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Real-time monitoring of temperature using pulsed laser diode based photoacoustic system

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Tissue local temperature information is necessary for guiding energy-based medical treatments. In cancer treatments like thermal therapy, heating is applied to local tissue to kill the tumor cells. These techniques require a temperature monitoring device with high sensitivity. In this work, we demonstrate a pulsed laser diode (PLD) based photoacoustic temperature sensing (PATS) system for monitoring tissue temperature in real-time. The system takes advantage of high repetition rate (7000 Hz), near-infrared wavelength (803 nm), and relatively high energy 1.42 mJ/pulse laser. The system is capable of providing local temperature information at high temporal resolution 1 millisecond and high sensitivity 0.31 °C. The temperature data measured with PLD-PATS system are compared with the data provided by the commercial fiber Bragg grating (FBG) sensor. The proposed system will find applications in radiofrequency ablation, photothermal therapy, and focused ultrasound, etc. used for cancer treatments.

Monitoring tissue temperature is essential for optimal treatment efficiency and minimize damage to surrounding healthy tissue. This requires precise control over local tissue temperature. There are several energy based treatments, such as radiofrequency ablation, photothermal therapy, and high energy focused ultrasound that have been widely employed for cancer treatments. These techniques involve heating an unhealthy or cancerous tissue. To control the heating spatially as well as temporally, it is important to noninvasively monitor the local temperature of the tissue in real time. This will help clinicians to reach the desired temperature to kill cancerous cells for a sufficient duration and to minimize unwanted surrounding healthy tissue damage. Common method for monitoring temperature during thermal therapy include thermocouple and thermistor, which are invasive and have to be replaced. Infrared thermography is a noninvasive noncontact optical approach, although, the accuracy

could reach to 0.1 °C, but it is unable to detect temperatures deep inside tissue due to the diffusion of photons. Currently few clinical modalities such as magnetic resonance imaging (MRI), and ultrasound imaging have been used for temperature mapping during deep tissue thermotherapy noninvasively. Among these methods, MR thermometry is not fast enough for real-time temperature monitoring, bulky, and expensive. On the other hand Ultrasound thermometry can provide relative temperature changes, but its sensitivity is low 1 °C [1]. Photoacoustic tomography (PAT) is an advancing real-time imaging modality that can guide clinicians in diagnosis, therapy and surgery [2]. It can also monitor local temperature.

In PAT, upon absorption of pulsed laser light by the tissue, it undergoes a time-varying thermal expansion-relaxation process, which leads to the generation of acoustic waves in the tissue. By acquiring the photoacoustic (PA) signals at the tissue surface and using various reconstruction algorithms the absorption maps within the tissue can be generated. By combining high optical contrast and ultrasound resolution in a single modality, PAT offers several key advantages: (i) non-invasive and uses non-ionizing radiation, (ii) label-free and speckle-free imaging, (iii) *in vivo* penetration depth about ~4 cm, can be extended beyond 10 cm with the help of contrast agents [3, 4], (iv) faster and less-expensive, (v) allows imaging from organelles to organs with consistent optical absorption contrast [2], (vi) allows imaging of optical absorption with 100% relative sensitivity, [5] (vii) provides anatomical, functional, molecular and kinetic information in a single system [6]. The potential of PAT was demonstrated by imaging whole-body of live mouse/rat and human organs *in vivo* [3]. PAT was also demonstrated for temperature monitoring in deep tissues noninvasively [7-12].

In recent years, In PAT, the local pressure rise immediately after the excitation of the laser pulse is $p_0 = \Gamma(T)\eta\epsilon F$, where Γ is the Grüneisen parameter, T is the equilibrium temperature, η is the percentage of light energy that is converted to heat, ϵ is the optical absorption coefficient, and F is the local optical fluence. The Γ -parameter is a function of slow varying local temperature of the sample. The instantaneous temperature rise to the laser pulse will not affect the Γ -parameter. PAT takes advantage of the linear temperature dependence of the tissue's Grüneisen parameter [7].

Photoacoustic/Ultrasound systems with linear array transducer were reported for temperature monitoring in phantoms [12]. However, the temperature sensitivity of array-based transducers is low and its cost is high compared to single-element ultrasound transducers (USTs). PAT with a single element UST was reported for temperature monitoring using a 10 Hz, 1064 nm Nd:YAG laser. It could provide temperature sensitivity $\sim 1^\circ\text{C}$ at a temporal resolution of ~ 1 sec [13]. A sensitivity of $\sim 0.15^\circ\text{C}$ at a resolution of ~ 2 sec was reported using a 10 Hz, 532 nm Nd:YAG laser using a single element USTs [14]. Using dual wavelengths (780 and 800 nm), the measurement error was reduced by about 40% [8]. By using six wavelengths, measurement accuracy 0.099°C was achieved. These studies used a low repetition rate 10 Hz, Nd:YAG/OPO laser [15]. In these studies, the temporal resolution of PA measurement is limited by the low repetition rate of the laser. Recently, high-repetition rate pulse laser diodes (PLDs) were successfully used as a substitute to Nd:YAG/OPO laser. Compared to the standard Nd:YAG lasers, PLDs are very compact, low-cost, and can generate thousands of pulses for real-time imaging. However, there are few disadvantages associated with current PLD technology such as low-pulse energy, long-pulse duration and single wavelength emission (not tunable). Nevertheless, the fast-growing laser technology promises that it is possible to achieve PLDs suitable for clinical applications in the near future. Several *in vitro* and *in vivo* experimental results reported in Ref. [16-19] confirmed that PLD can be a suitable source for clinical applications.

In this work, we developed a PLD based PA temperature sensing system for real-time monitoring of temperature. The system takes advantage of high repetition rate 7 kHz and near-infrared (~ 803 nm) wavelength of the PLD. The proposed system was used to monitor the fast temperature rise of black ink and fresh animal blood. A Fiber Bragg grating (FBG) sensor was also used for the temperature monitoring and compared with the PA method. We obtained a temperature sensitivity of 0.31°C degree with 1 millisecond temporal resolution.

Fig. 1. (a) Schematic of the PLD-PATS system for real-time temperature monitoring, where, PLD- Pulsed laser diode, UST- Ultrasound transducer, USA- Ultrasound amplifier, LCU- Laser controlling unit, DAQ- Data acquisition card, FBG- Fiber Bragg grating. (b) Schematic of the coaxial tube system. Inner tube contains test sample (Ink or blood). Hot water was injected through the outer tube. (c-f) The pattern of PA signals generated by the laser pulse burst when local temperature is constant and when local temperature is rising.

The schematic of the PLD based photoacoustic tomography (PLD-PAT) system is shown in Figure 1(a). The PLD (Quantel, France) is capable of providing ~ 136 ns pulses at high repetition rate up to 7000

Hz. The PLD delivers ~ 1.42 mJ wavelength pulses at near-infrared wavelength of ~ 803 nm. The laser controlling unit (LCU) consisted of a temperature controller (MTTC1410, LaridTech), a power supply unit (12V, PPS-11810, Voltcraft), a tunable power supply (BT-153, BASETech), and a simple function generator (FG250D, Funktionsgenerator). Thus, the LCU drives the PLD source to deliver pulses with variable energy and repetition rate. The function generator provides a TTL signal to sync DAQ card with PLD output. A single-element ultrasound transducer with central frequency 2.25 MHz, and 13 mm active element size (V306-SU-NK-CF1.9IN, Olympus) was used to acquire generated PA signals. The acquired PA signals were amplified, and filtered with 1-10 MHz band filter by pulse receiver (Olympus, 5072PR). The signals were acquired using a 25 Ms/s data acquisition card (DAQ) (compuscope 4227, GaGe) installed inside a desktop computer.

Fig. 2. Comparison between PA amplitude profiles measured with PLD-PAT and OPO-PAT. Amplitude profiles of an ink sample measured with PLD (a) when the outer tube contains water at room temperature, and (b) when the hot water was injected through the outer tube. (c) and (d) are the corresponding PA amplitude profiles of an ink sample measured with OPO laser. Here, single averaging was carried out over seven PA signals in case of PLD and OPO. (e) Temperature sensitivity as a function of number of measurements averaged in log-log scale.

The sample holder used for the entire study is shown in Figure 1(b). Here a thin low-density polyethylene (LDPE) tube [inner diameter (ID) = 0.59 mm, wall thickness (WT) = 0.19 mm] was inserted inside a thick LDPE tube (ID = 1.68 mm, WT = 0.37 mm). The inner tube contains test sample (black ink or fresh animal blood) and the outer tube contains water. Hot water in the range 80°C - 90°C was used to heat the test sample in the inner tube. To compare the temperature profiles measured with the PLD-PAT system, a fiber Bragg grating (FBG) sensing system with 1 millisecond temporal resolution was also inserted in the inner tube [Fig. 1(b)]. The Bragg wavelength of the

FBG sensor used in this study is 1550 nm. The Bragg wavelength of the FBG sensor is sensitive to mechanical strain and temperature both. The strain and temperature sensitivities of the FBG sensor at 1550 nm Bragg wavelength are 1.2 pm/ $\mu\epsilon$ and 13 pm/ $^{\circ}\text{C}$ [20, 21]. In this study, the FBG sensor is free (mechanically unbonded) and is inserted in the test sample as shown in Figure 1(b). Hence, it measures only the temperature variations in the test sample.

In Figures 1(c-f), we showed schematic diagrams to explain the concept on which the PLD-PAT measures temperature changes. Figure 1(c) shows a train of laser pulses with same amplitude. We considered a case where the sample temperature, say, initially is constant and later raised due to heating [Figure 1(d)]. When a train of laser pulses strikes such sample, the PA amplitude changes according to the local temperature of the sample as illustrated in Figure 1(e). The rise in local temperature leads to increased PA signal amplitudes. By plotting the peak-to-peak amplitude of PA signals in real-time, one can monitor the local temperature of the sample in real time as shown in Figure 1(f). Note that this method only monitors the relative change in the temperature not the absolute local temperature. PA based measurement can also measure absolute temperature [7, 11], however, for this work we only use the relative temperature rise.

In PAT, signal originates from optical absorption of pulsed light by the tissue chromophores. When the absorber or surrounding temperature changes, photoacoustic amplitude changes accordingly. To monitor the temperature changes in real-time, the PLD-PAT in Figure 1(a) was used. The system performance was demonstrated on two different samples: black ink and fresh rat blood. First, black ink was injected into the inner tube and water at room temperature (22°C) was injected in to the outer tube. The tank contains water at room temperature. The diverging beam from the PLD illuminates the sample and the PA signals from the ink were collected using the UST for 5 sec. Here, averaging was done over seven PA signals, i.e., the sampling time was reduced from 143 μs to 1 millisecond. The peak-to-peak PA signal amplitudes were plotted as a function of time as shown in Figure 2(a). In the 5 sec acquisition time, the PA signal amplitude profile shows that the ink temperature is constant and there is no temperature rise due to laser exposure for 5 sec. Later, water at room temperature was injected in to the outer tube. Then we start collecting the PA signals for 5 sec. During the 5 sec, we injected hot water through the outer tube to quickly heat up the black ink. The peak-to-peak PA signal amplitude (with 7 point averaging) were plotted as shown in Figure 2(b). Here the relative temperature of the black ink and hence the PA amplitude increased due to heating. After heating, the PA amplitude increased by 0.74 V, i.e. from 0.8 V to 1.54 V. A 4.4% increase in PA amplitude corresponds to 1°C raise in temperature [11]. From the 92.5% increase in PA amplitude, the estimated temperature raise of black ink after heating was approximately 21°C . The sensitivity of the PAT system was quantified from the standard deviation of PA amplitude measurements. For ink, it was 0.011V. So, the measurement sensitivity is $0.011 \cdot (21/0.74) \approx 0.31^{\circ}\text{C}$. For comparison, these measurements were carried out using a conventional laser source which consists an optical parametric oscillator (Continuum, Surelite) pumped by a 532 nm Nd:YAG laser (Continuum, Surelite Ex). The OPO generates 5 ns duration pulses at 10 Hz repetition rate with wavelength tunable from 680 nm to 2500 nm. The OPO was tuned to deliver 803 nm. Due to the significant power fluctuations in OPO output, it was necessary to use averaging to improve the measurement sensitivity. The OPO measurement sensitivity was 0.74°C without averaging and was improved to 0.32°C after averaging over seven signals. Basically, we kept the sensitivities of PLD and OPO measurements similar in this experiment. Figures 2(c) and 2(d) show the PA profiles of ink measured with OPO/PAT without and while heating, respectively. Due to the low repetition rate

(10 Hz) of the Nd:YAG/OPO laser, the PA profile show poor temporal resolution (~ 0.1 sec with no averaging, 0.7 sec with averaging seven signals). Thus OPO/PAT is not an ideal candidate for providing accurate information about the tissue local temperature in real-time. In PLD-PAT, we used 7 point averaging to exactly match the sampling rate of commercial FBG sensor i.e. 1 millisecond. Figure 2(e) shows the impact of averaging on the measurement sensitivity. As expected, it is clear from this plot that the measurement sensitivity improved with averaging more number of signals. Averaging over 140 signals (i.e., 50 Hz sampling rate) will provide sensitivity 0.1°C and is good enough for real-time temperature monitoring.

Fig. 3. PLD-PAT and FBG temperature profiles of an ink sample: (a) when hot water was injected through outer tube. The 115% increase in amplitude corresponds to a temperature rise of ink by 27.54°C with reference to the base temperature. (b) Representative PA signals at different temperatures. PLD-PAT and FBG temperature profiles of fresh rat blood: (c) when hot water was injected through outer tube, and (d) representative PA signals at different temperatures. The 75.5% increase in amplitude corresponds to a temperature rise of blood by 17.5°C with reference to the base temperature. Here, PAT- photoacoustic tomography, and FBG- fiber Bragg grating.

To demonstrate the real-time monitoring capability of the PLD-PATS system, we measured the fast rise of ink temperature while heating it with hot water. Hot water was injected through the outer tube and PA signals were acquired for 5 sec. At the same time FBG sensor data was collected at 1 millisecond temporal resolution. The profiles measured at same time and same resolution are compared in Figure 3(a). With respect to the background, the PA amplitude raised to a maximum value of 0.92 V. And the corresponding temperature profile measured with FBG sensor shows temperature rise of 27.5°C . So, a 4.2% increase in ink PA amplitude corresponds to 1°C temperature rise. Figure 3(b) compares three representative PA signals corresponding to different temperatures. With increase in sample temperature, the acoustic velocity is increased, and the acoustic flight time reduced accordingly. It is clear from Figure 3(b) that the PA signal 'C' reached detector earlier compared to signals at 'A' and 'B'. The performance of the system was tested on a fresh rat blood sample as well. Blood sample was injected in to the inner tube and room temperature water was injected through the outer tube. In order to heat the blood sample, hot water was injected through the outer tube. While injecting hot water, PA signals were acquired for 5 sec. The temperature profiles of blood measured with PLD-PAT and

FBG sensor are plotted in Figure 3(c). After heating, the PA amplitude was increased by 0.4 V and FBG temperature by 17.5°C. It indicates a 4.3% rise in PA amplitude of blood corresponds to 1°C temperature rise. Figure 3(d) compares three representative PA signals corresponding to different temperatures of blood. These results prove that the PLD-PAT system can monitor the temperature of blood, tissue or tumor etc. at high temporal resolution accurately.

In this study, if no signal averaging is used, temperature can be monitored at a resolution of $\sim 143 \mu\text{s}$ using the proposed system. However, without any averaging the laser pulse to pulse variation will affect the temperature sensitivity. The system uses a NIR 803 nm wavelength which show better penetration in tissue. The sensitivity of the system is limited by the pulse energy, so by using high energy NIR PLDs, it is possible to enhance the sensitivity of the system further.

In this letter, a pulsed laser diode based photoacoustic system for temperature sensing with high resolution and high sensitivity was demonstrated. The system could provide temperature information at 1 millisecond temporal resolution and **0.31°C** temperature sensitivity. The system could clearly monitor the rapid changes in the temperature of sample or tissue by plotting the peak-to-peak values of PA signals as a function of acquisition time. Also the PA temperature profiles match well with the intensity profiles of commercial FBG sensor. The proposed PLD-PATS system is simple, noninvasive, less-costly yet can provide temperature data (at 1 ms resolution and **0.31 °C** sensitivity). **By operating the system at reduced sampling rate, say 50 Hz (20 milliseconds), it is possible to achieve 0.1 °C sensitivity.** In future, we will use this system to study the thermal properties of materials, and for monitoring tissue or tumor temperature *in vivo*. It may find applications in medicine including radiation therapy, thermal therapy, photothermal therapy, photodynamic therapy, etc.

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