Noninvasive blood glucose measurement by ultrasound-modulated optical technique

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We present a method for the noninvasive measurement of blood glucose levels, which are determined by the ultrasound-modulated optical technique. The method is based on the optical scattering coefficient. A sensitivity analysis of the ultrasound-modulated light signals in a scattering medium is conducted. Glucose concentrations in intralipid and hemoglobin solutions are measured using the modulation depth of ultrasound-modulated scattered light. The effects of incident light intensity and sample temperature on the ultrasound-modulated signals are also estimated. Preliminary experimental results suggest that the proposed method is a promising technique for noninvasive blood glucose measurement.

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Diabetes mellitus, a common endocrine disease, is one of the four most dangerous illnesses that pose a threat to human health. In 2011, the number of diabetics worldwide amounted to nearly 350 million, twice that 30 years ago[1]. China has more than 92 million diabetics, with another 150 million expected to be diagnosed with the disease[2]. Effectively treating diabetics necessitates measuring their glucose levels several times a day to appropriately regulate intensive insulin therapy programs. The normal procedure for blood glucose measurement is to draw a small blood sample from a patient's finger for assay, relying on an enzymatic chemical reaction. However, this procedure is inconvenient and unpleasant, as well as increases the risk of infection. A secure, noninvasive blood glucose monitoring approach has therefore become a pressing requirement for diabetics.

Noninvasive blood glucose monitoring based on optical methods is currently a popular research topic. Several noninvasive optical methods have been proposed, including near-infrared spectroscopy[3−5], scatter measurement[6,7], Raman spectroscopy[8], and optical coherence tomography (OCT)[9,10]. These optical methods are categorized into two types: spectroscopic and scattering approaches. Absorption signals are considerably reduced by light scattering, and interfering light absorbers (such as water) persist. Thus, the changes induced by blood glucose in absorption spectra are minimal and unspecific. In contrast to spectroscopic techniques, scattering approaches (such as scatter measurement and OCT) do not need specific absorption bands. Nevertheless, these methods do not specifically measure glucose but derive glucose-induced changes in scattering coefficients. Therefore, other blood analytes and physiological factors (e.g., heartbeat, respiration, and vasoconstriction) may influence measurement results. These methods mostly present low measurement accuracy, sensitivity, and specificity, prompting further study before they can be successfully used in clinical settings.

In this letter, a new optical technique for the noninvasive measurement of blood glucose levels by the ultrasound-modulated optical technique is presented; the measurement is conducted on the basis of the optical scattering coefficient[11−13]. Ultrasound waves scatter much less than light waves in biological tissue. With the proposed technique, ultrasound waves are focused onto a medium to modulate the diffused light that passes through the focal zone. Ultrasound-modulated scattered light, which carries optical and mechanical information of tissue, can be detected. Because the variations in blood glucose concentration change the scattering coefficient of blood[14,15], the glucose concentration in tissue can be indirectly measured through ultrasound-modulated optical signals. Compared with other optical methods based on the optical scattering coefficient, the proposed approach minimizes the disturbance from non-target layers and has easily implementable reconstructive algorithms because of the localization of ultrasound waves. The method detects scattered photons rather than ballistic photons, thereby enabling detection of signals from deep tissue. It serves as basis for a new modality for noninvasive blood glucose measurement.

A correlation between the modulation depth of ultrasound-modulated scattered light and glucose concentration was observed in phantom experiments. The effects of incident light intensity and sample temperature on ultrasound-modulated signals were investigated, and then used for error compensation mapping. Preliminary experimental results suggest that the proposed method is a promising modality for noninvasive blood glucose measurement.

The propagation of ultrasound-modulated light in tissue proceeds in three main stages. Firstly, incident light travels from the surface to the focused ultrasound region. The light obeys diffuse theory if distance z from the surface to the focused ultrasound zone is sufficiently long ($z >>$MFP, mean free path). Light intensity I_z can be expressed as[16]

$$I_z = I_0 \mathrm{e}^{\frac{-z}{\delta}}, \tag{1}$$

where δ is the penetrating depth and is defined as

$$\delta = \{\mu_a[3\mu_a + \mu_s(1-g)]\}^{-\frac{1}{2}}. \quad (2)$$

Secondly, diffused light can be modulated in the ultrasonic focused region because of acousto-optical interaction[17]. The modulated light intensity I'_z at point Z can be determined as[18]

$$\begin{aligned} I'_z &= I_z[1 + M'(A,B,C)\cos\omega_a t] \\ &= I_0 e^{-\frac{z}{\delta}}[1 + M'(A,B,C)\cos\omega_a t], \end{aligned} \quad (3)$$

where M' is the modulation depth and ω_a is the angular ultrasound frequency. M' depends on the optical (A) and ultrasonic properties (B) of a sample in the focused region, as well as on ultrasonic intensity (C).

Finally, the modulated light from Z can be regarded as a point source, which emits the diffused modulated photons and propagates in the tissue. The photons are collected by a detector outside the tissue. The total diffused light detected at the surface is given as[19]

$$\begin{aligned} I_t(z,M) &= I_0 \exp\Big(-\frac{L}{\delta}\Big)\Big(1 + \frac{M'(A,B,C)}{L-z}\cos\omega_a t\Big) \\ &= I_0 \exp\Big(-\frac{L}{\delta}\Big)(1 + M\cos\omega_a t), \end{aligned} \quad (4)$$

where L is the total thickness of the sample, and M equals $M'/(L-z)$.

Equation (4) shows that the modulation depth (M) of the detected diffused light is associated only with the optical properties of the sample inside the focal zone, and not with those of the sample outside the focal zone when other factors (i.e., L, z, C, B) remain constant. This conclusion was confirmed by Monte Carlo simulation[20]. Therefore, the relationship between M and A should more easily occur than that between I_t and A. Glucose changes the scattering coefficient of blood; thus, variations in glucose concentration can be detected by measuring the changes in the modulation depth of diffused light.

The experimental setup is shown in Fig. 1. A 632.8-nm He-Ne laser (25-LHR-925-230, CVI Melles Griot, USA) was chosen as the light source because the wavelength dependence of the optical coefficient of the sample (intralipid solution or blood) is known. The scattering coefficient of 1% intralipid solution is 48.84 cm^{-1}[21]; the scattering coefficient and absorption coefficient of blood are 142.01 and 8.83 cm^{-1}, respectively[22]. The laser light delivered to the sample has a maximum power of 22 mW. The sample and a focused ultrasonic transducer (Panametric A314S; 1-MHz central frequency, 0.48-MHz pulse width, 0.75-inch element diameter, 1.006-inch focal length) were both placed in a water tank, whose dimensions were 8×9×1.1 (cm). The ultrasonic pulser-receiver (Panametric 5800PR) was used to drive the focused ultrasonic transducer to generate a 1-MHz pulsed ultrasonic wave (10-kHz pulse repetition frequency, 100-μJ pulse energy). The directions of the light and ultrasound were perpendicular to each other. The laser beam was passed through the ultrasonic focus zone to obtain the maximum value of the ultrasound-modulated light signal. The ultrasound-modulated light signal was detected by a photomultiplier tube (PMT; Hamamatsu R2949) after two apertures of 0.11 cm in diameter. Background light was effectively filtered by the two apertures, thereby improving the signal-to-noise ratio (SNR). The signals emitted by the PMT were amplified by an amplifier (Hamamatsu C6438) and displayed by an oscilloscope (Tektronix TDS3054C). The power supply (Hamamatsu C3830) provided −800-V power to the PMT and ±5-V power to the amplifier. The trigger of a digital storage oscilloscope was operated in external trigger mode. The trigger source was a horizontal sync signal of the ultrasonic pulser-receiver. An average acquisition mode of 512, which can reduce noise, was obtained. The detected light signal and trigger signal were displayed on the oscilloscope (Fig. 2). Ch1 is the ultrasound-modulated light signal, and Ch2 is the trigger signal. The ultrasound-modulated light signal lagged behind the trigger signal by ∼35 μs because the former originates from the ultrasonic focal zone; the ultrasound needs time to propagate from the ultrasonic transducer to the ultrasonic focal zone. The ultrasound-modulated light signal is shown in Fig. 3(a), and the nonmodulated light signal is shown in Fig. 3(b). The average and peak-to-peak voltages of the ultrasound-modulated light signal in Fig. 3(a) are defined as transmission light intensity (I_{dc}) and modulated light intensity (I_{ac}), respectively. The modulation depth (M) is defined as I_{ac}/I_{dc}.

Various turbid media diluted from the 20% intralipid suspension and mixed with ink or bovine hemoglobin solution were used to simulate blood. We dissolved the glucose powder in distilled water to change the glucose concentration of the sample. The bovine hemoglobin solution used in the experiment is a dark red liquid, and human albumin is a yellow transparent liquid.

A close relationship exists between the scattering

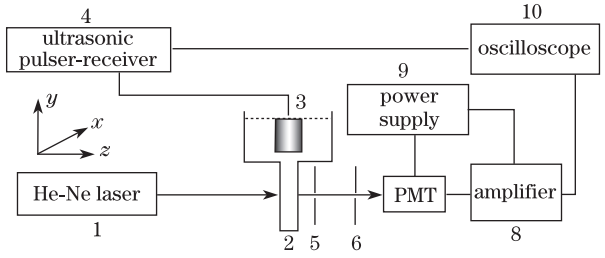

Fig. 1. Experimental setup. 1: He-Ne laser; 2: water tank; 3: ultrasonic transducer; 4: ultrasonic pulser-receiver; 5–6: apertures; 7: photomultiplier tube; 8: amplifier; 9: multipurpose power supply; 10: oscilloscope.

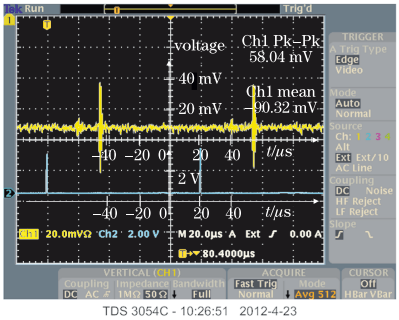

Fig. 2. Detected light signal and trigger signal displayed on the oscilloscope. Ch1 is the ultrasound-modulated light signal and Ch2 is the trigger signal.

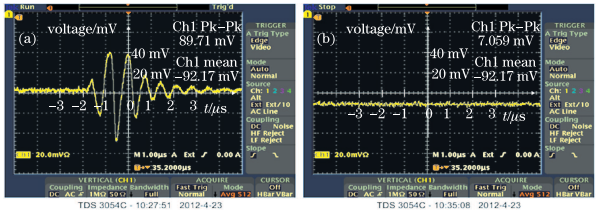

Fig. 3. Detected light signal displayed on the oscilloscope when the ultrasound is (a) on and (b) off. The sample solution is composed of 4.5-mL 20% intralipid solution and 350-mL distilled water. The scattering coefficient of the sample is about 12.4 cm^{-1}.

coefficient and blood glucose concentration. The relationship between scattering coefficients and ultrasound-modulated optical signals should be established if we are to measure blood glucose concentrations by the ultrasound-modulated optical technique.

In our experiments, we added different amounts of 20% intralipid suspension in 350-mL distilled water to change the scattering coefficient of the sample. The scattering coefficient ranged from 12.9 to 14.0 cm^{-1}. The measurement range of the scattering coefficient was narrow because the maximum anode current of the PMT was 0.1 mA. If the scattering coefficient of media is too low, the transmitted light intensity will be too high, thereby damaging the PMT. If the scattering coefficient of media is too high, light will be strongly scattered and the transmitted light intensity will be excessively low to be detected by the PMT. However, the range of scattering coefficients chosen in our experiment was large enough for blood glucose measurement because the influence of the scattering coefficient generated by changes in glucose solution concentration was small (about 0.136 cm^{-1}/mmol/L)[14]. The I_{ac}, I_{dc}, and M versus the optical scattering of the sample are shown in Fig. 4. I_{ac} and I_{dc} exponentially decreased as the scattering coefficient of the sample increased. More photons were scattered with increasing optical scattering coefficient, thereby decreasing I_{dc}. The fewer the photons that arrived at the ultrasound zoom, the fewer the photons modulated by the ultrasound wave. Therefore, I_{ac} decreased with scattering coefficient. The decrease trends of I_{dc}, and I_{ac} were approximately the same, but the I_{ac} decreased at a slightly faster pace than did I_{dc}. Thus, modulation depth linearly declined with increasing scattering coefficient. This result is in agreement with that in Ref. [23]; such agreement can be explained by the mechanism of the acousto-optical interaction in the turbid medium. A detailed explanation is provided in Ref. [23]. Figure 4 also shows that the scattering coefficient-induced changes in modulation depth are fewer than those induced by I_{ac} and I_{dc}. The decrease rate was about 9.96%/cm^{-1}. The modulation depth was dependent only on the optical and ultrasonic properties of the media in the ultrasonic focal field; I_{ac} and I_{dc} were also dependent on the optical properties inside or outside the ultrasonic focal zone[20]. Thus, modulation depth is a better physical parameter than I_{ac} and I_{dc} for studying the relationship between modulation depth and glucose concentration.

With a 1-cm^{-1} increase in scattering coefficient, the modulation depth decreased by about 9.96%, which is accurate only under certain circumstances. When experimental conditions (such as the changing position of the detector from the axis) change, the value of modulation depth and the relationship between modulation depth and scattering coefficient should also be modified.

The normal level of human fast-prandial blood glucose is about 3.9–6.1 mmol/L. We diagnosed diabetes by using the following criteria: fast-prandial blood sugar level >7 mmol/L and post-prandial 2-h blood sugar level >11.1 mmol/L. Figure 5 shows the relationship between modulation depth and glucose concentration in several turbid media. Glucose concentration ranged from 0 to 32 mmol/L; the turbid media used to obtain the results shown in Figs. 5(a) and (b) were intralipid aqueous solutions, with scattering coefficients of ~12.4 and ~13.7 cm^{-1}, respectively. We added ink into the intralipid aqueous solution to obtain the results shown in Fig. 5(c) and generate sample properties that are closer to the optical properties of blood. The absorption coefficient of ink is about 80 cm^{-1}/1% as indicated by our measurement. The optical properties of the sample in Fig. 5(c) were $\mu_s \sim 12.4$ and $\mu_a \sim 1.1$ cm^{-1}, and the ratio of the scattering coefficient to the absorption coefficient was close to that of human blood. Figure 5 shows that modulation depth linearly increased with increasing glucose concentration. This increase is attributed to the fact that the glucose increase in

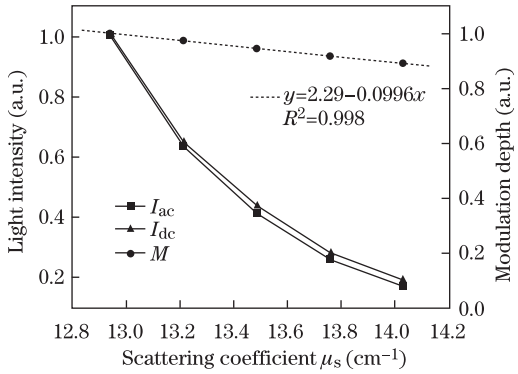

Fig. 4. I_{ac}, I_{dc}, and M versus the sample scattering coefficient.

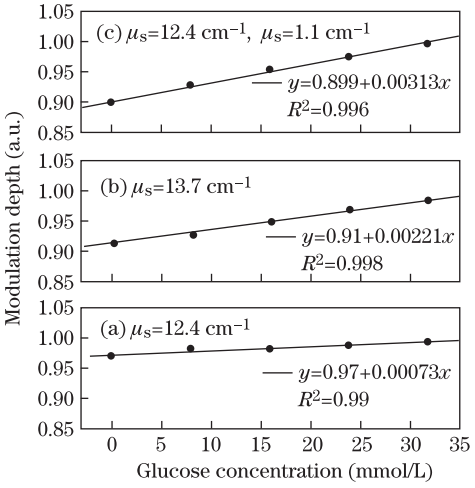

Fig. 5. Modulation depth versus glucose concentration in the intralipid solution with μ_s of (a) ~12.4, (b) ~13.7, and (c) ~12.4 cm^{-1} and μ_a is about 1.1 cm^{-1}.

the turbid medium decreased the scattering coefficient of the medium[14], and that modulation depth increased with the decreasing scattering coefficient of the medium. The slopes in Figs. 5(a)–(c), which represent sensitivities, are 0.073%/mmol/L, 0.221%/mmol/L, and 0.313%/mmol/L, respectively. The measurement sensitivity is better when the tissue phantoms are closer to blood. On the basis of OCT, Kinnunen *et al.* showed that the changes in optical properties caused by glucose were greater in tissue than in intralipid solution[9]. We believe that modulation depth can be used to measure slight changes in blood glucose concentration with high sensitivity, as long as the SNR of the experimental system is sufficiently high.

Because the SNR in our experimental system was moderate, the scattering coefficient of the sample was considerably lower than that of tissue. To extend this method to in vivo applications, we intend to improve the SNR in future studies. Some researchers have gained progress in this regard. Kim et al. used ring-shaped light illumination[24] and intense acoustic bursts[25] to enhance ultrasound-modulated optical signals. Murray *et al.* used a photorefractive crystal-based interferometry system to improve the efficiency with which ultrasound-tagged photons were detected[26]. Li *et al.* used spectral hole burning as a narrowband spectral filter for unmodulated light[27]. Therefore, using ring-shaped light illumination and intense acoustic bursts in the ultrasound-modulated optical technique may be a good and relatively easy solution to improving SNR in *in vivo* blood glucose measurement.

Hemoglobin and albumin are the main components of blood (hemoglobin: 6–18 g/dL; albumin: 3–5 g/dL)[28]. We used bovine hemoglobin solution to simulate blood. The highest concentration of hemoglobin detected under our experimental system was about 2.5 g/dL. The effect of glucose measurement in bovine hemoglobin solution is depicted in Fig. 6. The concentrations of bovine hemoglobin were 2 and 2.5 g/dL in Figs. 6(a) and (b), respectively. The level of albumin was about half of the hemoglobin in blood. Therefore, we added 1.25-g/dL human albumin in the 2.5-g/dL bovine hemoglobin (Fig. 6(c)). The experimental results showed that modulation depth linearly increased when glucose concentration increased from 0 to 23.8 mmol/L in the bovine hemoglobin solution. This result is attributed to the decrease in the scattering coefficient of the hemoglobin solution induced by the increase in glucose. The slope was equal to 0.176%/mmol/L in 2-g/dL bovine hemoglobin (Fig. 6(a)), and 0.418%/mmol/L in 2.5-g/dL bovine hemoglobin (Fig. 6(b)). The glucose-induced changes in optical properties were greater in higher concentrations of hemoglobin. When the solution contained bovine hemoglobin and human serum albumin (Fig. 6(c)), the change pattern of modulation depth was similar to that in Fig. 6(b); the slope was 0.441%/mmol/L in the glucose concentration range of 3–16 mmol/L (Fig. 6(c)). However, the measurement data fluctuated and the range of linearity was decreased to 3–16 mmol/L when albumin was added to the hemoglobin solution.

Fluctuations in laser output power and the temperature instability caused by the environment or the human body are inevitable. Figures 7 and 8 show the effects of incident light intensity and sample temperature on I_{ac}, I_{dc}, and M. In Fig. 7, I_{ac} and I_{dc} rapidly increased as incident light intensity increased in the intralipid solution; by contrast, modulation depth was almost unaffected by incident light intensity. The larger the scattering coefficient, the less the effect of incident light intensity on modulation depth. The scattering coefficient of human blood was considerably larger than that of the intralipid solution used in our experiments. Therefore, the effect of the instability of laser output power can be disregarded in blood experiments. Figure 8 shows that sample temperature considerably affects I_{ac}, I_{dc}, and M. In tissue-mimicking phantoms ($\mu_s \sim 12.7$ cm^{-1}), I_{dc} increased and I_{ac} decreased as sample temperature increased. Modulation depth more rapidly decreased than did I_{ac}, and showed better linear relationship (about 5.6%/1 °C). Modulation depth exhibited a close relationship with the acoustic properties of the sample, with water as a major component. The elasticity modulus of water increases as temperature rises[29]. Therefore, modulation depth decreases with temperature if ultrasonic intensity is invariant. The effect of sample temperature cannot be disregarded. Sample temperature should be strictly controlled or effective error compensation should be performed to accurately measure glucose.

In conclusion, the ultrasound-modulated optical technique is used to noninvasively measure glucose-induced

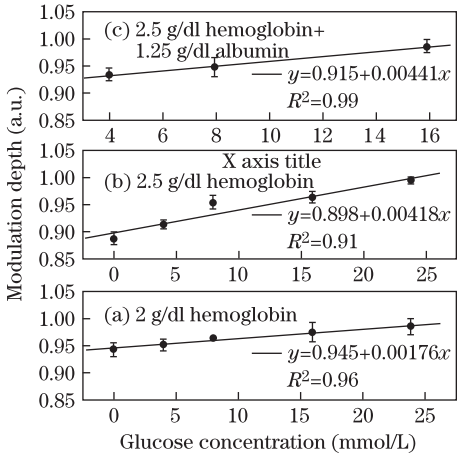

Fig. 6. Modulation depth versus glucose concentration. Bovine hemoglobin concentrations are (a) 2, (b) 2.5, and (c) 2.5 g/dL, respectively and human albumin concentration is 1.25 g/dL.

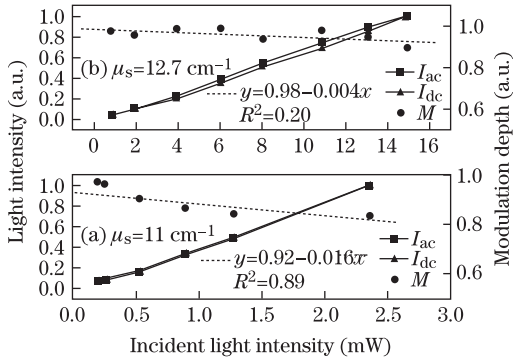

Fig. 7. I_{ac}, I_{dc}, and M versus incident light intensity. Scattering coefficients of intralipid solution are (a) 11 and (b) 12.7 cm^{-1}, respectively.

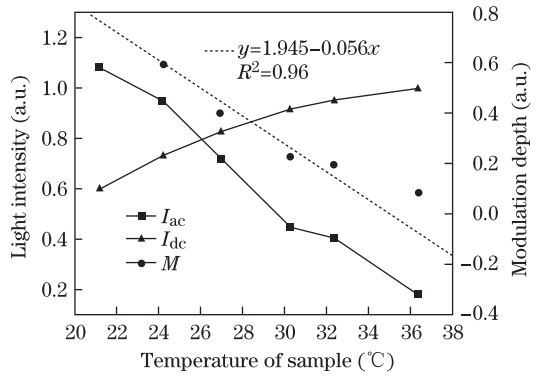

Fig. 8. I_{ac}, I_{dc}, and M versus sample temperature. The scattering coefficient of intralipid solution is 12.7 cm^{-1}.

changes in turbid medium. The results shows that modulation depth linearly increases with rising glucose concentration in intralipid solution, with high measurement sensitivity. Substantial glucose-induced changes in optical properties are found under high hemoglobin concentrations. Albumin only slightly influences the monitoring results for glucose concentration, but causes fluctuations in measurement data and decreases the range of linearity. The influence of the instability of laser power output is negligible, but that of sample temperature cannot be disregarded. The modulation depth decreases by 5.6% with an increase of 1 °C. Our preliminary experimental results suggest that the ultrasound-modulated optical technique is a promising modality for noninvasive blood glucose measurement. The ultrasound-modulated optical approach is one of the scattering approaches to blood glucose measurement. Thus, it presents a frequently encountered problem: distinguishing between the physiological and pathological changes in the results of *in vivo* measurement. The structural nature of biological tissue, other blood analytes, and physiological factors may affect measurement results. Therefore, solving these *in vivo* difficulties will make up key work in the future.

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