Three-dimensional quantitative optoacoustic tomography

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Background – The main clinical merit of three-dimensional (3D) optoacoustic tomography (OAT) is its potential capability to provide quantitative volumetric maps of molecular distributions [1]. With blood being pivotal component of human system, quantitative images of the total hemoglobin and blood oxygen saturation can help differentiate abnormal tissues, such as cancer, from normally functioning tissues These functional images have been the subject of extensive research since the first functional photoacoustic microscopy images were demonstrated by X. Wang and L. Wang in 2003 [2]. The goal of the functional imaging is to convert optoacoustic images of the absorbed optical energy, dependent on spatial distribution of the effective optical fluence, into the images of the optical absorption coefficient, independent on heterogeneous distribution of the optical fluence in the laser illuminated volume [1]. The main deficiency of the current methods of qOAT is in the model-based computations applied for the forward problem of the optical fluence distribution through the depth of tissue without *apriori* knowledge of the tissue optical properties. Furthermore, only two-dimensional (2D) *in vivo* functional images were reported using linear spectral unmixing of the optoacoustic signals obtained at multiple wavelengths [3]. While this approach produced an improved accuracy of functional parameters measured from 2D images, it has not yielded acceptable performance in 3D due to (i) the incapability to correct the detected signals for missing low frequencies, and (ii) application of a forward model based on representative (thus potentially inaccurate) values of tissue optical properties from literatures. In contrast, our approach is based on direct measurement of the effective optical attenuation coefficient as a function of the light penetration depth through the entire volume of tissue presented on optoacoustic images [4]. This purely empirical approach resulted in the first three-dimensional quantitatively accurate functional images of live tissue volumes [5].

Methods – We designed and assembled full view 3D optoacoustic tomography systems for preclinical research in small lab animals and clinical research in diagnostic imaging of breast cancer [6,7].

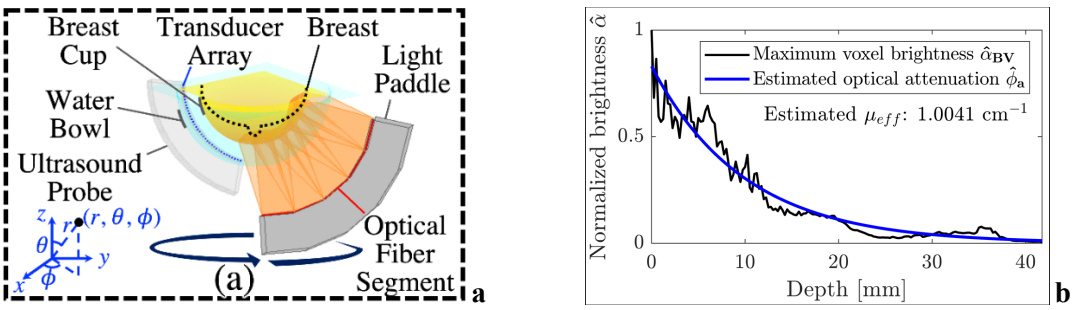

Figure 1. **(a)** Schematic diagram of the laser illumination and acoustic detection implemented in the 3D full view optoacoustic imaging system designed for detection of breast cancer. **(b)** Typical optical attenuation curve measured experimentally from a 3D optoacoustic image acquired using an array of ultrawide-band ultrasonic transducers from breast

of a patient at the wavelength of 757 nm. Similar curves have been measured from every point on the skin surface through the depth in the radial direction of light attenuation.

The first mandatory requirement of quantitative OptoAcoustic Tomography (qOAT) is that every point on the entire surface of the volume of interest is illuminated and optoacoustic signals are detected by transducers evenly placed on the spherical surface surrounding the volume of interest (see general schematic diagram in Fig 1a [4]. The major factor in our capability of quantitative optoacoustic tomography was the measurements of the exponential slope of the voxel brightness as a function of depth. This low frequency slope was measured only due to the fact we used ultrawide band ultrasonic transducers sensitive (see typical curve on Fig 1b).

The experimental protocol of functional (qOAT) required innovations and advanced implementation of the system hardware and algorithms of the signal processing and image reconstruction. After many years of research we have been able to achieve the following features of the proposed qOAT method: (1) obtain undistorted optoacoustic signals using ultrawide-band ultrasonic transducers and reversal of signal distortions by deconvolution of acousto-electrical impulse response (EIR) and spatial impulse response (SIR) [8]; (2) acquire coregistered images at two or more wavelengths using a newly designed fast switching the laser wavelengths with every pulse; (3) normalize optical fluence on the illuminated surface and through the volume of interest [4], generate images of the optical absorption coefficient; (4) calibrate images of the optical absorption coefficient using arterial blood as a tissue with well-defined optical properties; and finally (5) generate functional images of [tHb] and [SO2] [5].

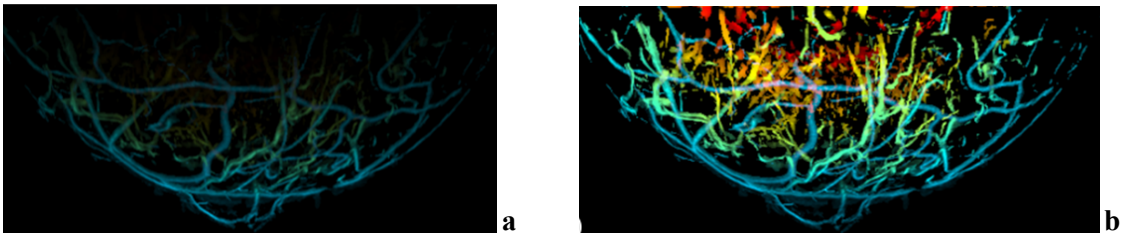

Figure 2. Maximum intensity projections of 3D full view clinical optoacoustic images obtained at the wavelength of 757 nm of a patient breast prior **(a)** and after **(b)** the optical fluence normalization on the surface and through the depth of 45 mm.

In our study, we acquired *in vivo* optoacoustic signals of the mouse at 757 nm (Hb) and 1064 nm (HbO2+H2O) using proprietary ultrawide-band ultrasonic transducers (50 kHz-8 MHz), and the images (i.e., distribution of the absorbed optical energy) were reconstructed incorporating transducer impulse response. The functional images of blood oxygen saturation [sO2] and the total hemoglobin [tHb] were estimated from the coregistered dual-wavelength images via the measurement data-driven normalization of the optical fluence distribution for each wavelength.

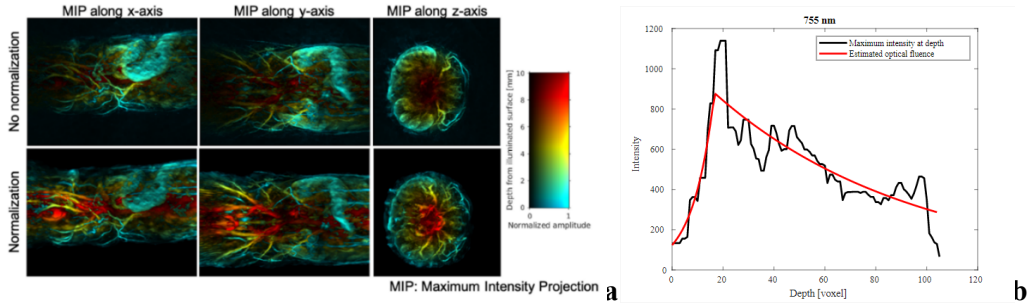

Figure 3. **(a)** Maximum intensity projections of 3D full view optoacoustic images obtained at the wavelength of 757 nm of a mouse body prior and after the optical fluence normalization on the surface and through the depth of the mouse; **(b)** Background absorbed optical energy measured from the experimental optoacoustic image acquired at 757 nm using an array of ultrawide-band ultrasonic transducers.

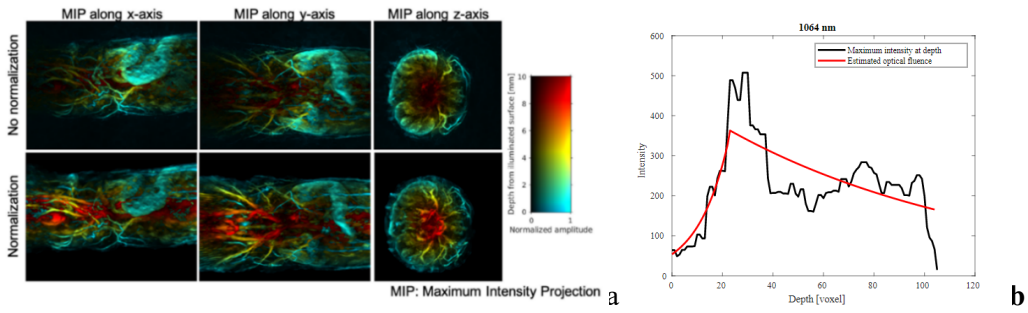

Figure 4. (a) Maximum intensity projections of 3D full view optoacoustic images obtained at the wavelength of 1064 nm of a mouse body prior and after the optical fluence normalization on the surface and through the depth of the mouse; (b) Background absorbed optical energy measured from the experimental optoacoustic image acquired at 1064 nm using an array of ultrawide-band ultrasonic transducers.

The reconstructed functional images reveal high-resolution details of anatomical structures through the entire mouse body. In the computed 3D functional images, arteries, veins and organs were separated based on the oxygen saturation estimates. Using a pair of artery (with assumed [sO2] of 100%) and a vein in a close proximity to each other, we have been able to perform absolute calibration of the venous [sO2], which we measured a value of 71%.

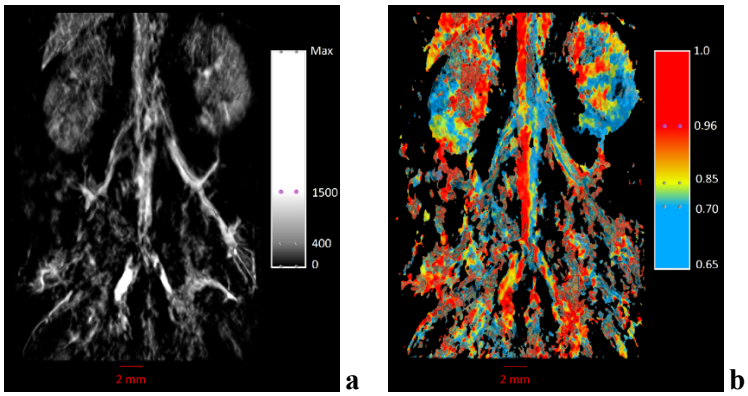

Figure 5. 2 mm thick slice of 3D full view quantitative optoacoustic images around the vena cava. **(a)** Image of the total hemoglobin and **(b)** image of the blood oxygen saturation.

Conclusions – While experimental method of the optical fluence normalization through the entire volume of live tissues requires further refinement through research, the first 3D volumetric functional images of [tHB] and [sO2] show viability of the proposed method for the 3D volumetric deep tissue functional imaging *in vivo*.

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