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Looking Deeper: Multimodal and Contrast Enhanced Photoacoustic Imaging offer a clearer view within tissues for more accurate diagnosis

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Optical imaging modalities such as fluorescence microscopy, multi-photon microscopy, and optical coherence tomography (OCT) have been well-established for high optical contrast and high spatial resolution imaging of biological tissues. However, as they are dependent on ballistic photons, these methods fail to image beyond ~1 mm or so inside biological tissue. In contrast, diffuse optical imaging (DOI), which uses multiple scattered photons for imaging, can image much deeper (up to a several centimeters) into the tissue. Unfortunately, due to strong light scattering in tissues, it fails to maintain the high resolution at deeper imaging depth. Photoacoustic imaging (PAI) bridges this gap of imaging deeper with high resolution and contrast by combining optical excitation with acoustic detection [1].

Multimodal Photoacoustic Imaging

In spite of PAI having a great potential as a stand-alone modality to provide functional and structural information, it is the multimodal approach that will bring out the best from PAI. Recently, multimodal imaging has received significant interest in clinical and preclinical applications because of the potential it has to provide complementary information for more accurate diagnosis and treatment. PAI also can be integrated with several other imaging modalities, such as thermoacoustic (TA), ultrasound (US), and optical imaging modalities (e.g., fluorescence imaging (FLI), diffuse optical tomography, and OCT).

Photoacoustic (PA) and thermoacoustic (TA) imaging are hybrid imaging modalities that can provide both high ultrasonic resolution and high contrast owing to light or microwave/radio-frequency (RF) absorption. The absorption reveals optical or dielectric properties of the tissue that are closely related to its physiological and pathological state. Attempts have been made to develop a dual-modality early breast cancer diagnostic imaging system using combined PA and TA techniques. Both PA and TA imaging share similar ultrasound receiving mechanisms used in conventional ultrasound pulse-echo imaging. The ultrasound pulse-echo images are produced based on the reflection of the sound waves from the internal tissue structures in the body. Thus, in the conventional ultrasound imaging, ultrasound pulses are sent inside the body and echoes (reflected sound waves from various parts of the body) are recorded using the same ultrasound probe. Therefore, it is technologically convenient to combine PA, TA,

and ultrasound in a single modality to offer triple modality imaging with three different contrasts (optical absorption, RF absorption, and ultrasound scattering).

Several dual and trimodality systems have been investigated that could provide complementary information to improve the diagnosis and for the evaluation of new drug therapies. For breast cancer staging, noninvasive photoacoustic imaging combined with a clinical ultrasound system was used [2] for the sentinel lymph node detection in a small animal model. An imaging depth of 5 cm was successfully demonstrated with this system. Currently, it is under clinical trial and positive results are expected on human patients as well in the near future.

A portable handheld probe (Fig. 1a) combining PA/US modalities was developed and demonstrated for *in vivo* imaging of the human finger proximal interphalangeal (PIP) joint [3]. The pulsed laser source was smartly integrated inside the ultrasound probe to make it a real portable device with great potential for the clinical use. Fig. 1b shows the combined PA/US image of the sagittal plane of the PIP joint. The sagittal ultrasound image shows the skin and the underlying bone. The PA image shows the skin and blood vessels running parallel to the finger. The deeper PA signals correspond to the reflections of the PA signals on the bone. Moreover, researchers are also looking into combining elasticity imaging and photoacoustic imaging using these types of integrated ultrasound systems with photoacoustic. Information about both mechanical and optical properties of the tissue may help doctors to diagnose certain diseased conditions better than using only mechanical or only optical properties in isolation.

Fig. 1 (a) Handheld probe integrating pulsed diode laser and ultrasound detection array. (b) PA/US image of a human finger proximal interphalangeal joint in sagittal plane. Here heat color is PA, and gray color is US data. Figure reproduced from Ref. [3] with permission.

Recently, trimodality systems combining PA/TA/US, PA/US/FL (Fluorescence), and also PA/TA/MRI (Magnetic Resonance Imaging) have been investigated. Fig. 2 shows a nude mouse (Fig. 2a) and corresponding complementary contrast image provided by an integrated PA/US/TA system [4]. Ultrasound revealed bone structures, PA is sensitive to hemoglobin distribution, and TA maps soft tissue and fat distribution. Optical and dielectric properties provided by the PA and TA imaging can also be combined with anatomical structure provided by MRI to make tumor identification easier. Researchers are also working towards combining these three modalities together.

Fig. 2 (a) Photograph of a nude mouse placed inside the tube, and (b) PA/TA/US co-registered image of the mouse. Here, red is PA, blue is TA, and green is US data. Figure reproduced from Ref. [4] with permission.

Pure optical imaging provides images with high optical contrast and high spatial resolution, albeit with shallower imaging depth due to high light scattering in tissue. The depth limitation in conventional optical imaging modalities could be surmounted by adopting PA imaging, which maps optical absorption at ultrasound resolution along the tissue depth. Fluorescence imaging is a highly sensitive molecular imaging technique that can provide the target information through fluorescence contrast at optical resolution. Optical absorption and fluorescence contrast can be simultaneously acquired by combining PAI and FLI in a single system. As a preclinical application, the combined PAI+FLI system was capable of simultaneously mapping vascular and lymphatic networks and providing multi-physiological parameters (Hb oxygen saturation and oxygen pressure) to study tumor angiogenesis, metastasis, and microenvironments *in vivo*.

In addition, OCT can provide optical scattering-based contrast, which can reveal surrounding tissue microstructure. Typically, OCT provides a 1–10 μm spatial resolution and a 1–2 mm penetration depth in biological tissues. Various PAI+OCT systems have been built and used for potential applications in dermatology and ophthalmology as they will be able to provide both scattering and absorption contrast simultaneously. Researchers were able to image microanatomy and microvasculature of the rat retina *in vivo* successfully with such multimodal systems.

Diffuse optical imaging (DOI) is a noninvasive technique that utilizes near infrared light to measure the optical properties of physiological tissue. The technique relies on the object under study being at least partially light-transmitting, so it works best on soft tissues such as breast and brain tissue. High resolution PAI can be combined with low resolution DOI. DOI can provide the local optical fluence distribution, which in turn can help in PAI to extract the optical absorption coefficient accurately as the PA signal is proportional to the product of the optical absorption coefficients and the local fluence. Thus, the combination of PAI+DOI can provide quantitative optical absorption

information. Quantitative measurement of optical absorber concentration is extremely important for accurate imaging of *in vivo* physiological functions such as tumor hyper-metabolism and brain functions.

Contrast Enhanced Photoacoustic Imaging

Endogenous contrasts in our bodies are hemoglobin, melanin, water, lipids, etc. These chromophores can produce strong PA signals in the visible (e.g., 400 – 700 nm) or infrared (e.g., > 1000 nm) spectral region, where light cannot penetrate tissue deeply. Thus, to achieve deep-tissue PAI we need to use near-infrared (NIR, 700 – 900 nm) light as a PA excitation source. Therefore, additional NIR absorbers (exogenous) are required to maximize the capability of PAI. Organic dyes, inorganic and organic nanostructures, color-enhanced microbubbles, and fluorescence proteins have been investigated as PA contrast agents. Small molecules such as indocyanine green (ICG) and methylene blue are the first and most clinically relevant PA contrast agents. However, the systemic circulation times, optical absorption abilities, and surface modification abilities of these small molecules are relatively poor.

Nano-formulations overcome these limitations. Among them, gold nanostructures have been extensively explored as PA contrast agents thanks to its bio-inertness and excellent optical absorption property. Yet, its renal clearance is not efficient, and thus gold nanostructures tend to be accumulated in livers and spleens. Light-absorbing organic nanoplateforms have also been demonstrated as PA contrast agents, including porphyrin-lipid conjugates and polymeric nanoparticles. The soft natures of the organic nanoparticles can enhance the biodegradability, but the biocompatibility has not been fully studied yet. Once targeting ligands are conjugated with the nanoformulated agents in order to bind to receptors overexpressed in diseased tissues, these nanocomplexes can be selectively accumulated in the diseased areas and the PA signals within the region of interest can be boosted. This type of molecular imaging is referred to as targeted contrast enhanced PAI.

As an example, organic nanoformulated naphthalocyanines (also called nanonaps) have been recently developed for PA gastrointestinal (GI) tract imaging. The nanonaps were designed to withstand harsh environments in stomachs and intestines and avoid systemic absorption [5]. Optically, nanonaps are extremely stable at a high concentration (i.e., non-shifting optical spectra) and absorbing in a NIR spectral region (i.e., optical density > 1000). The clinical translation of the nanonaps was potentially enhanced by solubilizing naphthalocyanines in Pluronic F127, an FDA-approved surfactant for oral administration. Fig. 3 shows noninvasive and nonionizing real-time PA and US imaging of the GI tract after oral administration of the nanonaps in a live mouse. The progression of the nanonaps through the intestine was clearly pictured by PAI, while ultrasound imaging provided the detailed surrounding anatomical features.

Fig. 3 (a) Optical absorbance of nanonaps synthesized from BPc (blue), ZnBNc (dark green), BNc (light green), or ONc (bronze). (b) Photograph of BPc, ZnBNc, BNc, and ONc nanonaps from left to right. (c) Non-invasive depth-encoded PA maximum amplitude projection image of the mouse intestine following gavage of 100 optical densities of ZnBNc nanonaps. (d) Real-time transverse PA (pseudo color) and US (grey) imaging of the mouse intestine following gavage of 100 optical densities of ONc nanonaps. Figure reproduced from Ref. [5] with permission.

In summary, several multimodal imaging systems have been developed with PAI and various application areas are being explored. Hopefully, more information coming from the multimodal imaging systems will help us to better understand our body and help prevent occurrence of diseases or at least diagnose them early. Contrast enhanced PAI is expected to play a major role in molecular imaging due to its deep penetration, high resolution, real-time imaging capability, cost-effectiveness, and nonionization. The key issue in contrast enhanced PAI is the use of clinically relevant (i.e., biocompatible and biodegradable) contrast agents with strong NIR absorption. The potential clinical applications for this technology include diagnosing cancers, delineating tumor margins, monitoring treatment outcomes, identifying metastatic lymph node, counting circulating tumor cells, monitoring GI tracts, as well as others.

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