Lock-in-photon-counting-based highly-sensitive and large-dynamic imaging system for continuous-wave diffuse optical tomography

Weiting Chen, Xin Wang, Bingyuan Wang, Yihan Wang, Yanqi Zhang, Huijuan Zhao, and Feng Gao

1College of Precision Instrument and Optoelectronics Engineering, Tianjin University, Tianjin 300072, China
2Tianjin Key Laboratory of Biomedical Detecting Techniques and Instruments, Tianjin 300072, China
gaofeng@tju.edu.cn

Abstract: We implemented a novel lock-in photon-counting detection architecture that combines the ultra-high sensitivity of the photon-counting detection and the measurement parallelism of the lock-in technique. Based on this technique, a dual-wavelength simultaneous measurement continuous wave diffuse optical tomography system was developed with a configuration of 16 sources and 16 detectors that works in a tandem serial-to-parallel fashion. Methodology validation and performance assessment of the system were conducted using phantom experiments that demonstrate excellent measurement linearity, moderate-term system stability, robustness to noise and negligible inter-wavelength crosstalk. 2-D imaging experiments further validate high sensitivity of the lock-in photon-counting methodology as well as high reliability of the proposed system. The advanced detection principle can be adapted to achieving a fully parallelized instrumentation for the extended applications.

©2016 Optical Society of America

OCIS codes: (120.0120) Instrumentation, measurement, and metrology; (170.2655) Functional monitoring and imaging; (170.3890) Medical optics instrumentation; (170.4090) Modulation techniques; (170.6960) Tomography.

References and links
1. T. Durduran, R. Choe, W. B. Baker, and A. G. Yodh, “Diffuse optics for tissue monitoring and tomography,” Rep. Prog. Phys. 73(7), 076701 (2010).
2. A. Gibson and H. Dehghani, “Diffuse optical imaging,” Philos. Trans. A Math Phys. Eng. Sci. 367(1900), 3055–3072 (2009).
3. C. E. Elwell and C. E. Cooper, “Making light work: illuminating the future of biomedical optics,” Philos. Trans. A Math Phys. Eng. Sci. 360(1855), 4358–4379 (2011).
4. Y. Hoshi, “Towards the next generation of near-infrared spectroscopy,” Philos. Trans. A Math Phys. Eng. Sci 369(1955), 4425–4439 (2011).
5. A. P. Gibson, J. C. Hebden, and S. R. Arridge, “Recent advances in diffuse optical imaging,” Phys. Med. Biol. 50(4), R1–R43 (2005).
6. X. Zhang, “Instrumentation in diffuse optical tomography,” Photonics 1(1), 9–32 (2014).
7. A. Siegel, J. J. A. Marota, and D. Boas, “Design and evaluation of a continuous-wave diffuse optical tomography system,” Opt. Express 4(8), 287–298 (1999).
8. H. Koizumi, T. Yamamoto, A. Maki, Y. Yamashita, H. Sato, H. Kawaguchi, and N. Ichikawa, “Optical topography: practical problems and new applications,” Appl. Opt. 42(16), 3054–3062 (2003).
9. J. M. Lasker, J. M. Masciotti, M. Schoenecker, C. H. Schmitz, and A. H. Hiescher, “Digital-signal-processor-based dynamic imaging system for optical tomography,” Rev. Sci. Instrum. 78(8), 083706 (2007).
10. F. Scholkmann, S. Kleiser, A. J. Metz, R. Zimmermann, J. Mata Pavia, U. Wolf, and M. Wolf, “A review on continuous wave functional near-infrared spectroscopy and imaging instrumentation and methodology,” Neuroimage 85(Pt 1), 6–27 (2014).
11. D. A. Boas, A. M. Dale, and M. A. Franceschini, “Diffuse optical imaging of brain activation: approaches to optimizing image sensitivity, resolution, and accuracy,” Neuroimage 23(1 Suppl 1), S275–S288 (2004).
12. A. T. Eggebrecth, S. L. Ferradal, A. Robichaux-Vieloveu, M. S. Hassanpour, H. Dehghani, A. Z. Snyder, T. Hershey, and J. P. Culver, “Mapping distributed brain function and networks with diffuse optical tomography,” Nat. Photonics 8(6), 448–454 (2014).

#253976

Received 16 Nov 2015; revised 21 Dec 2015; accepted 13 Jan 2016; published 15 Jan 2016

(C) 2016 OSA 1 Feb 2016 | Vol. 7, No. 2 | DOI:10.1364/BOE.7.000499 | BIOMEDICAL OPTICS EXPRESS 499
1. Introduction

Diffuse optical tomography (DOT), as an extension of near-infrared (NIR) spectroscopy, has evolved into a novel functional imaging modality that aims at spectrally and spatially resolved images of the optical properties and further quantifying oxy- and deoxy-hemoglobin (HbO/HbR) concentrations in biological tissues [1–4]. Although all the relevant systems exploit the relative transparency of biological tissues to NIR light (650–900 nm), the nature of the data obtained for the image reconstruction and the complexity of the optoelectronics used for the data acquisition vary markedly [5,6]. Among these, the instruments for continuous-wave (CW) measurements, despite of being inferior in informing abundance and depth sensitivity to those for frequency- and time-resolved measurements, enable fast data acquisition and the use of simple detectors and electronics [7–10]. The strengths lend themselves well to tracking the changes of oxygen status by functional or drug-induced stimulation, and to cost-effectively implementing high-density multichannel systems. In an overall sense, the practical advantages of CW technology e.g., favorable signal-to-noise ratio (SNR), high temporal resolution, potential portability, and easiness of operation, continuously allow us to employ it as the methodology for wide biomedical applications, particularly in brain imaging for neural activity probing or physiological status monitoring [11–14], as well as in pharmacokinetic imaging for specificity- and contrast-enhanced tumor diagnosis, malignancy staging and drug-delivery assessment [15–18].

To spatially resolve changes in tissue HbR and HbO concentrations, CW-DOT normally requires a sequence of scanning radiations with at least two NIR wavelengths which are either in the both sides of the isobestic point (800 nm) in the absorption spectra of the two chromophores, respectively, or in the range ≤780 nm [10], as well as a multiple of detection channels that is normally achieved by either an array of discrete photo-sensitive elements, e.g., avalanche photodiodes (APDs) and photomultiplier tubes (PMTs), or an integrated photo-sensing array, e.g., a charge-coupled device (CCD) or a complementary metal-oxide semiconductor (CMOS) sensor [6]. The state-of-the-art CW-DOT instruments adopted the...
lock-in detection schemes that are primarily implemented using the digital phase-sensitive detection (PSD). The lock-in detection not only significantly improves temporal resolution of the measurement by enabling multi-wavelength and multi-point illumination of a subject without information mixing, but also effectively enhances SNR of the data acquisition by rejecting the low frequency electronic noise and ambient light [8,9,19]. Nevertheless, the imaging systems have heretofore lacked the combination of the light-source-encoding-based parallelization of the lock-in detection and the ultra-high sensitivity of the photon counting, although the digital PSD naturally suits for photon counting applications [20,21]. Within the framework of the lock-in detection, the signal from a photon counting detector is intrinsically in a digital form as a train of discrete pulses, with its occurrence probability instantaneously proportional to the intensity of the total flux. For demodulating the signal at a given reference frequency, the digital PSD can be equivalently accomplished by a multi-periodic reference-weighted counting (RWC) strategy where the reference weight is simply accumulated at the occurrence of each single-electron response (SER) pulse. In comparison with the conventional PSD implementation where the measured signal is firstly temporally sampled using a multi-channel counter through synchronized multi-periodic integration, i.e., the multichannel scaler [22], and then demodulated by a reference multiplication and filtering process [9], the multi-periodic RWC implementation features low-complexity architecture that fits in commercially available low-cost reconfigurable devices, as well as nearly unlimited sampling configuration that is beneficial to improved noise rejection and large dynamic range.

In this work, a highly-sensitive and large-dynamic prototype 16×16 channel (16 sources and 16 detectors) CW-DOT system is developed based on the lock-in photon-counting detection. The system sequentially delivers frequency-encoded dual-wavelength NIR light to 16 illumination-sites on the surface of domain to be imaged and works with 4 channels of the lock-in photon counting to detect and spectrally resolve the outward light at 16 detection-sites in a tandem serial-to-parallel mode. The fiber-optic and discrete channel design is primarily devoted to brain functional and breast imaging applications where a skull- and breast-conforming sampling is normally required with moderate-density but ultrahigh-sensitivity. A series of assessments and imaging experiments are conducted to validate the performances of the proposed system in terms of sensitivity, linearity and measuring time.

2. Instrumentation

2.1. Overview

As illustrated in Fig. 1, the system is equipped with $L(=2)$ fiber-tailed laser diodes (LDs) at the wavelengths of 675nm and 785nm (LPS-675-FC and LPS-785-FC, Thorlabs), respectively, each driven by a combination of a current controller (LDC205C, Thorlabs) and a temperature controller (TED200C, Thorlabs). The driving currents of the two LDs are modulated at two different frequencies of $f_1 = 7.0$ kHz and $f_2 = 10.0$ kHz, respectively, using a customized frequency-configurable 2-channel direct digital synthesis (DDS) module. The module core contains two channels of paired 12-bit digital in-phase (sinusoidal) and quadrature (cosinusoidal) signals programmed using the Coordinated-Rotation-Digital-Computer algorithm, and is implemented in FPGA hardware (Spartan-3E, Xilinx, USA). The digital in-phase signals are fed to a digital-to-analog convert circuit (AD9765, 12bit) to generate two channels of analog sinusoidal signals for the LD modulation, and both the digital signals are used as the PSD references in the lock-in photon counting. Lights from the two LDs are combined by a wave-division-multiplexer (WDM) (Oz Optics, Canada), and sent to a programmable $1 \times 16$-fiber-optic-switch (FSW1 $\times$ 16-SM-B, Guilin Institute of Optical Communications, China) and is then sequentially directed to $S(=16)$ source-fibers with 62.5-μm core diameter and 0.22 numerical aperture (NA). For signal collection, $D(=16)$ detection-fibers with 500-μm core diameter and NA = 0.37 are connected to an integrated
module of four 1 × 4-fiber-optic-switches (FSW4-1 × 4-MM-B, Guilin Institute of Optical Communications, China) with its four outputs coupled to four photomultiplier tube (PMT) counting heads (H8259-02, Hamamatsu Photonics, Japan) and converted into TTL electrical pulses corresponding to the PMT single-electron responses. The demodulation of the signals from the four PMTs is conducted with a specifically designed lock-in photon-counting module, also implemented in FPGA hardware. Inside the module, four independent demodulation channels, with each corresponding to one PMT detector, work in parallel.

Decoding of the signals in each channel is conducted by two digital PSD blocks based on time-gated weighted-counting, with each regarding one of the two reference frequencies, as shown in Fig. 2. A software interface is developed in LabVIEW for controlling the whole system, including setting of the working parameters (modulation frequencies, integration time), selection of the scanning mode, sequencing of the measurement procedure and data communication, etc.
### 2.2. Reference-weighted counting strategy

As the $d(=1,2,\ldots,D)$-th detection site for the $s(=1,2,\ldots,S)$-th illumination site, the detected signal in the above lock-in DOT measurement is the sum of all the responses to the two modulated sources

$$I_{s,d}(i) = \sum_{l=1}^{L} S_{s,d}^{(l)}(i) + N_{s,d}(i),$$  \hspace{1cm} (1)

Where $N_{s,d}(i)$ is the noise term, $S_{s,d}^{(l)}(i)$ is the $f_{l}$-modulated response signal, and $L$ is the number of sources.

When measuring extremely weak light using PMT device, the detected optical signal emerges as discrete SER pulses out of the detector, which conforms to Poisson-distribution, and the expectation and standard deviation are the intensity of the light signal and its square root, respectively [23]. A random binary signal $a_{s,d}^{(l)}(i)$ is introduced to denote the SER pulses occurrence ($=1$) or not ($=0$), and the occurrence probability in a narrow time bin is proportional to the instantaneous signal intensity, i.e.,

$$P[a_{s,d}^{(l)}(i)=1] \propto A_{s,d}^{(l)} \sin[2\pi f_{l}i/f_s + \phi_{s,d}^{(l)}],$$  \hspace{1cm} (2)

where $A_{s,d}^{(l)}$ is the intensity to be measured, and $f_s$ is the sampling frequency corresponding to the width of the time bin, that is uniquely decided to be 50MHZ by the system clock. This means that, in this case, the occurrence of SER pulses is periodical. To label the periodic information of each coming SER pulse, the total integration time $T$ is divided into $M$ units by the signal frequency ($M^{(l)}=T/f_s$), and in each unit, $N^{(l)}(=f_s/f_l)$ phase channels are obtained. Consequently, $S_{s,d}^{(l)}(i)$ is expressed by $m$ (locating period information) and $n$ (locating phase information), i.e.,

$$S_{s,d}^{(l)}(m,n) = a_{s,d}^{(l)}(i) \delta\left[(f_{l}) - n - (m-1)N^{(l)}\right].$$  \hspace{1cm} (3)

Here, the rounding term $(f_{l})$ is to position the time bins of occurrence, and $\delta$ is to symbolize the discreteness of $a^{(l)}_{s,d}(i)$.

The goal of the measurement herein is to extract the amplitude of the detected modulated response $A_{s,d}^{(l)}$ or a quantity that is proportional to it. To do so, we introduce a pair of in-phase and quadrature reference signals corresponding to each of the modulation frequencies: $I_{s}^{(l)}(n) = A_{s} \sin(2\pi f_in/f_s)$ and $Q_{s}^{(l)}(n) = A_{s} \cos(2\pi f_in/f_s)$, $l'=1,2,\ldots,L$, on the basis of the principle of digital quadrature lock-in detection [19,24], and the PSD/Lowpass (LP)-filtering process in traditional digital phase-lock detection can be regarded as in-phase and quadrature reference weighted counting processes expressed below

$$X_{s,d}^{(l)} = \sum_{m=1}^{M} \sum_{n=1}^{N} \left[ \sum_{l=1}^{L} S_{s,d}^{(l)}(m,n) \times I_{s}^{(l)}(n) \right] \propto \sum_{m=1}^{M} \sum_{n=1}^{N} P(a_{s,d}^{(l)}(n+(m-1)N^{(l)})=1) \times A_{s} \sin(2\pi f_{l}n/f_s) \times A_{s,d}^{(l)} \cos \phi_{s,d}^{(l)},$$

$$Y_{s,d}^{(l)} = \sum_{m=1}^{M} \sum_{n=1}^{N} \left[ \sum_{l=1}^{L} S_{s,d}^{(l)}(i) \times Q_{s}^{(l)}(n) \right] \propto A_{s,d}^{(l)} \sin \phi_{s,d}^{(l)}. \hspace{1cm} (4)$$

#253976  
Received 16 Nov 2015; revised 21 Dec 2015; accepted 13 Jan 2016; published 15 Jan 2016  
(C) 2016 OSA  
1 Feb 2016 | Vol. 7, No. 2 | DOI:10.1364/BOE.7.00499 | BIOMEDICAL OPTICS EXPRESS 503
According to Eqs. (2) and (3), it is obvious that a simple counting of SER pulses at fixed phase for multiple periods results in sine of the phase, which is in accordance with intensity of the response, as shown in Fig. 3(a). Therefore, the accumulation of the reference weights in terms of SER occurrence at fixed phase for multiple periods is equal to pulse counted and then multiplied by the reference, as shown in Fig. 3(b) and expressed by Eqs. (4) and (5). In this way, SER pulse in each phase channel is phase-locked detected. Finally, a summation (averaging) for a whole period is performed to complete the LP-filtering for the harmonic component suppression (not included in Fig. 3).

Fig. 3. Diagram of the multiple period accumulation: (a) conventional and (b) in-phase reference-weighted counting.

Finally, a \( A_{A_d}^{(l)} \)-proportional quantity is simply extracted for the reconstruction task

\[
A_x A_{A_d}^{(l)} \propto \sqrt{X_{A_d}^{(l)} + Y_{A_d}^{(l)}}.
\]

It is noted that, to take advantage of the zero-magnitude bins of the averaging filter, the filter length \( L_x \), the sampling rate \( f_s \), and the modulation frequency \( f_l \) should satisfy the relationship of \( f_l = k f_s / L_x \) \( (1 \leq k < L_x / 2) \) \[24\]. This equivalently means that, for fixed \( f_s \), the periodic sample number \( N^{(l)} = f_s / f_l \) for both the modulation signals should theoretically be an integer, and the gating time chosen to be integer multiples of both the modulation signal periods \( (1/f_l) \), i.e., \( M^{(l)} = T f_l \) is an integer. Since \( f_s \) significantly larger than \( f_l \), the former condition is always nearly satisfied.
The hardware structure of the RWC-PSD is presented in Fig. 4, where a pair of parallel accumulators are triggered by phase-aligned SER pulses (accomplished by the AND Logic between the PMT output and the system clock), to perform the in-phase and quadrature RWC operations, respectively, within a gating time.

3. System assessment

To verify the proposed lock-in photon-counting detection and assess the effectiveness of the system, a series of phantom experiments was performed. A slab phantom with a thickness of 25mm was adopted, with its background optical properties were $\mu_a = 0.0040 \text{ mm}^{-1} (675 \text{ nm}) / 0.0034 \text{ mm}^{-1} (785 \text{ nm})$ and $\mu_s' = 0.8000 \text{ mm}^{-1}$. The transmission measurement schemes were conducted for the assessment of different performances, where one source fiber and one detection fiber were arranged on the opposite side of the phantom with coaxial alignment configuration. For the assessments in both Section 3.1 and Section 3.3, the measurements were repeated for 10 times with the gating time $T_g$ consistently set to 1s, and the average values were calculated to reduce the stochastic errors.

3.1. Linearity and crosstalk

To verify the validity of the proposed approach, we experimentally assess the linearity of the lock-in photon-counting scheme for both the wavelengths, respectively. The light intensity of the source was varied by changing the amplitudes of the DDS modulation signal from 100mV to 220mV with a step of 20mV, while the other light source was powered off, and then the corresponding demodulation results were recorded, referred to as a single-source mode. To investigate the crosstalk in the simultaneous two-wavelength measurement, both the sources were powered on, with one modulated with a fix amplitude (160mV for both the 675-nm source and the 785nm-source), which was chosen according to the typical values used for the routine imaging, and another modulated with an amplitude varying linearly as described for the linearity evaluation, referred to as a dual-source mode.

Experimental data were firstly normalized by their respective maximums, and then evaluated for both the linearity and crosstalk performances by the linear regression analyses. Figure 5 shows the normalized measurements for the two wavelengths, in contrast to their respective linearly-regressed curves.
To further quantify the crosstalk in the dual-source measurements, a measure referred to as Crosstalk-Index (CI) was calculated that is defined as the ratio of the difference between the experimental single-source and dual-source data, to the single-source one, for each modulation amplitude, and are listed in Table 1.

The results from the proposed lock-in photon-counting scheme exhibit excellent linearity with high correlation coefficients of R>0.99 for all the settings. The main source of errors might be ascribed in part to the discretization effects of the DDS modulation amplitudes, and in part to the nonlinearity of the source intensity with regard to the modulation amplitude. On the other hand, a negligible crosstalk between the dual-wavelength measurements is clearly demonstrated by the high-overlap between the linearly regressed curves of the single-source and dual-source modes for both the wavelengths, and also quantitatively indicated by the small CI values in Table 1. In summary, the validity of the lock-in photon-counting detection was adequately proved.

### Table 1. CIs for 675nm- and 785nm-measurements

| Wavelength (nm) | Modulation amplitude (mV)     |
|----------------|--------------------------------|
|                | 100   | 120   | 140   | 160   | 180   | 200   | 220   |
| 675            | 1.57% | 2.14% | 1.03% | 0.71% | 0.43% | 0.59% | 0.81% |
| 785            | 0.74% | 1.52% | 1.10% | 0.61% | 0.86% | 1.01% | 0.05% |

#### 3.2. Dark counting and stability

For the sake of the measurement reliability, the system was carefully evaluated for its dark counting and stability performances. Firstly, the conventional photon counting was conducted for 60 minutes using a gating-time of 60 s, with the sources powered off and the system placed in a dark room, for the purpose of quantifying the dark counts of the PMT detectors. Secondly, the two sources were modulated simultaneously with the modulating parameters set to the typical values used for the routine imaging: 26mA (DC) drive current and 7kHz/160mV (AC) modulation amplitude for the 675-nm wavelength, and 26mA (DC) drive current and 10kHz/160mV (AC) modulation amplitude for the 785-nm wavelength, and the lock-in detection was conducted for 60 minutes, using a gating-time of 60 s, to investigate the counting stability, with the laser source pre-warmed-up for 40 minutes for stable output. All the three measurements were normalized by its mean value to highlight the fluctuation.

As an example, the time-courses of the first PMT counting performance are shown in Fig. 6. An overall 5% decreasing trend of the dark counts is observed in Fig. 6(a). Figure 6(b) and 6(c) show the fluctuation of less than 1.5% and 0.5% for 675-nm and 785-nm wavelengths, respectively. The results consistently demonstrate the demodulation stability of the lock-in photon-counting methodology. The slight difference between 675-nm wavelength and 785-nm wavelength may be attributed partially to the sensitivity difference of the detector and partially to the environmental disturbance to 675nm.
3.3. Anti-noise performances

The anti-noise performances of the lock-in photon-counting detection were assessed for its capability of rejecting two interferences: the stray light and the DC component. The former mainly comes from the ambient light that might limit the method to a shielding environment, and the latter originates from the inherent DC bias of the laser sources that might exert a large interference to the PSD. As to the stray light rejection, we have compared the proposed lock-in scheme with the conventional photon-counting one, as well as surveyed the feasibility of the daylight rejection by the lock-in technique in contrast to the darkroom measurement. Two experimental tasks were established for the purpose: 1) Background measurements in both darkroom and daylight environments were made with no light injection, using the lock-in and conventional photon-counting methods, respectively; 2) Regular measurements in both darkroom and daylight environments were made using the lock-in and conventional photon counting, respectively, where, for the lock-in detection, two sources were driven by 26 mA (DC) current, and modulated with the typical amplitudes, i.e., 7kHz/160mV (AC) for case of 675-nm source and 10kHz/160mV (AC) for 785-nm source, and for the conventional photon counting, typical DC drive current (32mA) was adopted for both the sources. For the DC suppression, the lock-in measurement was done with 26 mA (DC) drive current and the null modulation amplitudes for the two wavelengths.

Two criteria were established for quantifying the performances of the stray-light rejection and the DC-component suppression, namely the Stray-Light Rejection Index (SRI), and the DC-Component Suppression Index (DSI), respectively, with the former defined as the ratio of the background measurement to the regular measurement for both the lock-in and the conventional photon-counting modes and the latter defined only for the lock-in mode as the ratio of the DC-only demodulated data (with the null modulation amplitudes as aforementioned) to the regularly measured data (with the given modulation amplitudes as described in Step 2).

| Detection mode | SRI (darkroom) | SRI (daylight) | DSI  |
|----------------|----------------|----------------|------|
|                | 675nm | 785nm | 675nm | 785nm | 675nm | 785nm |
| Lock-in        | 0.05% | 0.03% | 2.10% | 1.03% | 1.43% | 0.59% |
| Conventional   | 0.22% | 0.21% | 45.02% | 45.70% | –     | –     |
The SRIs and DSIs for the experimental scenarios are calculated in Table 2, which demonstrate evident superiority of the lock-in photon-counting method in the stray light rejection to the traditional one and excellent performance in the DC-component suppression. In particular, for application in daylight, the lock-in detection works with an excellent performance while the traditional method was overwhelmed by the stray-light noise, meaning the applicability of the method in the unshielded space. The performance difference between 675nm and 785nm is attributed to the difference counting rate in routine imaging. With the outstanding anti-noise performances, the lock-in photon-counting detection, in addition to the parallelization of the multi-wavelength and multi-channel measurement, lends itself to accomplishment of the ultrahigh sensitivity as well as enhancement of the application flexibility.

4. Phantom experiments

The DOT imaging capability of the system was validated using phantom experiments of the dual-source mode, especially for its sensitivity and temporal-resolution performances. A nonlinear algorithm for absorption-only reconstruction was adopted under the Newton-Raphson framework, with the algebraic reconstruction technique (ART) embedded for the linear inversion [25].

A cylindrical solid phantom with 80-mm length and 40-mm diameter was used, as shown in Fig. 7(a). The phantom was made from polyformaldehyde and the background absorption and reduced scattering coefficients, \( \mu_b^{(a)} \) and \( \mu_s^{(a)} \), were determined to be \( \mu_b^{(a)}(675 \text{nm} / 785 \text{nm}) = 0.0040 / 0.0034 \text{mm}^{-1} \) and \( \mu_s^{(a)} = 0.8 \text{mm}^{-1} \) (the reduced scattering difference at the two wavelengths was ignored), using a time-resolved spectroscopy (TRS) [26]. A cylindrical hole with 10-mm diameter and 70-mm height was drilled along but 10 mm apart from the Z-axis. To construct a heterogeneity target, the hole was filled with a mixture of Intralipid-10% and India-ink with its optical properties measured also by the TRS. For all the following experiments, 16 optodes, with each containing a pair of coaxially-aligned source and detection fibers, were placed with equal spacing at the middle plane of the target hole (z = 45mm), as shown in Fig. 7(b).

The typical parameters afore-mentioned were adopted for the two sources, i.e., the driving current of 26 mA (DC) and the modulation settings of 7 kHz/160 mV (AC) for the 675-nm source; the driving current of 26 mA (DC) and the modulation settings of 10 KHz/160 mV (AC) for the 785-nm source. Due to the different output power of the two sources and the different counting sensitivity of the detector at the two wavelengths, the parameters results in approximately the same order of counting rate at the two wavelengths. The differential imaging scheme was employed, where the ratio of the target data to the reference one (the
hole filled with Intralipid-10% only) was calculated to eliminate the requirement for the absolute system scaling, and to reconstruct essentially the difference between the target and reference absorption images.

To evaluate the sensitivity of the system, targets with four target-to-background absorption contrasts (defined as the ratio of the absorption coefficient in the target region $\Omega_T$ to that in the background region $\Omega_B$) of 1.125 (Target 1: $\mu^{a(675nm/785nm)} = 0.0045 / 0.0038$ mm$^{-1}$), 1.250 (Target 2: $\mu^{a(675nm/785nm)} = 0.0050 / 0.0042$ mm$^{-1}$), 1.500 (Target 3: $\mu^{a(675nm/785nm)} = 0.0060 / 0.0051$ mm$^{-1}$) and 2.000 (Target 4: $\mu^{a(675nm/785nm)} = 0.0080 / 0.0068$ mm$^{-1}$), and a unique target-to-background scattering contrast (analogously defined to the absorption one) of 1.0 ($\mu^{s(675nm/785nm)} = 0.8$ mm$^{-1}$) were used that were accomplished by filling the hole with solution of different concentrations of the ink.

From the PSD point of view, a long integration time, i.e., gating-time in measurement, is theoretically expected to improve the SNR of the measured signals as well as optimize the harmonic component suppression in RWC-PSD and thus enhances imaging fidelity. In practice, however, choice of a proper gating-time is subject to the temporal resolution that is mainly required by a specific application. To investigate the system performance with the gating-time, we experimentally compared the imaging quality for three gating-times of $T_g = 250$ms, 500ms, and 1000ms (corresponding to the total measurement times of 16s, 32s and 64s, respectively, due to the fiber switching tandem measurement mode). It is noted that the above gating-times generate three sets of measurements with an increased SNR by a factor of $\sqrt{2}$, in terms of the photoelectron statistics [23].

Figure 8 illustrates the reconstructed images of the four absorption contrasts against the three different gating-time cases, at the two wavelengths. Since the decreasing of gating-time leads to less photon counting and lacking of averaging in RWC-PSD, the anti-noise performance is weakened, and the reconstruction image tends to be more fluctuated. However, even if the gating-time is lowered to 250ms and the contrast is as low as 1.125, the target are well resolved with reasonable performance, demonstrating the high sensitivity of the system in probing interior changes in the absorption, as well as the potential of acquiring high temporal-resolution dynamic image.

Fig. 8. Reconstructed images at (a) 675-nm and (b) 785-nm wavelength. The target-to-background contrasts double increased from the top to the bottom, and the gating-time double increased from the left to the right. The black circles in the images indicate the true target region.
5. Discussions

The observations were further quantitatively evaluated using two criteria, referred to as the Signal-to-Noise Ratio Index (SNRI) and the Quantitativity (Q). The former is defined as the ratio of the reconstructed absorber (high absorption compared to the background) energy in the target region $\Omega_T$ to that in the background region $\Omega_B$, i.e.,

$$\text{SNRI} = \frac{\sum_{r \in \Omega_T} \mu_{a}(r)^2}{\sum_{r \in \Omega_B} \mu_{a}(r)^2},$$

and the latter is defined as the ratio of the mean value of the reconstructed absorption coefficient $\mu_{a}(r)$ in the target region $\Omega_T$ to the true target absorption coefficient $\mu_{a}^{(T)}$, i.e.,

$$Q = \frac{\text{mean}[\mu_{a}(r)]}{\mu_{a}^{(T)}}.$$

The results are given in Table 3 for 675nm wavelength and Table 4 for 785nm wavelength, respectively.

| Absorption contrast | SNRI/Q       |
|---------------------|--------------|
|                     | Gating-time  |
|                     | 250ms  | 500ms  | 1000ms |
| 1.125               | 1.0983/95.6% | 1.2689/95.6% | 1.4193/95.6% |
| 1.25                | 1.1197/94.0% | 1.2690/94.0% | 1.4153/96.0% |
| 1.5                 | 1.3989/86.7% | 1.2579/90.0% | 1.5148/91.7% |
| 2.0                 | 1.7209/83.8% | 1.9016/83.8% | 1.8957/85.0% |

| Absorption contrast | SNRI/Q       |
|---------------------|--------------|
|                     | Gating-time  |
|                     | 250ms  | 500ms  | 1000ms |
| 1.125               | 1.4088/96.7% | 1.6375/96.7% | 1.5433/96.7% |
| 1.25                | 1.2479/94.1% | 1.2867/94.1% | 1.2515/94.1% |
| 1.5                 | 1.3109/86.3% | 1.3253/88.2% | 1.4419/88.2% |
| 2.0                 | 1.4955/79.4% | 1.8234/80.9% | 1.9584/82.4% |

Results are summarized as listed follow. Firstly, for each gating-time case, the increasing of the target contrast leads to the increasing of SNRI, which means less fluctuation and higher positioning accuracy in the reconstructed image. However, the quantitativenss is decreased. This is mainly resulting from the saturation effect of the DOT reconstruction [27]. Secondly, for each contrast case, the increasing of gating-time gives rise to the increasing of not only SNRI but also quantitativenss. This can be ascribed to the improvement of reconstruction performance due to the high SNR data acquired with long integration time.

In addition, there exist some exceptions in the calculation at 785nm wavelength. The SNRI in low contrast case is somehow higher than that in high contrast case. This is mainly because the absorption coefficient at 785nm wavelength is lower than that at 675nm wavelength, and thus concentration changes under same contrast requires much higher sensitivities at 785nm wavelength. The reconstruction at 785nm is more easily influenced by accident errors during measurement.

It is worthy mentioning that the temporal-resolution is up to now severely restricted by the cost-effective fiber-switch-based tandem serial-to-parallel measuring mode, and multi-channel measurement stability can also be slightly affected in the long time measurement, causing damage on image fidelity. A fully parallelized instrumentation, with all the sources
and all working wavelengths coded and full PMT-based RWC-PSD channels without optical switching [8,12], is urgently required, to accomplish the measurement within one gating-time (less than 1s per frame), so that more improvements in the imaging fidelity and real-time performance might be expected.

Finally, it should be noted that, we focus on in this study the validation of the novel lock-in photon-counting detection architecture and the evaluation of the relevant DOT instrumentation, for which the Newton-Raphson based nonlinear image reconstruction algorithm embedding the ART linear inversion is uniquely employed in the phantom experiments. This algorithm has been proved to be noise-robust but the performance is sub-optimal due to the row-fashioned operation of the ART. A huge number of advance reconstruction methods that are based on inverting the whole weight matrix can be introduced for further enhancement of the image quality that are beyond the scope of the study.

6. Conclusions

We have described a DOT system with a high sensitivity and a large dynamic range, which works in a tandem serial-to-parallel mode and enables 2-D or 3-D tomographic imaging with a configuration of 16 sources and 16 detectors. The fundamental innovation is elaborately devising a lock-in photon-counting core for detecting extremely weak light signals from the multiple wavelengths in parallel and for realizing an effective suppression of ambient light in an open environment. The overall performances of the system were assessed by demonstrating excellent measurement linearity, negligible inter-wavelength crosstalk, strong anti-noise ability and moderate-term system stability. Furthermore, 2-D imaging experiments were conducted on a cylindrical phantom for comprehensive evaluation of the system. The reconstructed images for absorbing targets of different contrasts validate very well the high sensitivity of the lock-in photon-counting methodology as well as high reliability of the proposed system.

In summary, the developed lock-in photon-counting method represents a significant advancement in simultaneously improving the detection sensitivity and the temporal resolution. This will make a great progress in dynamically tracking the blood concentration distribution for extended applications, including small animal disease modeling, pharmacokinetic imaging and brain function profiling.

Acknowledgement

The authors acknowledge the funding supports from the National Natural Science Foundation of China (81271618, 81371602, 61475115, 61475116, 81401453, 61575140, 81571723), Tianjin Municipal Government of China (13JCZDJC28000, 14JCQNJC14400, 15JCZDJC31800).