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Review article

Hand-held optoacoustic imaging: A review

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ABSTRACT

Optoacoustic imaging is a medical imaging modality that uses optical excitation and acoustic detection to generate images of tissue structures based up optical absorption within a tissue sample. This imaging modality has been widely explored as a tool for a number of clinical applications, including cancer diagnosis and wound healing tracking. Recently, the optoacoustic imaging community has published a number of reports of *hand-held* optoacoustic imaging devices and platforms; these hand-held configurations improve the modality's potential for commercial clinical implementation. Here, we review recent advancements in *hand-held* optoacoustic imaging platforms and methods, including recent pre-clinical applications, and we present an overview of the remaining limitations in optoacoustic imaging that must be addressed to increase the translation of the modality into commercial and clinical use.

1. Introduction

Optoacoustic Imaging(OAI), also known as Photoacoustic Imaging(PAI), is a method of imaging that utilizes the generation of mechanical waves due to light absorption by chromophores within tissue (Fig. 1) [1]. More specifically, the terminology of OAI is used to describe the light-induced sound phenomena that occurs when the excitation light is within the visible and near-infrared portion of the electromagnetic spectrum [2]. If the excitation energy is within the radio-frequency or microwave region, the imaging technique is instead referred to as *Thermoacoustic Imaging*. These two mechanisms of signal generation have been exploited for a wide range of applications over the past several decades, from gas spectroscopy [3], to thin film characterization [4], to studies of photosynthesis [5]. In 1982, Olsen published the first paper reporting successful 2D imaging with biomedical potential [2]. In the 1990s, optoacoustics began to be more seriously explored for applications in medical imaging due to advances in both laser light sources and acoustic detection equipment [6]; this was followed soon after by the first report of an *in vivo* imaging system in 1993 by Chen et al. [2].

The premise of using optoacoustics in medical imaging is straightforward. First, the tissue of interest is illuminated by a sufficiently short pulse of light, such that the pulse length satisfies both the thermal and stress confinement conditions [7]. This light is absorbed by specific components within the tissue, such as hemoglobin or lipids, generating a mechanical wave whose frequency is in the ultrasound regime. These signals can be detected by an ultrasound sensor, or array of ultrasound sensors, and the signals can be used to form an image with any of a variety of image reconstruction algorithms currently available in the literature [8]. The resulting contrast of the image is based upon the distribution of absorbed optical energy within the tissue, which is related to the wavelength of light used and the optical properties of the tissue under study [7].

The primary safety concern in OAI is the damage to tissue due to light exposure [9]. Most studies use the maximum permissible exposure (MPE) limits set forth by the American National Standards Institute (ANSI), which has written guidelines for the use of lasers in medicine [9,10]. The limits described by the ANSI define the MPE for a single, short pulse of laser light (1–100 ns pulse length) with a wavelength between 400–700 nm to be 20 mJ/cm^2, and 100 mJ/cm^2 for wavelengths between 700 and 1400 nm. The ANSI also provides MPEs for applications that used repeated pulsed light. Other safety concerns for OAI include damage to the eyes of patients and practitioners. This may be addressed using common safety controls for lasers, which includes appropriate eye protection and engineering controls such as curtains.

Because OAI relies upon the absorption of light for signal generation and the detection of ultrasound waves for signal acquisition, it presents several advantages over other medical imaging modalities, such as optical microscopy and ultrasound imaging. For example, typical high resolution, light-based imaging, such as optical microscopy or optical coherence tomography (OCT), have limited penetration depths in tissue due to the significant scattering of light within the tissue, making it

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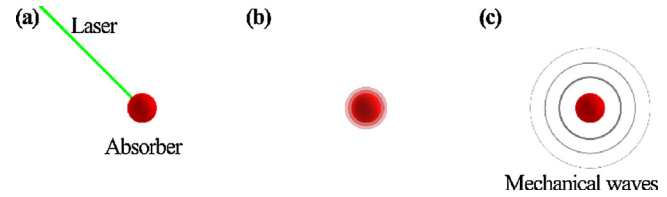

Fig. 1. The process of signal generation in optoacoustic imaging. (a) Light is absorbed. (b) The absorber undergoes thermoelastic expansion. (c) A mechanical wave is generated.

difficult to clearly image fine structures beyond ~1 mm [6,11,12]. Ultrasound-based imaging systems, on the other hand, have a greater imaging depth than light-based systems, but are hampered in their ability to differentiate between soft tissue structures because of their similar mechanical properties. The modality relies on the acoustic mismatch between tissues to generate contrast, which is associated with their mechanical properties; soft tissues do not generate a substantial amount of acoustic differences [13]. In contrast, OAI combines the excellence of structure differentiation of light-based imaging with the imaging depth of ultrasound-based imaging: generation of optoacoustic signals is dependent on light absorption, making it possible to target specific biological compounds, such as hemoglobin and lipids, depending on the wavelength used [1]. The incident light, then, only needs to reach the target and be absorbed in order to generate the acoustic signal. Moreover, unlike light, ultrasound waves experience relatively little scattering in tissue, allowing for signals that are generated deep within the tissue to be reliably detected, pushing the OAI modality far beyond the limits of either light-based or ultrasound-based modalities [14].

In addition to the aforementioned advantages, OAI is scalable in terms of the resolution at which it can image: it can be used for macroscopic (753,500 μm) [15,16], mesoscopic (4.530 μm) [17,18], and microscopic imaging (1550 μm) [19]. Macroscopic imaging *via* the OAI modality, which is frequently accomplished using Optoacoustic Computed Tomography (OACT), is, for instance, capable of imaging entire organs [20]. Optoacoustic Microscopy (OMi), on the other hand, can be used to image small sections of tissue, such as capillary beds and subcellular structures. This OAI method can be divided further into two classes based on how resolution is achieved: acoustic resolution (AR-OMi) and optical resolution (OR-OMi). In AR-OMi, the resolution of the system is determined by the acoustic detection components, whereas in OR-OMi, the resolution is determined by the properties of the excitation light. In order to capture the continuous scalability of OAI, so-called 'switchable' or 'hybrid' AR- and OROMi systems have been developed [21,22]. These systems can employ either AR- or OR-OMi methods by simply adjusting some of their components, demonstrating the power of OAI scalability. Lastly, Optoacoustic Mesoscopy (OMe) fills the gap between OACT and OMi, and has recently emerged as a valuable addition to the OAI suite [23–26]. Different OAI methods relevant to *hand-held* platforms are discussed in detail in Section 2. Hand-held optoacoustic imaging platforms are typically defined as platforms that contain either a 'free' imaging head, *i.e.*, are not rigidly attached to some supporting structure and whose position is able to be manipulated by the user, *or* are connected to an articulated arm and easy to manipulate by the user. Fig. 2 shows the different OAI methods and the relationships among the methods.

As previously mentioned, specific targets can be singled out using different wavelengths for optoacoustic signal generation. This is known as multispectral or spectroscopic OAI and has been used to selectively image compounds such as oxy-/deoxygenated hemoglobin or lipids [27,28]. In this technique, at least two separate wavelengths are used to interrogate the tissue, and the magnitude of the resulting optoacoustic response at each wavelength is used to determine the prevalence of the target of interest. This can become complicated, however, by the need

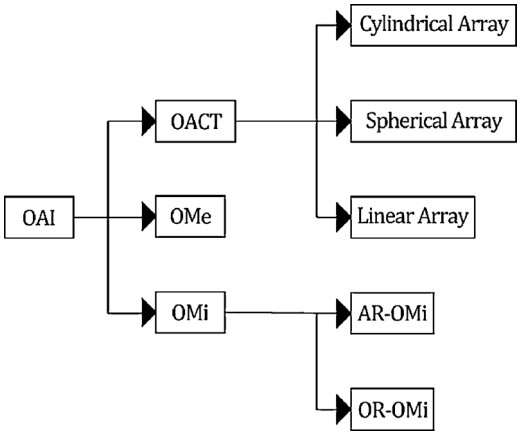

Fig. 2. A diagram showing the different methods of the OAI modality that are currently used in hand-held platforms, based on published literature. In this figure, we have separated the OAI modality into three general methods, based on the instrumentation and image forming methods used. Some of these methods can be further classified by the specifics of their instrumentation or their operation. We note that all of these methods can use both single wavelength excitation and multiple wavelength excitation (multispectral aka spectroscopic OAI), which provides another layer of functionality for the OAI modality.

to account for the wavelength-dependent nature of light propagation in tissue when analyzing the amplitude of optoacoustic signals that originate from a particular volume of tissue [29]. Multispectral or spectroscopic OAI can be used with all of the aforementioned OAI methods. For instance, spectroscopic OACT, often termed multispectral optoacoustic tomography (MSOT), has found much success in applications such as visualizing oxygen saturation in the vasculature around tumors, imaging tumors in breast tissue, visualizing sentinel lymph nodes (SLNs), and visualizing vasculature deep in tissues, among others [30–39]. Additionally, spectroscopic OMe, often termed multispectral optoacoustic mesoscopy (MSOM), has been used for selectively imaging melanin and blood, as well as visualizing the structure of skin in patients with psoriasis [18,40]. Lastly, quantitative OAI, a technique that uses multispectral OAI, seeks to quantitatively determine the concentration of a target; Quantitative OAI has proven more challenging because the fluence must be accurately modeled throughout the tissue so that it may be accounted for during signal processing [8]. Interested readers are referred to references [41] and [42] to learn more about spectroscopic OAI methods.

There are several metrics for evaluating OAI platforms. The first three are the axial, lateral, and elevational resolutions, analogous to ultrasound imaging [43–45]. These describe the spatial resolution of the platform along the imaging axis (axial), perpendicular to the imaging axis on the image plane (lateral), and between image planes (elevational). Other metrics include temporal resolution, contrast, and sensitivity. Temporal resolution is a measurement of how quickly a platform can acquire and generate images; high temporal resolution platforms are critical for improving the utility of OAI and reducing image artifacts [1,46]. Contrast is typically measured as either the signal-to-noise ratio (SNR) or the contrast-to-noise ratio (CNR). SNR is defined as the average background signal over the standard deviation of the background signal [47], whereas CNR is defined as the intensity of signal that arises from the region of interest minus the average noise, divided by the standard deviation of the background signal. Lastly, sensitivity describes the minimum concentration of a target compound that the platform can detect [12].

Over the last two decades, OAI has been used in numerous studies, some of which we will list here to showcase its clinical applications. Common applications include imaging melanoma [19,48–50], imaging vasculature in various organs to indicate the presence of tumors