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High-speed, low-cost, pulsed laser diode based second generation desktop photoacoustic tomography system (PLD-PAT-G2)

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Bulky, expensive Nd:YAG lasers are used in conventional photoacoustic tomography (PAT) systems making them difficult to translate into clinics. Moreover, real-time imaging is not feasible when single-element ultrasound transducer is used with these low pulse repetition rate lasers (10-100 Hz). Low-cost pulsed laser diodes (PLD) can be used instead for photoacoustic imaging due to their high pulse repetition rates and compact size. Together with acoustic reflector based multiple single element ultrasound transducers portable desktop PAT system was developed. This second generation pulsed laser diode based photoacoustic tomography (PLD-PAT-G2) achieved 0.5 s cross-sectional imaging time with a high spatial resolution of $\sim 165 \mu\text{m}$ and an imaging depth of 3 cm. The performance of this system was characterized using phantom and *in vivo* studies. Dynamic *in vivo* imaging was also demonstrated by monitoring the fast uptake and clearance of indocyanine green in small animal (rat) brain vasculature.

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Photoacoustic (PA) imaging has been gaining a lot of attention in the biomedical imaging community over the past two decades. PA imaging is based on acoustic detection of optical absorption from chromophores (hemoglobin melanin, lipids, cytochromes etc.) present in tissue. Major applications of this technique include breast cancer detection, total hemoglobin concentration (HbT) mapping, oxygen saturation (SO_2) mapping, skin cancer vascular imaging, whole body imaging of small animals and so on [1-4]. In photoacoustic computed tomography / photoacoustic tomography (PACT/PAT), a nano second duration laser pulses produces ultrasound waves (known as PA waves) when irradiated on biological tissue due to light absorption and thermoelastic expansion. These PA waves are received by a broad band ultrasound transducer (UST) outside the tissue boundary. Various reconstruction algorithms can be used to map the initial

pressure rise distribution to generate cross-sectional PA image representing the tissue absorption map [5, 6].

Conventional PACT/PAT systems employ bulky, expensive and low repetition rate (~ 10 – 100 Hz) Nd:YAG laser [7] coupled with optical parametric oscillator (OPO)/dye laser as excitation source in near-infrared (NIR) region and a single-element UST (SUT) or an array UST for PA signal detection. These lasers need a vibration-isolation optical table to house them in order to produce optimum laser output (~ 100 mJ pulse energy). Portable high pulse energy OPO lasers (e.g., OPOTEK) are available now but they are even more expensive. Due to low repetition rate laser, one SUT takes several minutes to rotate around the sample in full circle to acquire the PA signals. This inhibits imaging speed of the PACT system, thus dynamic imaging of rapidly changing biological phenomena is not feasible. Dynamic imaging is needed for monitoring of pharmacokinetic, biodistribution of exogenous contrast agents, blood-velocity imaging, oxygen saturation imaging, small animal neurofunctional imaging, etc. [8] For high-speed imaging, customized full-ring array transducers can be used, e.g., recently a state-of-the-art single impulse PACT system at 50 Hz frame rate was reported [9]. But these custom-made array transducers require complex back-end parallel signal amplifiers and digitizer electronics which in turn increases the cost, making it challenging for clinical translation.

In recent years, pulsed laser diode (PLD) [10-12] or light emitting diode (LED) [13, 14] are being used for PA imaging due to its compact size (no need of optical table), low cost, and higher pulse repetition rate (kHz) for real-time imaging compared to conventional Nd:YAG/OPO laser. PLD based PAT imaging system was successfully demonstrated for brain imaging [15], high-frame rate imaging using array transducers [16], rheumatology [17], and the diagnosis of cardiovascular disease [18]. First generation portable PLD-PAT system was developed by mounting the PLD inside the PAT scanner and using one SUT [11], and *in vivo* imaging was demonstrated in 5 s scan time [15]. Instead of using the UST horizontally, acoustic reflector based single-element ultrasound transducer (SUTR) can be used in vertical direction, which reduces the scanning radius thereby the size of the PAT

scanner. The performance of the SUTR was shown for phantom and *in vivo* imaging and compared with that of SUT using OPO-PAT system [19]. To improve the frame rate further, instead of using one SUT multiple SUTs can be used [20, 21], and instead of stop-and-go scan continuous scan can be used [22]. By consolidating all these techniques we developed a second generation pulsed laser diode based desktop photoacoustic tomography (PLD-PAT-G2) system using PLD laser inside the scanner and 8 SUTRs. We have characterized the spatial resolution, imaging depth of this system and also demonstrated its dynamic imaging ability using uptake and clearance process of indocyanine green (ICG) *in vivo* rat brain vasculature.

Fig. 1. (a) Schematic of the PLD-PAT-G2 system; LDU - laser driving unit; DAQ - data acquisition card; AMP - amplifier; SM - stepper motor; AM - anesthesia machine; PLD - pulsed laser diode; SUTR - acoustic reflector based ultrasound transducer. (b) Closer view at the transducers and laser illumination. (c) Photograph of the system. (d) Photograph of the horse hair phantom. (e) LDPE tubes filled with ICG and blood on chicken breast tissue. (f) Stacked layers of chicken tissue.

The schematic of the PLD-PAT-G2 system (with photograph) is shown in Figs. 1(a) to 1(c). PLD laser (QD-Q1924-ILO-WATER) capable of delivering 2000 pulses per second of ~ 107 ns pulse width at ~ 816 nm wavelength onto the sample. The PLD laser was controlled by a laser driving unit (LDU) consisting of a water cooling system, a 12 V power supply (Votcraft, PPS-11810), a variable power supply (EA-PS 8160-04 T) to change the laser power, and a function generator (RIGOL DG1022) to control the pulse repetition rate (up to 2 kHz). The output laser power after the diffuser was 6.8 W at 2 kHz pulse repetition rate. The laser energy density was maintained to be 0.17 mJ/cm², well below the ANSI safety limit [23] for a scan time of 0.5 s (1.58 mJ/cm²). The generated PA waves were acquired by 8 unfocused SUTRs (SUT: V309-SU/ U8423013, augmented with 45° acoustic reflector: F102, Olympus NDT) of 5 MHz central frequency with 70% fractional bandwidth and 13 mm active area diameter. All 8

SUTRs were placed around the sample at 45° interval in a circle. To acquire the PA data in full circle each transducer needs to rotate 45° around the target object. For comparison purpose, we also collected the data for one full rotation (360°) of 1 SUTR around the target object. Three different scan speeds of 30 degree/sec, 45 degree/sec, and 90 degree/sec were used for comparison between the PA data obtained using 8-SUTRs and 1-SUTR. The acquired PA signals were amplified by using low noise signal amplifiers by 48 dB (Mini-circuits, ZFL-500LN-BNC, used 2 of them in series for each channel) and stored using a 8-channel data acquisition (DAQ) card (Spectrum, M2i.4932-exp) inside a Windows operating desktop (Intel Xeon, 3.7 GHz 64-bit processor, 16 GB RAM). All the PA data were acquired at 25 MHz sampling rate. A TTL (transistor-transistor logic) signal from the function generator was used to synchronize the data acquisition with the laser pulse excitation. For better comparison purpose, PA data for all the cases were averaged into 400 A-lines before reconstruction. In this work all the reconstructions were done using simple delay-and-sum reconstruction method.

Fig. 2. Reconstructed PLD-PAT-G2 images of triangular shaped horse hair phantom. (a-c) Reconstructed images obtained using 1-SUTR for different acquisition times of 4, 8, and 12 s, respectively. (d-f) Reconstructed images obtained using 8-SUTRs for acquisition times of 0.5, 1, and 1.5 s, respectively. SNRs values are shown on each image.

Figure 2 shows the reconstructed cross-sectional PA images of a triangular shaped horse hair phantom of 150 μ m thickness and a side length of ~ 8 mm [Fig. 1(d)]. Figures 2(a)-2(c) show the reconstructed images for the PA data obtained around 360° using 1-SUTR for different scan times of 4 s, 8 s, and 12 s, respectively. Figures 2(d)-2(f) represent the reconstructed images for the PA data obtained using 8-SUTRs rotating 45° around the sample for scan times of (4/8) s, (8/8) s, and (12/8) s, respectively. The quality of the images obtained using 8-SUTRs was compared with that of images obtained using 1-SUTR using signal-to-noise-ratio (SNR). SNR was calculated for each reconstructed image as $\text{SNR (dB)} = 20 \log_{10}(V/n)$, where V is average PA amplitude of the target object and n is the standard deviation of the background noise. The reconstructed images obtained for 0.5 s, 1 s, and 1.5 s scan time were similar to that of the reconstructed images obtained for 4 s, 8 s, and 12 s scan time, respectively, in terms of SNR values (shown on each image) and the shape of the target objects were also similar. Hence, highest frame rate of 2 Hz (0.5 s per frame) can be obtained using the PLD-PAT-G2 system. At this imaging speed we don't see any noticeable artefact (blur due to the high scan speed [11]) in the reconstructed images. We also

have another artefact due to the use of 8 UST versus 1 UST (especially in the angles of the triangle), which we have not corrected in this work. The resolution of this system was calculated from the full-width at half-maximum (FWHM) of the point spread function (obtained from the hair phantom image) and was found to be $\sim 165 \mu\text{m}$. Use of multiple SUTRs did not compromise the system resolution or the SNR.

Fig. 3. *In vivo* PLD-PAT-G2 imaging of cortical vasculature of rat. (a-c) PAT images obtained using a single SUTR for different acquisition times of 12, 8, and 4 s, respectively. (d-f) PAT images obtained using 8-SUTRs for acquisition times of 1.5, 1, and 0.5 s, respectively. SS - sagittal sinus; TS - transverse sinus; and CV - cerebral veins. SNR values are shown on each figure. (g) Photograph of the rat head before PA imaging. (h) Photograph of the animal brain, the top skin layer on the head cut open after the completion of PA imaging. The yellow arrows in (a) points to the corresponding vascular structures in (h).

Next *in vivo* brain imaging was carried out on healthy female rats weighing ~ 80 -100 gm purchased from InVivos Pte. Ltd., Singapore. All the animal experiments were carried out according to the approved guidelines and regulations by the institutional Animal Care and Use Committee of Nanyang Technological University, Singapore (Protocol No: A0263). The animals were anesthetized using a mixture of Ketamine (85 mg/kg) and Xylazine (15 mg/kg) by injecting intraperitoneally (0.2 ml/100 g). The hair on the animal head was trimmed and then epilated using hair removal cream. During the experiments an anesthesia mixture of 0.75 % isoflurane along with oxygen (1.2 L/min) was maintained. A custom-made animal holder and a translational stage were used to hold the animal and adjust the imaging plane. After the completion of PA data acquisition, animals were euthanized by injecting Valbarb (sodium pentobarbitone 300 mg/ml) intraperitoneally. Figures 3(a)-3(c) show the reconstructed PA images using 1-SUTR rotating around 360° for different scan times of 12 s, 8 s, and 4 s, respectively. Figures 3(d)-3(f) represent the reconstructed PA images using 8-SUTRs rotating around 45° for different scan times of 1.5 s, 1 s, and 0.5 s, respectively. Figure 3(g) shows the photograph of the rat head before taking PAT images. Figure 3(h) is the photograph taken after removing the skin layer on the head once PAT imaging was finished. The PAT images obtained for 0.5 s, 1 s, and 1.5 s scan time were similar to that of the PAT images obtained for 4 s, 8 s, and 12

s scan time in terms of SNR values (shown on each image, SNR was calculated using the signal from SS region and background noise from region away from the whole brain). Also, the sagittal sinus (SS), transverse sinus (TS), and cerebral veins (CV) can be clearly seen in the images obtained from the 45° rotation of 8-SUTRs for 0.5 s, 1 s, and 1.5 s and are similar to images obtained for 360° rotation of 1-SUTR for 4 s, 8 s, and 12 s, respectively.

Next a study was conducted to determine the imaging depth of the PLD-PAT-G2 system. Two low-density polyethylene (LDPE) tubes one filled with ICG (12633-25mg, SigmaAldrich) and other filled with rat blood were placed on chicken breast tissue as shown in Fig. 1(e). ICG was prepared with $323 \mu\text{M}$ concentration to have absorption peak around 800 nm. Layers of chicken breast tissue were stacked on top of the LDPE tubes to image ICG and blood at different depths of 1 cm, 2 cm, and 3 cm [Fig. 1(f)]. PA data was acquired at different depths for all the scan times of 12 s, 8 s, 4 s using 1-SUTR and 1.5 s, 1 s, 0.5 s (only these images are shown here for brevity) using 8-SUTRs. The comparison of SNR for ICG and blood at different depths for all the scan times can be observed in Fig. 4(a). The reconstructed cross-sectional PA images of ICG and blood for 0.5 s acquisition scan at different depths of 1 cm, 2 cm, and 3 cm can be seen in Figs. 4(b)-4(d), respectively. ICG had higher contrast and SNR compared to blood at all depths. We can successfully image at 3 cm deep inside the tissue (*in vitro*) using this PLD-PAT-G2 system.

Fig. 4. Deep-tissue imaging of ICG and blood tubes embedded inside chicken breast tissue using 8 USTR PLD-PAT-G2 system. (a) Signal-to-noise ratio of ICG and blood at different depths for various scan times. (b-d) PAT images at 1 cm, 2 cm, and 3 cm depth (scan time 0.5 s).

Next, high-speed *in vivo* dynamic imaging ability of the PLD-PAT-G2 system was demonstrated at 0.5 s acquisition scan time. We had conducted a study to visualize the hemodynamic changes in the cortical vasculature of rat brain due to the fast uptake and clearance process of ICG ($323 \mu\text{M}$ conc.). ICG was administered (0.3 ml/100 gm) into the tail vein of the healthy female rat weighing ~ 80 -100 gm. Before administering ICG, pre-injection baseline PAT images were obtained. After injecting ICG, for the first 5 min the PA data was continuously obtained at ~ 0.9 -1.1 s time interval (scan and saving the data, reconstruction was done later) and later at 2 min interval until the next 5 min and at 5 min interval for the next 25 min. Due to the increase in optical absorption by ICG at 816 nm wavelength, the average PA signal in

the superior SS started to increase and subsequently decrease over time as can be seen in Fig. 5. A polynomial fit with a degree of 15 was used to model the data in Fig. 5. Similar trend was observed on multiple rats. This trend was similar to the one reported earlier in Ref [15]. The uptake of ICG was maximum at ~4.35 min post-injection and the clearance process of the dye was monitored for 35 min post-injection.

In this letter, we had demonstrated an ultra-compact, portable, affordable desktop PAT imaging system with the use of PLD that renders high temporal and spatial resolutions making it more suitable for real-time imaging. The system is capable of imaging cross-sectional PA images in 0.5 s (the fastest imaging system with multiple single-element UST reported so far). The cross-sectional *in vivo* brain images were obtained in 0.5 s (10 times faster than the first generation PLD-PAT system [15]). There is no compromise on the image quality (in terms of SNR) or resolution or imaging depth. The spatial resolution was ~165 μm (with 5 MHz unfocused UST). Due to the low frequency ultrasound detection in PAT (typically 1-10 MHz), the longer pulse width of the PLD (107 ns) will not affect the spatial resolution. By using PLD with low pulse width and high frequency UST, spatial resolution can be further improved. Using this PLD-PAT-G2 system, it was also shown that an imaging depth of 3 cm can be achieved (*in vitro*), which is deeper than previously reported [11]. The potentiality of this system for dynamic *in vivo* imaging was demonstrated by monitoring a fast uptake and clearance process of ICG in the cortical vasculature.

Fig. 5. Pharmacokinetics of ICG in rat brain showing the uptake and clearance over 35 min post-injection time. Red arrow shows the ICG injection time into the tail vein.

The current imaging speed can be further improved by using higher torque motor and/or by using more number of SUTRs (this will increase the cost of the overall system). However with further reduction in scan time, there may be artefacts introduced in the PAT image, which can be corrected by more efficient reconstruction algorithm. Although the circular ring-array based PAT system offers real-time imaging, they are custom-made. Hence, the cost is high (array transducers and the back-end electronics will cost several hundred thousand dollars). In addition, the ring array transducers have fixed central frequency, bandwidth, and radius. Whereas the SUTRs offers flexibility, and can be placed at desired location and are readily available in the market at low price (few hundred dollars) and with various frequency and bandwidth options. Overall, PLD-PAT-G2 system will cost ~5-10% of the full ring array-based Nd:YAG/OPO PAT system. However, PLD poses few limitations which needs attention and improvement in the future. For example, (a) low per

pulse energy, (b) wavelength tunability, although multiple-wavelength PLDs are available, but only with few wavelength options. More wavelength options for PLD will lead to better functional and spectroscopic imaging. In spite of these drawbacks, due to its compactness, portability, high-speed, and low cost, the proposed PLD-PAT-G2 system will find applications in neurofunctional activities, characterization of pharmacokinetic and biodistribution profiles in the development process of drugs or any other exogenous contrast agents in small animal studies.

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