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Review article

Photoacoustic tomography of blood oxygenation: A mini review

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ABSTRACT

Photoacoustic tomography (PAT) is a hybrid imaging modality that combines rich contrast of optical excitation and deep penetration of ultrasound detection. With its unique optical absorption contrast mechanism, PAT is inherently sensitive to the functional and molecular information of biological tissues, and thus has been widely used in preclinical and clinical studies. Among many functional capabilities of PAT, measuring blood oxygenation is arguably one of the most important applications, and has been widely performed in photoacoustic studies of brain functions, tumor hypoxia, wound healing, and cancer therapy. Yet, the complex optical conditions of biological tissues, especially the strong wavelength-dependent optical attenuation, have long hurdled the PAT measurement of blood oxygenation at depths beyond a few millimeters. A variety of PAT methods have been developed to improve the accuracy of blood oxygenation measurement, using novel laser illumination schemes, oxygen-sensitive fluorescent dyes, comprehensive mathematic models, or prior information provided by complementary imaging modalities. These novel methods have made exciting progress, while several challenges remain. This concise review aims to introduce the recent developments in photoacoustic blood oxygenation measurement, compare each method's advantages and limitations, highlight their representative applications, and discuss the remaining challenges for future advances.

1. Introduction

Photoacoustic (PA) Tomography (PAT), also referred to as optoacoustic tomography, is a hybrid imaging modality that combines optical contrast and ultrasound image formation. In PAT, the target is illuminated by a short laser pulse and the absorbed photon energy is converted into heat, leading to a transient local temperature rise. The temperature rise induces a thermal-elastic expansion that generates a local pressure rise and emits acoustic waves. Therefore, PAT detects the acoustic signals generated by optical absorption from either endogenous chromophores (*e.g.*, oxygenated (HbO_2) and deoxygenated hemoglobin (HbR)), or exogenous contrast agents (*e.g.*, nanoparticles and organic dyes) [1,2]. As acoustic waves are much less scattered in tissue than photons, PAT can generate high-resolution images in both the optical ballistic and diffusive regimes. Two major implementations of PAT exist: photoacoustic computed tomography (PACT) and photoacoustic microscopy (PAM) [1–5]. PACT reconstructs the image in the diffusive regime with wide-field illumination and acoustic detection at multiple locations using a transducer array. PAM images targets in the quasi-ballistic and quasi-diffusive regime with focused excitation light and/or a focused single-element ultrasonic transducer for direct image formation [1,6].

The wide choices of contrast agents allow PAT to play an increasingly important role in both preclinical research and clinical practice with its applications in vascular biology [7–9], oncology [10–12], neurology [13–15], ophthalmology [16–18], dermatology [19–21], gastroenterology [22,23], and cardiology [24,25]. Among all the endogenous chromophores, hemoglobin is one of the major absorbers at wavelengths below 1000 nm. Using HbO_2 and HbR, PAT can image vascular structure, oxygen saturation of hemoglobin (sO_2) [26], blood flow speed [27], and metabolic rate of oxygen [28]. sO_2, or blood oxygenation, is defined as the fraction of HbO_2 relative to total hemoglobin concentration in blood. At wavelengths between 650 nm and 900 nm, both HbR and HbO_2 have an optical absorption coefficient that is at least one magnitude larger than those of other chromophores such as lipids and water at physiologically realistic concentrations (Fig. 1) [29,30]. Although within this wavelength range melanin has a higher absorption coefficient than HbR and HbO_2, it is highly localized in the skin or retina and thus does not contribute to the oxygenation quantification. Such strong preferential absorption of HbO_2 and HbR allows high-contrast visualization of the blood-perfused vasculature in PAT images [31].

The measurement of oxygen saturation of hemoglobin (sO_2) is no doubt one of the most important applications of PAT. Normal

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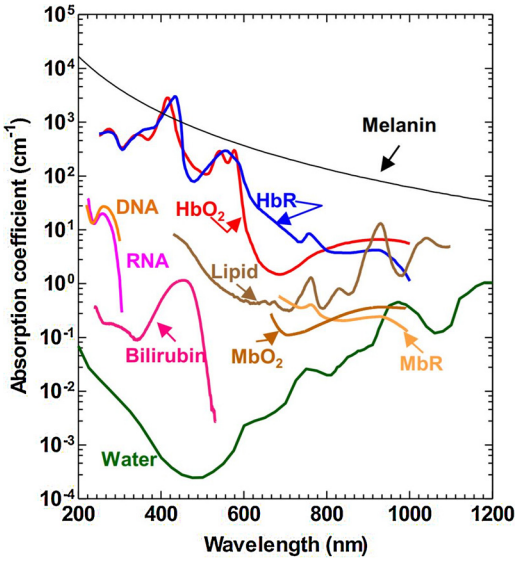

Fig. 1. Absorption coefficient spectra of endogenous tissue chromophores. HbO_2 and HbR, 150 g/L in blood; Water, 80% by volume in tissue; Lipid, 20% by volume in tissue; Melanin, 14.3 g/L in medium human skin. Figure adapted with permission from [30].

oxygenation levels range between 95%–100% in the arteries and 60% to 80% in the veins [32]. In many cases, disease processes alter the balance of oxygen delivery and consumption and change the blood oxygenation level and oxygen distribution [33]. For example, a fast-growing tumor has a high oxygen consumption rate, leading to new blood vessel development (angiogenesis) but an overall low oxygenation level (hypoxia) in the core region. The irregular blood perfusion network (torturous vascular path, interrupted blood flow, and leaky vessel wall) in the tumor results in limited oxygen supply to the tissue and elevated oxygen extraction, which in turn reduces the overall blood oxygenation in the tumor region. As a result, sO_2 plays an important role in tumor progression, and a large region of hypoxic core typically indicates a poor prognosis. By using fluence-compensated PA measurements at multiple wavelengths, the concentrations of oxygenated (C_{HbO_2}) and deoxygenated hemoglobin (C_{HbR}) can be mathematically estimated, from which the total hemoglobin concentration (HbT) and sO_2 can be computed [1]. PA imaging of sO_2 is expected to help improve cancer screening, cancer diagnosis, and therapy monitoring [1]. Moreover, the brain is highly sensitive to the changes in blood flow and oxygenation, as continuous oxygen delivery and CO_2 clearance are paramount in maintaining normal brain functions. Monitoring sO_2 inside the brain using PAT is of great interest in neurophysiology, neuropathology, and neurotherapy [34,35].

Compared to other blood oxygenation imaging modalities, PAT has the following merits: (1) Compared to functional magnetic resonance imaging (fMRI), PAT allows noninvasive *in vivo* oxygenation imaging at high spatial-temporal resolutions with a relatively low cost [36,37]. (2) Compared to positron emission tomography (PET), PAT uses non-ionizing laser illumination and provides a much higher spatial resolution. (3) Compared to other high-resolution optical imaging methods, PAT can reach much deeper into tissue while maintains a reasonably high resolution [38]. These advantages readily make PAT a powerful fit-in-line tool for blood oxygenation measurement.

Nevertheless, PAT still faces certain challenges in measuring blood oxygenation in deep tissue beyond the optical diffusion limit (~1 mm in soft tissue). Since PAT's acoustic signal amplitude is proportional to the local optical absorption, the wavelength-dependent optical attenuation limits the ultimate imaging depth and confounds the spectral unmixing of HbO_2 and HbR. Measuring local optical fluence is a long-standing challenge faced by quantitative PAT, and several methods were proposed to solve this problem. For example, Guo et al. used the acoustic spectra of PA signals to quantify the absolute optical absorption and thus the blood oxygenation level [39]. Kirchner et al. utilized machine learning to deduce the corresponding optical absorption [40]. Xia et al. monitored sO_2 transition with multiple wavelength measurements to cancel out the contribution of optical fluence [41]. Tzoumas et al. demonstrated improved blood oxygenation measurement by modeling several fundamental optical absorption spectra (eigenspectra) in the tissue, with the consideration of unknown optical fluence [42]. Daoudi et al. showed the feasibility of compensating for optical fluence by acoustically tagging photons in deep tissue [43]. In this concise review, we introduce the principles of and recent advances in PAT of blood oxygenation. The advantages and disadvantages of different methods are compared, with representative applications. We also opine the current technical challenges of PAT of blood oxygenation, which point to further potential breakthroughs.

2. The progress in PAT of blood oxygenation

Fundamentally, quantifying blood oxygenation requires measurement of the PA absorption spectra of the blood. By extracting key parameters such as peak amplitudes (maximum signal strength of the received RF signal) from the detected signal at multiple wavelengths, photoacoustic spectra of the blood can be determined. Given the known molar absorption coefficients of HbR and HbO_2, C_{HbO_2} and C_{HbR} can be recovered from the measured photoacoustic spectra using different methods, which will be discussed in the following sections and summarized in Table 1. Then, sO_2 can be calculated as [44]:

$$sO_2(x,y) = \frac{C_{HbO_2}(x,y)}{C_{HbO_2}(x,y) + C_{HbR}(x,y)} \times 100\%, \quad (1)$$

where x and y denote the spatial coordination.

2.1. Linear-model-based sO2 measurement

The most commonly employed method of sO_2 measurement is the linear spectral fitting, such as the least square method (LLS) [10,44,45].

$$P(\lambda_i, x, y) = \Phi(\lambda)(\varepsilon_{HbR}(\lambda_i)C_{HbR}(x,y) + \varepsilon_{HbO_2}(\lambda_i)C_{HbO_2}(x,y)) \quad (2)$$

Here $\Phi(\lambda)$ is local optical fluence, $P(\lambda_i, x, y)$ is the reconstructed PA image at a specific wavelength λ_i, $\varepsilon_{HbR}(\lambda_i)$ and $\varepsilon_{HbO_2}(\lambda_i)$ are the known molar extinction coefficients ($cm^{-1}M^{-1}$) of HbR and HbO_2 at wavelength λ_i, respectively. $C_{HbO_2}(x, y)$ and $C_{HbR}(x, y)$ are the molar concentrations of HbR and HbO_2, respectively. After optical fluence normalization, by employing multiple wavelengths, $C_{HbO_2}(x, y)$ and $C_{HbR}(x, y)$ can be estimated by solving the following linear equations [10]:

$$\begin{bmatrix} C_{HbR}(x,y) \\ C_{HbO_2}(x,y) \end{bmatrix} = (\varepsilon^T\varepsilon)^{-1}\varepsilon^T P, \quad (3)$$

in which

$$P = \begin{bmatrix} P(\lambda_1, x, y) \\ P(\lambda_2, x, y) \end{bmatrix}$$

is the PA measurement matrix at two wavelengths, and

$$\varepsilon = \begin{bmatrix} \varepsilon_{HbR}(\lambda_1) & \varepsilon_{HbO_2}(\lambda_1) \\ \varepsilon_{HbR}(\lambda_2) & \varepsilon_{HbO_2}(\lambda_2) \end{bmatrix}$$

is the molar extinction coefficient matrix. Fig. 2(a) shows one example of sO_2 map of the mouse brain vasculature using LLS, in which different colors represent different oxygenation levels in the blood vessels [10,46]. Fig. 2(b) shows the sO_2 distribution in normal and tumor blood vessels.

However, the working assumption of the linear model is that the local optical fluence is the same at different wavelengths after