Noninvasive monitoring of glucose concentration using
differential absorption low-coherence interferometry based on
rapid scanning optical delay line

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Abstract A non-invasive method of detecting glucose concentration using differential
absorption low-coherence interferometry (DALCI) based on rapid scanning optical delay line
is presented. Two light sources, one centered within (1625 nm) a glucose absorption band,
while the other outside (1310 nm) the glucose absorption band, are used in the experiment. The
low-coherence interferometry (LCI) is employed to obtain the signals back-reflecting from the
iris which carries the messages of material concentration in anterior chamber. Using rapid
scanning optical delay line (RSOD) as the reference arm, we can detect the signals in a very
short time. Therefore the glucose concentration can be monitored in real-time, which is very
important for the detection in vivo. In our experiments, the cornea and aqueous humor can be
treated as nearly non-scattering substance. The difference in the absorption coefficient is much
larger than the difference in the scattering coefficient, so the influence of scattering can be
neglected. By subtracting the algorithmic low-coherence interference signals of the two
wavelengths, the absorption coefficient can be calculated which is proportional to glucose
concentration. To reduce the speckle noise, a 30 variation of signals were used before the final
calculation of the glucose concentration. The improvements of our experiment are also
discussed in the article. The method has a potential application for noninvasive detection of
blood glucose concentration in vivo and in real-time.

1 introduction

Diabetes mellitus is a medical condition in which a person cannot maintain a normal blood glucose
level effectively. There are two common types of the diabetes. Type-I diabetes is characterized by the
loss of the pancreatic beta cells responsible for the production of insulin [1]. Therefore, Type-I
diabetes need therapeutic insulin to compensate for this loss and is known as Insulin-Dependent Diabetes Mellitus. Type-II diabetes is characterized by insulin resistance which causes an individual to secrete more insulin, but often this is still insufficient to regulate the blood glucose levels properly [2]. It has been estimated that over 23.6 million individuals in the US have diabetes mellitus [3]. Frequent monitoring of blood glucose is crucial to facilitate the treatment of this disease.

The current glucose sensing techniques approved by FDA are invasive methods. These methods often require taking a sample of blood from the individual to measure their corresponding glucose levels. This type of testing not only causes pain to individuals, but coupled with possibility of infection at the test site. Therefore, noninvasive methods have been thought to be an attractive alternative. Several teams have made research in this field and several approaches have been under investigation for more than thirty years [4]. These approaches include the glucose absorption measurement with Raman spectroscopy [5], near infrared spectroscopy [6], polarimetric [7], optical coherence tomography (OCT) [8], etc. Because of the complexity of biological media, there are few repeatable and quantifiable results that have reported in vivo. As will be explained below, the method we used was different from these mentioned above.

We present a noninvasive method to monitor the glucose concentration in aqueous humor using a differential absorption low-coherence interferometry. Experiment shows that glucose concentration in the aqueous humor correlate well with it in blood and there is a minimal delay on the order of 5 minutes [9]. And as the aqueous humor is optically more accessible glucose-contain biological fluid, it is suggested that it could serve as a surrogate for blood for noninvasive analysis of glucose concentration. Schmitt et al. were probable the first one to introduce differential absorption technique in the field of OCT [10]. Then Pircher et al. developed this technique to measure water concentration in human cornea [11]. Recently, our group utilized the DALCI technique to measure glucose concentration in aqueous humor, and the feasibility of it has been proved [12]. In this article, we measure glucose concentration in real-time, which is very important for the detection in vivo. Two light sources, one centers within (1625 nm) an absorption band of glucose, the other locates outside (1310 nm) the absorption band of glucose, are used to monitor the concentration of glucose. Two OCT systems with rapid scanning optical delay line are used to measure glucose concentration in real-time and eye model experiments are reported in this article to demonstrate the viability of our improvement.

2 Methods and Materials
Anterior chamber is located in the front part of eye between the iris and the cornea, with the thickness of 3.13 ± 0.50 mm [13]. The aqueous humor is filled within the anterior chamber and the total volume of it is about 0.25 ml [14].

After passing through a medium, the light is attenuated because of the scattering and absorption. The quantity relationship can be described by Beer's Law

\[
I(\lambda, d) = I_0(\lambda) e^{-\mu_d(\lambda)\mu_s(\lambda) d}
\]

(2.1)

where \(I(\lambda, d)\) denotes the output light after passing through the medium, \(\lambda\) the wavelength of the light, \(d\) the depth of the medium, \(I_0\) the incident light, \(\mu_d\) the absorption coefficient of the medium, \(\mu_s\) the scattering coefficient. The OCT signal can be described as:
\[ S_{\text{OCT}}(\lambda, z) = K(\lambda) \sqrt{I_r(\lambda)I_s(\lambda, z)} \]  

(2.2)

where \( K(\lambda) \) is a constant factor, which is decided by the system specifications, \( I_r(\lambda) \) the light reflected from the reference arm, \( I_s(\lambda, z) \) the light reflected from the sample at the depth of \( z \). Subtracting the logarithm of the signals got with two wavelengths, we got

\[
\ln\left(\frac{S(\lambda_1, z)}{S(\lambda_2, z)}\right) = \ln\left(\frac{I_{r_1}(\lambda_1)}{I_{r_2}(\lambda_2)}\right) - (\mu_a(\lambda_1) + \mu_s(\lambda_1) - \mu_a(\lambda_2) - \mu_s(\lambda_2))z
\]  

(2.3)

where \( \lambda_1 \) denotes the light of wavelength in 1625 nm, \( \lambda_2 \) the light of wavelength in 1310 nm. And \( I_0(\lambda_1) \) represents the light 1310 nm reflected from the back of the cornea, and \( I(\lambda_1, z) \) the light 1310 nm reflected from the front of the iris, and \( I_0(\lambda_2), I(\lambda_2, z) \) have the same meaning but in the wavelength of 1625 nm. Because the absorption coefficient in 1625 nm is much larger than 1310 nm, so the absorption coefficient in 1310 nm can be neglected. In our experiment, as the cornea and the anterior chamber where the light propagate through are transparent and one light source is located in an absorption band of glucose, the scattering coefficients are much smaller than the absorption coefficient, therefore, the influence of the scattering can be neglected. In Eq. (2.2), the double pass configuration have been taken into account, i.e. we have set the medium thickness \( d=2z \), where \( z \) denotes the depth of medium in our experiment.

**Figure 1.** Co1 Co2 Co3, couplers. WDM1 WDM2 WDM3, wavelength division multiplexers. R1 R2, two sets of RSOD with two wavelengths, respectively. Cir1 Cir2, circulators. De, detector. Com, computer.

Above all, we can rewrite the Eq. (2.3) as follow,

\[
\ln\left(\frac{S(\lambda_1, z)S(\lambda_2, z)}{S(\lambda_1, z)S(\lambda_2, z)}\right) = \mu_a(\lambda_1)z_{ci}
\]  

(2.3)
where $S(\lambda_1, z_c), S(\lambda_1, z_i)$ denote the interference signal from the back of the cornea and the front of the iris with wavelength $1625$ nm, respectively, and the same meaning as $S(\lambda_2, z_c), S(\lambda_2, z_i)$ but in wavelength $1310$ nm. And $z_c, z_i$ the depth of the back of the cornea and the front of the iris, respectively, $z_{ci}$ the distance from the back of the cornea and the front of the iris. The absorption coefficient can be calculated by the signals detected and the depth $z_{ci}$ which can be measured directly by the images got from OCT. In Eq. (2.3), we denote $R=S(\lambda_1, z_c)/S(\lambda_2, z_c)$ just for short.

If we know the absorption cross section $\sigma_a$ of the pure substance, which can be measured by traditional spectroscopy, the concentration $c$ of the absorbing material can be calculated via

$$C = \frac{\mu_a(\lambda)}{\sigma_a(\lambda)}$$

(2.4)

We prepared an eye model to simulate the human eye. The outside and inside diameters of this glass shell are $16$ mm and $10$ mm, respectively and the diameter of its cross-section is $20$ mm. The bottom of it is adhered to a paper sheet with the center painted black to simulate the iris and the pupil. A set of glucose water solution with the concentrations of 0, 100, 200, 300, 400, 500 and 600 mg/dl were prepared.

3 Experiment setup

The experiment schematic is shown in Figure 1. The whole system is based on a fiber based Michelson interferometer. The $1310$ nm wavelength light (FWHM bandwidth $\Delta \lambda = 50$nm) (Denselight Inc., Singapore) first input into a coupler, which with an optical divide ratio 5:95. The 5 percents light from the output of couple was used as the input of the reference arm of this wavelength. The 95 percents light first passed through a circulator and then was coupled with the other wavelength light $1625$ nm (FWHM bandwidth $\Delta \lambda = 28$nm) (Denselight Inc., Singapore) into a wavelength division multiplexer (WDM). The output light of this WDM was the input of the sample arm. The backscattering light from the sample propagated back through the WDM and the circulator, and then was coupled with the light $1625$ nm which was also the backscattering light from the sample into another WDM. The coupled light used as an input of the coupler before detected by the detector. The other input of this coupler is from another WDM with the coupled the light from the two reference arm of two wavelengths.

We used two rapid scanning optical delay lines (RSOD) as the reference arms of this two wavelengths system. Using this type, at least 400 A-scans can be detected in one minute. First, we coupled the light from fiber to free space using an objective, and then a oscillating mirror was used to achieve B-scanning of the sample. Finally, a normal achromatic lens was used to focus the light on the spot of sample we wanted to detect. Here, we averaged the B-scans to decrease the speckle noise.

4 Results and discussions

The results of the eye model experiments are shown in Figure 2. The correlation coefficient of the linear fitting is 0.99. The resolution $\delta C$ can be expressed as

$$\delta C = \frac{\Delta C}{\Delta (\ln R)} \delta (\ln R),$$

(4.1)
where $\Delta C$ is the concentration difference (100mg/dL in this experiment), $\Delta (\ln R)$ the average difference of $\ln R$, $\delta (\ln R)$ the mean value of the standard deviation in each measurement.

![Figure 2. The relationship between $\ln R$ and concentration $C$.](image)

After we measured a series of glucose water solution, 7 groups of data were recorded. Taking a weighted average from 30 times experiments over each group, $\ln R$ was plotted in Fig.5 (A). As is shown in Fig.3, the resolution calculated by equation (4.1) in this experiment is 25.4mg/dL. Although we can detect and measure the concentration in real time using RSOD, we will have more high frequent noise in the signals. Therefore, in the future, the thing we need to do is finding a balance between fast detection and low noise.

5 Conclusions
A developed differential absorption low-coherence interferometry to measure glucose concentration and in vitro experiments were carried out using an eye model. Results show the good linearity between the concentration $C$ and $\ln R$. Using RSOD, we can detect the concentration of glucose in real time. The results show the considerable promise of this method towards application in noninvasive glucose sensing.

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