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Phase-domain photoacoustic sensing

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As one of the fastest-growing imaging modalities in recent years, photoacoustic imaging has attracted tremendous research interest for various applications including anatomical, functional, and molecular imaging. The majority of the photoacoustic imaging systems are based on the time-domain pulsed photoacoustic method, which utilizes a pulsed laser source to induce a wideband photoacoustic signal, revealing optical absorption contrast. An alternative way is the frequency-domain photoacoustic method utilizing the chirping modulation of laser intensity to achieve lower system cost. In this paper, we report another way of the photoacoustic method, called phase-domain photoacoustic sensing, which explores the phase difference between two consequent intensity-modulated laser pulse induced photoacoustic measurements to reveal the optical properties. The basic principle is introduced, modeled, and experimentally validated in this paper, which opens another potential pathway to perform photoacoustic sensing and imaging, eliminating acoustic detection variations beyond the conventional time-domain and frequency-domain photoacoustic methods. *Published by AIP Publishing.*

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Combing the merits of optics and ultrasound, photoacoustic (PA) sensing and imaging techniques have attracted tremendous research interest in recent years ranging from various biomedical applications to different system implementations.^{1–7} Among all of the previous works, the majority of the PA systems are based on the time-domain photoacoustic sensing method, which utilizes pulse laser illumination and wideband pulsed PA signal detection.^{8–11} By evaluating the amplitude of the received PA signal, optical absorption properties could be revealed. To lower down the cost of the laser source, an alternative PA sensing method, called frequency-domain PA, has been proposed in recent years, which modulates the laser intensity in a frequency-chirping mode and retrieves the depth-information by matched filtering.^{12–17} Phase-sensitive PA has also been reported for viscoelastic measurement, which, however, is not revealing the optical properties from the phase information.^{18–20} In this paper, we will introduce another way of the PA sensing method, named phase-domain photoacoustic (PDPA) sensing, which is capable of representing the conventional PA amplitude by calculating the phase difference, or time delay, between two consequent intensity-modulated photoacoustic measurements. As another kind of PA sensing method that does not directly measure the absolute PA amplitude, PDPA may be potential to achieve higher detection reliability by eliminating the acoustic detection variation (attenuation, distortions, etc.), which usually deteriorates the PA amplitude measurement accuracy but not phase difference. In the following paragraph, the principle and analytical modeling of the

phase-domain PA sensing will be elaborated, followed by proof-of-concept experimental validation.

The principle of the proposed PDPA technique is shown in Fig. 1. As shown in Figs. 1(a) and 1(b), conventionally, the time-domain PA detection characterizes the optical absorption by the amplitude of the PA signal, and the time delay of the PA signal reveals the distance d between the sample and the transducer together with constant acoustic velocity v_0 in the medium

$$t_d = \frac{d}{v_0}. \quad (1)$$

FIG. 1. The principle of the proposed PDPA technique. (a) Conventional time-domain photoacoustic detection method and (b) the constant acoustic velocity along the PA propagation distance. (c) The proposed PDPA concept and (d) the acoustic velocity along the PA propagation distance. (e) The consequent laser illumination and (f) phase delay calculation of the perturbation-based PDPA method.

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In this paper, we reconsider the PA propagation distance d as a combination of two parts: $d = d_t + d_0$. The first part d_t is within the thermal diffusion region following the laser illumination and temperature rising, and the second part d_0 is not affected by the laser heating. So, the acoustic velocity v_t in the first part is distinct from that in the second part. Therefore, as shown in Figs. 1(c) and 1(d), the new time delay could be expressed as

$$t_d = \frac{d_t}{v_t} + \frac{d_0}{v_0}. \quad (2)$$

As we know, the acoustic velocity in water (or biological tissues) is proportional to the temperature of the medium. To simplify the modelling for a more intuitive elaboration, an empirical equation relating the acoustic velocity and temperature is employed here in a linear manner^{21,22}

$$v_t = v_i + a(T + \Delta T), \quad (3)$$

where v_i is the acoustic velocity of water at 0 °C, a is the coefficient relating temperature and acoustic velocity increase, T is the ambient temperature (e.g., 25 °C), and ΔT is the transient temperature rise due to the laser illumination²³

$$\Delta T = \frac{\mu_a F}{\rho C_v}, \quad (4)$$

where μ_a is the optical absorption coefficient of the sample, F is the laser fluence, ρ is the density of the sample, and C_v is the specific heat capacity at constant volume. Substituting Eqs. (3) and (4) into Eq. (2), we have

$$t_d = \frac{d_t}{v_i + a\left(T + \frac{\mu_a F}{\rho C_v}\right)} + \frac{d_0}{v_0}. \quad (5)$$

From Eq. (5), we could observe that the time delay is inversely proportional to the optical absorption coefficient and laser fluence, which provides the underlying physics to utilize time delay for optical property characterization. However, it is also noted that the time delay is still dominantly determined by the second part of the PA propagation distance because of $d_0 \gg d_t$ and $v_0 \gg a\left(T + \frac{\mu_a F}{\rho C_v}\right)$. More severely, the time delay induced by the PA propagation distance cannot be easily distinguished from that induced by optical absorption without ambiguity. Therefore, the challenge here is how to extract the subtle time delay change induced by the optical absorption and meanwhile decoupling other factors, such as the dominant PA propagation distance related time delay.

To address this challenge, here we introduce perturbation-based PA measurement by modulating the laser intensity. As shown in Fig. 1(e), when two laser pulses with different fluences ($F_2 = AF_1$, $A = F_2/F_1 > 1$) are fired, the time delay of the induced PA signals based on Eq. (5) could be expressed as

$$t_{d1} = \frac{d_t}{v_i + a\left(T + \frac{\mu_a F_1}{\rho C_v}\right)} + \frac{d_0}{v_0}, \quad (6)$$

$$t_{d2} = \frac{d_t}{v_i + a\left(T + \frac{\mu_a AF_1}{\rho C_v}\right)} + \frac{d_0}{v_0}. \quad (7)$$

Then, after some mathematical derivations, the time delay difference could be calculated as

$$\begin{aligned} \Delta t = t_{d1} - t_{d2} &= \frac{d_t}{v_i + a\left(T + \frac{\mu_a F_1}{\rho C_v}\right)} - \frac{d_t}{v_i + a\left(T + \frac{\mu_a AF_1}{\rho C_v}\right)} \\ &= d_t \left[\frac{A - 1}{\frac{\rho C_v (v_i + aT)^2}{aF_1 \mu_a} + (v_i + aT)A + (v_i + aT) + \frac{aF_1 \mu_a}{\rho C_v} A} \right]. \end{aligned} \quad (8)$$

To simplify the analysis of the time delay difference in a more intuitive way, we assume two constant terms: $M = (v_i + aT)$, $N = \frac{aF_1}{\rho C_v}$. Then, the above equation could be simplified as

$$\Delta t = d_t \left[\frac{A - 1}{\frac{M^2}{N\mu_a} + MA + M + N\mu_a A} \right]. \quad (9)$$

Next, we would like to quantitatively analyze and simulate the time delay difference versus laser intensity difference A and optical absorption coefficient μ_a . The values of other constant parameters are listed in Table I.

(1) Time delay difference versus laser intensity difference

Considering the condition $A \gg 1$, the above equation could be further expressed as

$$\Delta t = d_t \left(\frac{\frac{M^2}{N\mu_a} + M}{A} + M + N\mu_a \right)^{-1}. \quad (10)$$

It is showing that with increasing laser intensity difference A , the time delay difference is also increasing accordingly, which conforms well to the intuitive analysis: higher laser intensity difference, higher local temperature rise, and then larger time delay difference. By replacing the parameters with those values in Table I, the simulation result in Fig. 2(a) indicates that with increasing laser intensity difference from 4 to 100, the time delay difference increases linearly first and then goes to saturation at a higher value of A in the range from 4 ns to ~26 ns. To guarantee both the sufficient PA signal amplitude and laser safety limit, the absolute value of the laser fluence needs to be selected carefully. In this simulation study, the low laser fluence F_1 is set to be 1 mJ/cm², equivalent to the high laser fluence F_2 sweeping from 4 to 100 mJ/cm², which is still within the laser safety limit using near infrared light for practical use in photoacoustic imaging. In addition, the time delay difference from 4 ns to 26 ns could be well measured by using a high-speed oscilloscope (>1 GSPS). Considering the curve in Fig. 2(a) that is going to saturate with an increasing laser intensity difference, a proper selection, e.g., 50 a.u., could be a good choice to induce enough time delay (e.g., 18 ns) for practical use.

TABLE I. Values of physical parameters in the equations.

Parameter	Value	Unit	Comments
A	1–100	a.u.	Laser intensity difference, $A \gg 1$
d_t	50	μm	Thermal length
ρ	1	g/cm^3	Density of water
C_v	4	$\text{J}/\text{g}^{-1} \text{ } ^\circ\text{C}^{-1}$	Specific heat capacity at constant volume
a	4.6	a.u.	Coefficient relating temperature and acoustic velocity
F_1	1	mJ/cm^2	Low laser fluence
μ_a	$0.1\text{--}10^5$	cm^{-1}	Optical absorption coefficient
v_i	1448	m/s	Acoustic velocity of water at 0°C
T	25	$^\circ\text{C}$	Ambient temperature

Compared with time-domain PA, the proposed PDPA requires a higher sampling rate for the data acquisition module to resolve the nanosecond scale time delay.

(2) Time delay difference versus optical absorption coefficient.

From Eq. (9), it is showing that the time delay difference is not monotonically increasing with an increasing optical absorption coefficient. At both $\mu_a \rightarrow 0$ and $\mu_a \rightarrow \infty$, we have $\Delta t \rightarrow 0$. From the simulation results in Fig. 2(b) by sweeping μ_a from 1×10^{-1} to $1 \times 10^5 \text{ cm}^{-1}$, the time delay difference increases first and then decreases as expected. However, in the range of 1×10^{-1} to $1 \times 10^4 \text{ cm}^{-1}$, which is the major optical absorption band of biological tissues, the time delay difference is increasing monotonically as shown in Fig. 2(c). This guarantees the potential of the proposed PDPA method to characterize the optical coefficient for biomedical applications. The underlying reason of the time delay difference decreasing is with a higher optical absorption coefficient, it reaches optical absorption saturation and time delay saturation accordingly. Thus, the time delay difference will decrease when the time delay of each PA signal is reaching saturation.

Now the concept and analytical modeling of the PDPA have been introduced and simulated. Then, the potential

FIG. 2. (a) Time delay difference versus laser intensity difference ranging from 4 to 100. (b) Time delay difference versus optical absorption coefficient ranging from 0.1 cm^{-1} to 10^5 cm^{-1} and (c) the zoomed-in plot with an optical absorption coefficient ranging from 0.1 cm^{-1} to 10^4 cm^{-1} , which covers the major absorption range of biological tissues.

advantage of the proposed PDPA over the conventional time-domain PA deserves to be discussed. The most straightforward advantage of PDPA will be its insensitivity to environmental interferences. For example, in conventional time-domain PA measurement, the random and bulk movement of the transducer in terms of distances and angles between the sample and transducer will fluctuate the amplitudes of the time-domain PA signals, leading to detection inaccuracy. On the other hand, the proposed PDPA is relatively insensitive to such kind of environmental interferences, given that the two consequent laser pulses are temporally close enough, which means that the perturbation-based PDPA measurement may provide higher measurement reliability than amplitude-based time-domain PA measurement.

The experimental setup to prove the concept of the PDPA method is shown in Fig. 3. A pulsed laser (Opolette 355, OPOTEK Inc.) with the 20 Hz repetition rate was employed to generate two consequent laser pulses with 650 nm wavelength, 50 ms pulse interval, and different fluence, which was guided and focused on the sample by a pair of condenser lens (LB1471, Thorlabs). A small portion of the light source was reflected by using a beam splitter (BSF10-B, Thorlabs) and detected by using a photodiode (DET10A, Thorlabs) to monitor the laser intensity. A focused ultrasound transducer (V303SU, Olympus; diameter: 1.5 cm and focal length: 3 cm) with 1 MHz central frequency was used to receive the PA signals generated from the sample. The transducer was linked to a linear translational stage, which could change both the distance and angle between the transducer and the sample. Both the sample and the ultrasound transducer were immersed in water for both optical and acoustic coupling in a water tank. The PA signals detected by the transducer were amplified by using a low-noise amplifier (5662, Olympus) with 34 dB gain and then fed into the oscilloscope (WaveRunner 640Zi, LeCroy) with the 10 GSPS sampling rate for data recording.

Proof-of-concept experiments were performed based on the above-mentioned setup. To be a good absorber and

FIG. 3. The schematic of the experimental setup. ConL: condenser lens, BS: beam splitter, PD: photodiode, UT: ultrasound transducer, and LNA: low-noise amplifier.

an efficient PA generator, the sample used here was a black tape (1 cm $\times$ 1 cm) attached to the bottom of the water tank. By sweeping the laser intensity from 1 mJ/cm² to 20 mJ/cm², the time-domain PA signals were measured and plotted in Fig. 4(a). The oscillation of the PA signals may be caused by two reasons: the first reason is the acoustic mismatch between the tape and the bottom of the water tank that induced multiple reflections. The second reason could be the limited bandwidth of the transducer. As expected, for the time-domain PA method, with increasing laser fluence, the amplitudes of PA signals were increasing linearly, as shown in Fig. 4(b), with good correlation ($R^2 = 0.996$). In addition, by zooming-in the time-domain PA waveforms in Fig. 4(c), it was also observed that the time delay of all the PA signals is shortening with increased laser fluence, which matched well with the prediction of the analytical model. To quantitatively characterize the time delay difference, cross correlation was performed between each PA signal with Pa1 (the PA signal induced by the lowest laser fluence). From the cross correlation results shown in Fig. 4(d), we could observe that with higher laser fluence (larger PA signal), the time delay is increasing accordingly. The quantitative comparison between the time-domain PA amplitude and the phase-domain time delay difference was plotted in Fig. 4(e), which exhibits a logarithmic-like curve: relatively linear when the PA amplitude is < 0.4 V, leading to saturation at higher laser fluence. This result conforms

FIG. 4. (a) The time-domain PA signals by sweeping the laser fluence. (b) The amplitude of time-domain PA signals versus laser fluence. (c) The zoomed-in time-domain PA signals showing shortened time delay. (d) The cross-correlation results of each PA signals with Pa1. Inset: The zoomed-in peak of the cross-correlation results showing shifted time delay. (e) The comparison between the time-domain PA signal amplitude and the phase-domain PA time delay difference with a relatively linear relationship.

well to the theoretical prediction by Eq. (10). This measurement results matched well with the quantitative simulation results in Fig. 2(c), proving the validity of the analytical modelling.

To demonstrate the advantage of the proposed PDPA method over conventional time-domain PA measurement, another set of experiments were performed by randomly positioning the distance and angle between the sample (black rubber wire with 1 mm diameter) and the ultrasound transducer. Figs. 5(a)–5(d) show the time-domain PA waveforms measured at four different transducer positions. With random positioning of the transducer, the amplitudes of the time-domain PA signals (Pa1 and Pa2) varied significantly. To extract the time delay difference, cross-correlation was performed for these four sets of PA signals shown in Figs. 5(e)–5(h). It shows that all the maximum positive peaks of the cross-correlated signals are near the center of the figures for all the four different transducer positions, inferring that the time delay difference could be quite stable. Then, the absolute time delay difference could be extracted by measuring the time shift of the peak away from 0 ns, just like in Fig. 4(d). To compare the variations of the conventional time-domain PA and proposed PDPA, both the PA signals' amplitude and phase delay difference were plotted in Figs. 5(i) and 5(j), which indicate that the time delay difference of the PDPA method exhibits a much smaller variation than the amplitude of the time-domain PA method. The quantitative comparison in Fig. 5(k) shows that the PA amplitude's variation is as large as 70%, while the phase delay's variation is less than 6.4%, which could be calculated by dividing the error value over the mean value. The improvement in terms of sensing reliability is more than 10 times, which demonstrates the potential of the proposed PDPA method for reliable PA sensing applications.

Regarding the applications of the proposed PDPA method for photoacoustic imaging applications, it could be expected that the majority of the photoacoustic applications, e.g., PA microscopy of vascular, functional imaging of oxygen saturation and metabolism, cancer diagnostics, melanin detection etc., could be feasible for the proposed PDPA method. Moreover, some other applications like continuous PA sensing in a movable and harsh environment is also feasible owing to the merit of low acoustic detection variation of this method. Note that the phase difference measurement requires a higher data sampling rate (> 1 GSPS) for the data-acquisition card than conventional time-domain PA, and the imaging system based on the PDPA method may be more costly and time-consuming. Last but not least, the absolute values of the laser fluence need to be properly selected. To guarantee both the sufficient PA signal amplitude and laser safety limit, one suggestion is to select the high laser pulse reaching the safety limit (e.g., 20 mJ/cm² for the green laser).

In conclusion, the PDPA method has been proposed, modelled, simulated, and experimentally validated. The advantage of the PDPA method eliminating acoustic detection variations has shown a much higher detection reliability (> 10 times) than the conventional time-domain PA method. This merit of the PDPA method may enable more applications for continuous PA sensing in a movable and harsh

FIG. 5. (a)–(d) The measured time-domain PA signals at four random positions with different distances and angles between the sample and the transducer. (e)–(h) The cross-correlation results of the two PA signals (Pa1 and Pa2) at these four different transducer positions. (i) The peak-to-peak amplitude of the time-domain PA signals (Pa2) and (j) time delay difference of the PDPA method at these four different transducer positions. (k) The comparison of the detection variations between time-domain and phase-domain PA methods.

environment, e.g., wearable health monitoring sensors. A further study of the PDPA method with higher accuracy and reliability is deserved towards real applications *in vivo* in the future.

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