Investigation of glucose concentration measurement based on tunable pulsed laser induced photoacoustic technique

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A tunable pulsed laser induced photoacoustic (PA) measurement set-up is established in the forward mode to monitor *in vitro* glucose concentration. A series of experiments are investigated to verify the feasibility of this set-up and scheme. Peak-to-peak values (PPVs) of several glucose aqueous solutions are recorded and averaged 512 times at each wavelength. Experimental results demonstrate that the time-resolved PA profile of glucose solutions has a good agreement with the PA theories. The characteristic wavelengths of glucose solution are determined via differential method. The root-mean-square error (RMSE) of predicted concentration reaches 3.15 mg/dl at the optimum wavelength of 1 510 nm via least square (LS) fitting algorithm.

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The noninvasive blood glucose concentration (BGC) measurement has been become a research hot-spot in recent decade years. In contrast to the traditional biochemical method, noninvasive method completely eliminates the pain and economic burden brought to diabetic patients by the frequent blood sample collection. Although some progresses have been achieved by optical methods[1−6], many problems are still difficultly resolved, especially the strong interference of tissue scattering light. Photoacoustic (PA) detection is a well-established, hybrid, and most promising candidate for noninvasive measurement technique, which greatly overcome the influence of scattered light on glucose measurement due to the detected ultrasonic waves instead of photon. In addition, the PA method differs from pure optical techniques having the unique directly measured ability to the tissue's optical, thermal, and acoustic properties, e.g., the attenuation, absorption coefficient, and sound velocity. To date, PA based BGC measurement has been studied by many people[7−13].

This letter presents a PA-based scheme and detection system for *in vitro* measuring the glucose level of aqueous solution as the first step toward a noninvasive *in vivo* BGC measurement. In this system, the PA signals are induced by a near infrared tunable optical parametric oscillator (OPO) pulsed laser and detected by a confocal ultrasound transducer in the forward mode[14]. In experiments, different aqueous glucose solutions with concentrations from 0 to 300 mg/dl at intervals of 50 mg/dl are measured and the time-resolved PA signals are captured. In order to determine the characteristic wavelength of glucose, the PA peak-to-peak values (PPVs) of different glucose solutions are recorded with averaged 512 times at the excitation wavelength from 1 300 to 2 300 nm. Experimental results demonstrate that time-resolved PA profiles of glucose aqueous solutions are highly consistent to the bipolar shape. In addition, the cylindrical mode of PA source is fully verified. Compared with the PPVs of distilled water (0 mg/dl), the characteristic absorption wavelength are determined. At the optimum wavelength of 1 510 nm, by using four kinds of least square (LS) fitting algorithms, the best root-mean-square error (RMSE) value of predicted concentrations reachs 3.15 mg/dl.

The semi-quantitative description of PA generation has been discussed by Diebold *et al.*[15,16]. The shape of a PA source produced in a homogeneous medium can be described as being planar, cylindrical, and spherical mode. The PA amplitude (P) derived from thermal-elastic expansion mechanism[17] is determined by pulsed laser parameters, optical, thermal, and acoustic coefficients of medium, which can be defined as

$$P = k_{\mathrm{c}} \frac{E \cdot \mu_\alpha \beta v^n}{C_{\mathrm{p}} r^i R_s^j}, \tag{1}$$

where k_{c} is a proportional constant; E is the output energy of laser pulse; μ_α is the optical absorption coefficient of the medium; β is the volume expansion coefficient; C_{p} is the specific heat at constant pressure; v is the ultrasound velocity in the medium; R_s is the PA source radius; r is the distance between the PA source and the ultrasonic detector; the indexes of i and j are in the region of $0-1$ and $0-2$, respectively, which is dependent on the shape of the acoustic source; n is the region of $1/2-2$, which is relate to the duration of excitation laser pulse.

For the case of weakly absorbing liquid is irradiated by a short pulse laser, the cylindrical acoustic source mode is described by Gusev *et al.*[17−20], that is, the laser pulse width τ_{L} is shorter than the propagation time τ_{a} of acoustic pressure travels across the radial direction of acoustic source. In this case, for Eq. (1), i, j, and n are identified as 1/2, 3/2, and 2, respectively.

Figure 1 is the schematic diagram of experimental set-up. A 532-nm pumped Q-switched Nd: YAG OPO pulsed laser (OPOletteTM, 532 II, OPOTEK Inc., USA) was utilized as the excitation light source, its output energy of laser pulse was less than 2 mJ, its pulse repetition rate was 20 Hz, and pulse duration time was 10 ns. A glucose solution circulation system was employed

to simulate the blood flowing in human body, which was composed of quartz cuvette, plastic tube with diameter of 2 mm, beaker, and water pump, wherein the diameter and wall thickness of cuvette was 10 and 2 mm, respectively. A confocal piezoelectric transducer (PZT) ultrasonic transducer (I1P10NF40, Doppler, China) with the central resonance frequency of 9.52 MHz and relative echo sensitivity of −29.32 dB was used to detect the glucose PA signals, and its diameter and disk thickness were about 20 and 2 mm, respectively. To diminish the mismatch of acoustic impendence between the PA signals and response of ultrasonic transducer, medical ultrasound coupled gel was evenly smeared between the ultrasonic transducer and cuvette. A signal pre-amplifier (5 678, Olympus, Japan) with gain of 40 dB and bandwidth of 50 kHz−40 MHz are used to amplify the detected PA glucose signals, then a digital oscilloscope (54642D, Agilent, USA) are used to display the real time amplified glucose PA signals and capture single-shot signal, finally the digitalized signals were send by a GPIB I/O card (GPIB-USB-HS, National Instruments, USA) into computer for further processing.

In order to validate the feasibility of this set-up and PA based glucose measurement scheme, a series of experiments were performed. The OPO pulsed laser was preheated one hour before the experiments were done. Different aqueous glucose solutions with the concentration range from 0 to 300 mg/dl at intervals of 50 mg/dl were pre-prepared and loaded into seven beakers, respectively. In order to minimize the effect of temperature change, all experiments were performed at the stabilized room temperature of 22 °C.

0.1-L glucose aqueous solutions with concentration from 0 (distilled water) to 300 mg/dl at 50-mg/dl intervals were in turn pumped by water pump into the circulation system and loaded into the cuvette. After the laser pulse output about 8 μs, the PA signals of the glucose solutions were captured by PZT transducer and recorded by digital oscilloscope. In each measurement, the recorded PA signals were averaged 512 times to reduce the random noises and each PA measurement was taken less than 5 s to perform. Figure 2 presents the time-resolve PA signals of distilled water and other glucose solutions at laser wavelength of 1 450 nm.

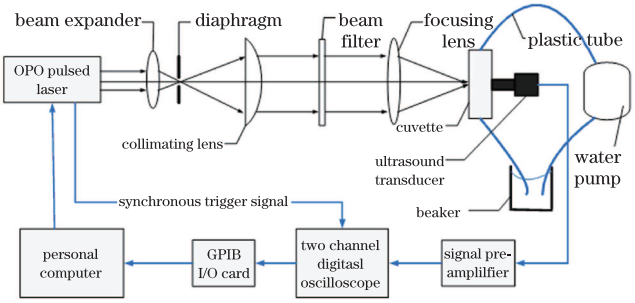

Fig. 1. The schematic diagram of experimental set-up.

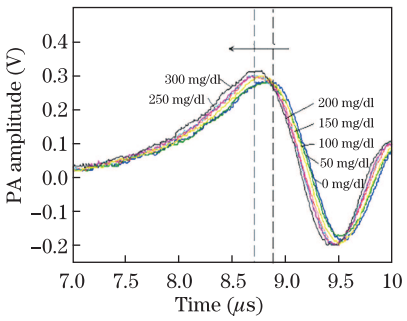

Fig. 2. (Color online) Time-resolved PA signals of glucose solutions with different concentrations.

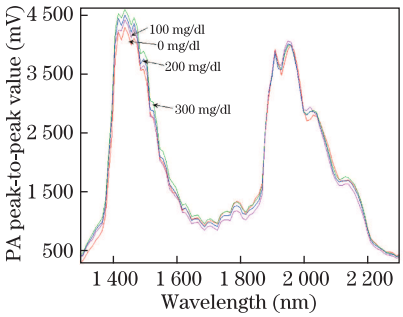

Fig. 3. (Color online) PPVs curves of four glucose aqueous solutions.

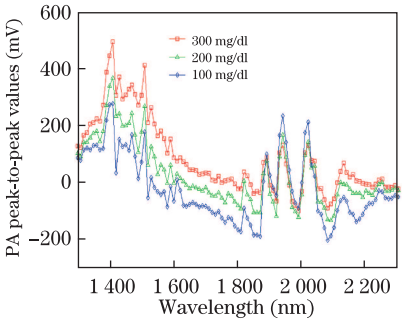

Fig. 4. (Color online) PA difference between distilled water and other glucose solutions.

In Fig. 2, the PA signal peak position of the distilled water is about 8.8 μs. According to the acoustic velocity in water is about 1 450 m/s, we can calculate the distance between the PA source and the PZT transducer is about 12.7 mm. At the same time, we can calculate the depth of PA source is about 1.3 mm, which is almost consistent with the actual value. And we can see that the peak position shifts left, which verified that the ultrasonic velocities were increased with the increasing of concentration.

In Fig. 2, the experimental results fully illustrate that the PA profiles have a good match with the ideal bipolar response reported in Ref. [21] and successfully validate the PA source of the aqueous solution is accorded with the cylindrical model. Moreover, we can see that the bipolar curve of the PA signal consists of two parts: the one is the first exponential rising curve, and another is the fast falling and the second exponential rising curve. The profile presents a good consistent with that reported in Ref. [22].

In order to find the characteristic absorption wavelengths of the glucose solution, four solution samples with concentrations of 0−300 mg/dl at 100-mg/dl intervals were irradiated by OPO laser with output wavelength increased from 1 300 to 2 300 nm with intervals of 10 nm.

Table 1. Measured, Fitted PA Data and Predicted Concentrations

Concentration (mg/dl)	0	50	100	150	200	250
Measured PPVs (mV)	1295	1309	1323	1331	1341	1350
Fitted PPVs (mV)	1297.8	1308.6	1319.4	1330.2	1341.1	1351.9
Predicted Concentration (mg/dl)	–12.75	51.89	116.53	153.47	199.65	241.20

Table 2. Comparison of Predicted Concentration Errors of Four Fitting Algorithms

Concentration (mg/dl)	0	50	100	150	200	250	RMSE
1st Degree Fitting	–12.75	51.89	116.53	153.47	199.65	241.20	9.55
2nd Degree Fitting	–1.11	49.70	107.11	144.11	196.75	253.77	4.31
3rd Degree Fitting	0.61	46.95	105.64	145.85	200.98	250.04	3.15
Exponential Fitting	–0.65	49.25	106.72	144.12	197.27	253.54	4.10

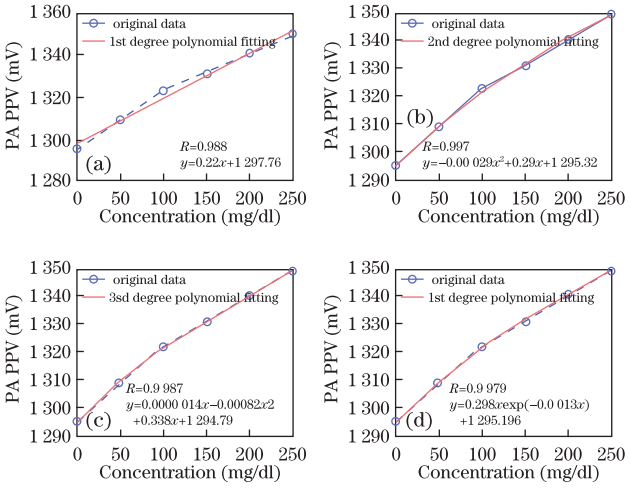

Fig. 5. (Color online) Fitted curves of the results of (a) first, (b) second, and (c) third degree polynomial fitting, and (d) exponential polynomial fitting.

PA amplitude is used as the useful information about glucose concentration in previous reports[23,24], while the PA signal PPVs are used as the measurement values of BGC in this experiment. This experiment was repeated 3 times in 1 h, the PA PPVs at all wavelengths were recorded and shown in Fig. 3.

From Fig. 3, we can see that the time-resolved PA profiles of glucose solutions with different concentrations are same except the changed PPVs. Additionally, the PPVs for all samples at the wavelengths of 1 470 and 1 940 nm are largest and the peak position is similar to that of distilled water, which verified that the glucose had a strong property of hydrophilicity, and these two wavelengths can be firstly determined as the characteristic absorption wavelengths of distilled water.

To get the characteristic wavelengths from Fig. 3, the differential method was performed between PPVs of 100-, 200-, and 300-mg/dl glucose solutions and that of distilled water. The differential results are shown in Fig. 4. From it, we can see that the different values of several wavelengths (i.e., 1410, 1510, 1890, 2020, and 2130 nm) are relatively large and can be determined as the characteristic absorption wavelengths of glucose solution.

To validate the BGC measurement accuracy of this PA based scheme and set-up, six different concentrations of glucose solutions (0−250 mg/dl at intervals of 50 mg/dl) were employed at the characteristic wavelength of 1 510 nm. Because the linear relationship existed between the PA values and the glucose concentrations had been reported in Ref. [13], the first degree polynomial is firstly used by LS fitting algorithm to fit the experimental measured PA data. The original measured PPVs, fitted PPVs, and predicted concentrations of six different glucose solutions were presented in Table 1. The original measured data and the fitted curve of first degree polynomial were shown in Fig. 5(a).

To explore the possibility of smaller prediction concentration error, nonlinear fitting algorithms were employed. Figures 5(b), (c), and (d) are the fitted results of second degree, third degree and exponential polynomial fitting, respectively. The comparison of concentration predicted errors for four fittings is shown in Table 2. From it, we can see that the RMSE of concentration prediction error of nonlinear fittings are smaller than that of first degree polynomial linear fitting, wherein the RMSE of the third degree polynomial fitting is smallest and less than 0.18 mmol/L. The correlation coefficients between the fitted data and the measured PPVs data of four different fittings were compared. It was found that the correlation coefficient of third degree polynomial fitting was largest, which reached 0.9987. It can be illustrated that nonlinear fitting may be better used to interpret the relationship between the PA amplitudes and the concentration changes.

In conclusion, as the preliminary work for the *in vitro* BGC measurement, this letter successfully verify the availability of measuring glucose concentration based on PA technique via establishing PA based BGC measurement set-up and a series of basic experiments. Experimental results demonstrate that the PA profile of the glucose solution is consistent to the results of theory and others reports. The wavelengths of 1 410, 1 510, 1 890, 2 020, 2 130, and 2 250 nm are determined as the glucose characteristic absorption wavelengths via the PPVs differential to that of distilled water. Finally, four LS polynomial fittings are used to predict the concentration error of glucose solutions. It is found that the smaller concentration prediction error can be gotten via nonlinear fitting. More results involve in the *in vitro* PA experimental of blood-protein-glucose mixed solution and whole blood will be brought in our next works.

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