Application of photoacoustic imaging in biomedicine.

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Editorial

Photoacoustic (PA) signal is induced thermo elastically by the absorbed electromagnetic (EM) energy. The development of laser and detection instruments, signal reconstruction algorithms, and functional and molecular diagnosis *in vivo* bloomed its investigation since this century [1,2]. A small temperature rise (<0.1°C) in the tissue is well below the threshold for irreversible physiological damage, and the acoustic emission is in the broad bandwidth (tens of MHz) at low amplitude (<10 kPa) from the penetration up to a few centimeters. PA signal presents high contrast (2-3 orders higher than sonography) and resolution simultaneously with great differentiation and specificity. The nondestructive, noninvasive, and nonionized PA diagnosis have applications for the anatomy and physiology of small animals, the anatomical tissue/organ structure, oxygenation status, blood flow, abnormal morphology, functional vasculature characteristics, skin burns, hypermetabolism, and vulnerable plaques in the coronary arteries.

In comparison to optical molecular imaging (e.g., fluorescence and diffusion optical tomography) and sonography, photoacoustic tomography (PAT) has higher spatial resolution and better tolerance to variations in the speed of sound (SOS). The cylindrical or spherical detectors assess the complete field around the target. Planar geometries are versatile, but resulting in artifacts and reduced spatial resolution in the reconstructed image to a finite volume [3]. The simple ad hoc back-projection, where all PA signals are spatially resolved using SOS, back-projected toward the excitation site at a spherical surface, and summed throughout the excitation volume, is intuitively amenable, but unsatisfactory in accuracy and computational burden [4]. Filtered and universal back-projection, the spectral decomposition of PA signals temporally and spatially followed by mapping to spatial spectrum, have an exact and easy reconstruction for all geometries. Using a fast Fourier transform (FFT) algorithm, a complete 3D pressure field could be reconstructed for the planar case quickly. Time-reversal invariance can achieve the focusing in homogeneous media for the improved signal-to-noise ratio (SNR) and resolution. Model-based inversion employs a forward model to calculate the detection and iteratively update the estimates by minimizing the prediction error [1].

PA microscopy is achieved by scanning a focused ultrasonic transducer (AR-PAM) or laser beam (OR-PAM) [5]. The laser used for AR-PAM is much weaker than that for PAT, which allows higher PRFs, a tunable power, and the illumination of the coinciding region with the beam profile of the receiving transducer. Overall, PAT has excellent spatial resolution and acquisition speed, but in more complex setup and at higher cost. AR-PAM has been successfully applied to illustrate the skin vasculature in the dermis and sub-dermis, benign skin melanomas, and mouse brain. The lateral resolution of OR-PAM on the order of a few microns is defined by a tightly focused diffraction-limited laser beam and strictly superficial [6]. However, its vertical resolution is ~10 mm and limited by acoustic attenuation or the transducer's bandwidth. The use of adaptive optics may correct aberrations in the scanning lens, illuminating optics, and optical wave front distortion. Endoscopic or intravascular PA designs are analogous to ultrasonic ones for imaging coronary arteries, prostate, and gastro-intestines [7]. Although a variety of excitations and measurement are proposed, few are evaluated *in vivo*.

The spectroscopic EM absorption makes the quantitative determination of the concentrations of specific chromophores possible by adjusting the excitation wavelength to their absorption peaks. Blood oxygen saturation can be quantified by measuring the spectral differences between oxyhaemoglobin and deoxyhaemoglobin [5]. The intravenous administration of certain targeted contrast agents (dye molecule or nanoparticle) would accumulate and bind to a disease-specific receptor (cell-surface protein or enzyme) in PA cellular functional and molecular imaging. Addressing the wavelength-dependent fluence distribution can increase the measurement accuracy. In a nonlinear inversion model, light transport is determined by accounting the spectral light distribution in the forward model. A light transport model can recover absorption coefficients at individual wavelengths and chromophore concentrations by a linear inversion. However, determining absorption coefficients at a single wavelength without incorporating the scattering distribution or fluence measurements is impossible because of the association of non-unique scattering with energy absorption. However, absolutely or even relatively quantitative chromophore concentrations in PA spectroscopy are challenging.

PA flowmetry with velocities of 3.5-200 mm/s in a resolution of 1 mm/s using time-resolved spectral analysis of tone burst excitation offers high SNR especially for microvasculature with low echogenicity because the blood has stronger EM absorption than vessel and surrounding tissues [8]. In OR-PAM flowmetry, optical illumination beam similar to a single red blood cell (RBC) could directly resolve the *in vivo* heterogeneous blood absorption with the speed as high as ~7.4 mm/s in a resolution of 0.1 mm/s, which allows the functional capabilities of oxygen supply and delivery at the capillary level. One of the current challenges is increasing the penetration depth to more than 1 mm.

The Grüneisen PA generation coefficient is proportional to the local temperature surrounding the absorber, which permits the noninvasive thermometry for photothermal, RF, and high-intensity focused ultrasound (HIFU) ablation in the resolution

of about 0.15°C at the frame rate of a few seconds [9]. Time-resolved detection and analysis of PA signals allows the calculation of temperature for hyperthermia in real time with an accuracy of ~17%, which may serve as temperature-sensitive biosensors even at single-cellular level without staining.

Some challenges are still unsolved to realize the clinical potential of this technology, such as appropriate ultrasonic transducer with broad bandwidth and high sensitivity, new optical-acoustical sensing approaches, compact and portable laser systems with high pulse energies, high pulse repetition frequency (PRF), and easy re-alignment and cooling, high tuning speeds and large tuning range, parallel signal processing and inversion algorithm for real-time image reconstruction without compromising SNR and computation cost, and frequency domain excitation schemes. Multiple-wavelength PA images can reveal the biological details in higher spatial resolution. Development of proteins and nanoparticles for the absorption at longer wavelengths is critical for diagnosing the mammalian cells at the greater penetration depth. Optic interactions with the biological tissues mainly include four mechanisms: linear and nonlinear absorption, elastic and inelastic scattering. The intrinsic correlation between them could offer a potential for innovative beyond PA sensing and imaging technique with enhanced sensitivity and specificity.

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