in human skin from different regions up to 1 mm beneath the surface of the skin. OR-PAM/AR-PAM systems also have the potential to image the same sample both ways and merge the results in order to capture both shallow (high resolution) and deeper (low resolution) structures simultaneously.

3.2.2 Vibronix endoscopy devices

Photoacoustic endoscopy (PAE) is still an emerging modality with respect to the other photoacoustic modalities. In PAE, the system has the technical challenge of delivering light pulses, detecting ultrasonic waves, and performing area or line scanning at the tip of a small probe[45]. It has shown promising results in terms of improving on existing endoscopic applications, such as early stage tumor detection, submucosal lesion diagnosis, and in situ characterization of diseased tissues[59]. The Vibronix intravascular photoacoustic (IVPA) catheter was developed at Purdue University to detect unstable plaque in cardiovascular disease. The team identified that slow imaging speeds was a significant shortcoming in existing IVPA systems. Such systems lack an ideal laser source with the capacity to induce

high speed excitation of molecular overtone vibrations. The Vibronix IVPA utilizes a 2-kHz master oscillator power amplifier pumped, Barium nitrate Raman laser to improve imaging speed by two orders of magnitude. By constructing a Raman laser that can output at 1 210 nm wavelengths, it is possible to excite the greater concentration of hydrocarbon bonds in lipids at their absorption peaks. This functionality enables imaging to decipher thickness of the lipid core in the artery. Being able to combine both ultrasound and photoacoustics, could allow a physician to not only observe the chemical properties of the lesion, but also the vulnerability caused by its vascular location[60]. To address the engineering challenge behind size, the device implants a ring-shaped transducer with a concentrically aligned optical fiber into the catheter. The optical fiber and the electrical wire are contained in a torque coil that rotates the tip of the probe directly.

4 Design considerations in commercial PAI systems

The aforementioned devices are highly representative of the current state of photoacoustic devices in the commercial domain. Each has specifications towards particular clinical and research applications, and are currently mainly being used towards research on small animals. As photoacoustics becomes more commercialized, the design considerations of the system will play a greater role at large. The major areas of consideration are quality control, light sources, multimodality imaging, and contrast agents.

4.1 Quality control

The most significant barrier of commercial entry is FDA and clinical approval determined by quality control and safety measures. The common method of testing photoacoustic systems in the non-approved state is the development of phantom controls. Developing a sound method to evaluate imaging systems is crucial before moving on to animal and human imaging studies. In one such study, a stable phantom was developed from polyvinyl chloride plastisol (PVCP) to be able to compare and evaluate the acquisition precision of photoacoustic imaging instruments[61]. Endra′s Nexus 128 and Fujifilm and VisualSonics VEVO LAZR were compared. The VEVO LAZR had a shorter acquisition speed, but the Nexus 128 had a better imaging depth because of the differences in ultrasound frequency detection. The more important finding was that the results aligned with the design specifications of each imaging device. Thus, the PVCP phantom was found to be a suitable control for evaluating the performance of imaging systems.

The safety of PAI systems is another area of concern. Exogenous contrast agents used to enhance molecule targeting and contrast resolution are typically unsafe due to tissue toxicity and nonspecific uptake all over the body. Endogenous contrast agents, on the other hand, such as hemoglobin, melanin, and lipids are by nature biologically safe [62]. Successful photoacoustic applications should prefer endogenous contrast agents over exogenous ones to accelerate the regulatory process.

The laser system is another important safety concern. The American National Standards Institute (ANSI) specifies a maximum exposure limit of 26.4 mJ/cm^2 given a 760 nm laser[63]. A research team at Johns Hopkins University studied the minimal energy required to image carotid arteries in a sheep brain hidden by bone. Their results show promise for imaging vessels within the safety standard limits by modifying the optical fiber bundle design in a way that optimizes laser diameter with energy output.

4.2 Light sources

In addition to safety concerns, one of the greatest difficulties with commercializing PAI is the cost and size of the laser system. Some laser companies are exploring alternatives to the laser light source in PAI. For example, light-emitting diodes (LED) are cheaper

and more compact than laser systems. The Prexion Corporation in Tokyo has created a PAI system that uses a LED light source instead of a laser. Prexion managed to capture the image of a needle in a handmade agar phantom using LED[64-65]. The LED system has been shown to overcome its lower pulse energy by adjusting to higher pulse repetition frequencies (200 Hz PRF) and averaging many signals over a short period of time. The Department of Medical Physics and Bioengineering at the University College London applied LED as an excitation source for a blood vessel phantom. The blood vessel phantom was excited by a 623 nm high power LED at 10 times its rated current in a solution of intralipid to reproduce biological scattering effects of tissue.

Another useful aspect of LEDs is the ability to enact a wide range of wavelengths from 400-905 nm simultaneously through a multicolored LED. A multicolored device can apply all of its wavelengths simultaneously. This is useful in improving signal to noise ratio. The UCL study drove all wavelengths of a four-colored device to improve the overall signal-to-noise ratio to 71 from 21, 6, 30, and 32, which were the values at the individual emitted wavelength. Pulsed-laser diodes are another possible cost effective replacement for lasers.

4.3 Multimodality imaging

Multimodality imaging, the pairing of two or more imaging modalities, presents another advantageous aspect of PAI [43,66-70]. The most common pairing is that of photoacoustic technology with existing ultrasound technology. For example, the previously discussed Erlangen gastroenterology study effectively mapped Crohn′s disease using the Thera Medical MSOT simultaneously with a B-mode ultrasound imaging system. A research team at the University of Buffalo and Pohang University of Science and Technology developed the first multimodal photoacoustic imaging machine based on an existing ultrasound imaging system[71]. The system includes an FDA approved commercial ultrasound machine with programmable function. A portable pulsed laser system with a Q-switched Nd:YAG pump laser was added to the ultrasound system to generate pulsed laser illumination. The laser system is coupled to fiber bundles that are integrated with an ultrasound transducer as a handheld probe that illuminates the object of interest and receives returning acoustic waves. The ultrasound machine is modified to mute ultrasound wave transmission, receive PA waves after laser illumination of the target, and implement an altered image reconstruction algorithm based on the different delays of the PAI and ultrasound imaging sequences. The system follows clinically mandated safety guidelines, and shows promising results for human applications.

4.4 Contrast agents

The diversity of contrast agents opens up the applications for PAI devices. Systematic coupling of safe contrast agents with a commercial PAI implementation can lead to even greater imaging performance than previously seen, and even have the potential to deliver therapeutic agents and enhance multimodal imaging[26,30,42,43,46,72-83].

Contrast agents can be roughly categorized into dyes, nanoparticles, fluorescent and nonfluorescent proteins. Dyes are usually molecules that bind at the nanometer scale and can be removed naturally through the urinary system. The combination of PAI and fluorescence molecular tomography can provide more accurate diagnosis than just PAI by itself. Dyes can also bind with great anatomic and functional specificity. The two most commonly used plasmonic noble metal nanoparticles used are of gold or silver. These contrast agents provide advantages with their optical absorption, surface plasmon resonance, surface modification, and maturity of preparation. Gold is a highly optically adaptable due to its malleability of size and shape. It can be implemented as a nanosphere, nanoshell, or nanorode among other options. The average size gold nanoparticle is able to absorb five orders greater than any conventional dye.

The use of silver nanoparticles is sometimes preferred as it demonstrates stability, less toxicity, and biocompatibility.

As discussed previously, multimodal imaging presents great engineering advantages for obtaining information from biological tissues, which would require multimodal contrast agents. For example, magnetic nanoparticles such as gold-iron oxide could be highly applicable to MRI-photoacoustic imaging systems. Such a contrast agent would yield even greater contrast for PAI systems than previously achieved. Microbubbles are contrast agents that can be used for ultrasound-PAI systems. The gas-filled bubbles would generate strong acoustic scattering with respect to the surrounding tissue. The irradiation of "triggered nanodroplets" containing drops of liquid perfluorocarbon caused a liquid-to-gas phase transition which produced an enhanced contrast compared to the traditional generation of acoustic waves from solely thermal expansion.

4.5 Engineering challenges

The engineering challenges vary by system category. For PACT, the difficulties lie in high-speed data acquisition with the multi-element transducer arrays. Data acquisition system with more than 128 channels are available commercially, but are costly. A potential solution is a multi-channel acoustic waveguide with a single-channel detection system. In OR-PAM, the biggest challenge is the confocal alignment of the optical excitation stream and the acoustic detection system. Endoscopy is again challenged by developing all systematic requirements within the tip of the catheter. Reducing overall size and cost is the overarching themes with engineering design of PAI systems. A calculated combination of light source, ultrasonic transducer system, and scanner should be chosen according to the desired imaging output. As demonstrated by the applications of the above devices, the applications of PAI include but are not limited to tumor analysis, gastrointestinal disease tracking, and plaque detection in cardiovascular disease. For all of these applications, the matching to a particular PAI system mainly concerns the desired imaging depth, imaging speed or temporal resolution, and imaging contrast.

5 Conclusion

Lastly, we′d like to mention that countless patents for new photoacoustic devices are currently pending approval. The last 10 years have seen a nearly tenfold increase in the photoacoustic device patent filings (https://relecura.com/reports/Photoacoustic_Imaging_Landscape.pdf). One such successful project comes from a collaboration between a group of European entities: MIRA, a biomedical photonics engineering group, Quantel Laser Diode, a laser company, SILIOS technologies, an optics company, and ESAOTE, an ultrasound company. The product is a compact and ergonomically designed handheld probe connected to a portable ultrasound system for real-time, inexpensive photoacoustic ultrasound imaging. Among some of the other novel patents being filed, Covidien has devised a system with noise reduction signal processing, Samsung has applied a mirror apparatus to achieve a specific optical incidence angle on the target, and Siemens has developed a photoacoustic gas sensor. As more and more innovation occurs in the space, PAI will increase its presence and applicability.

The commercial horizon for photoacoustic imaging signifies great potential for clinical and research-based imaging. The facilitation of this process is a design and engineering challenge based on a thorough understanding of the applications and users of the systems. If the developers of these systems keep in mind aspects such as quality control, light delivery, multimodality, and contrast agents, PAI devices should expect to see more FDA and clinical approval and adoption by physicians and scientists.

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