Specific detection of glucose by an optical weak measurement sensor

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Abstract: Diabetes is an important public health problem and finding quick testing methods with high accuracy, reliability, and convenience are important to control the blood glucose of diabetic patients. In this study, a sensor based on a weak measurement scheme was developed for the specific detection of glucose for the first time. The detection of glucose using the proposed method was completed by the high sensitivity and resolution of the weak measurement based on optical rotation detection, as well as the change in the optical rotation before and after the specific oxidation of glucose. The resolution of the as-obtained glucose sensor was around 2.71×10^{-3} g/L (1.50×10^{-2} mmol/L), and the detection range was 0–11 g/L (0–61 mmol/L).

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1. Introduction

Diabetes is a serious chronic metabolic disease and an important public health problem according to the World Health Organization, 2014 [1]. The number and prevalence of diabetes have steadily increased in the past few decades, in which approximately 463 million adults (age 20–79) suffer from diabetes worldwide, as of 2019. Moreover, this number is expected to reach 578 million by 2030, according to the International Diabetes Federation, 2019 [2]. Besides, no effective clinical cure is currently available for diabetes, and management is mainly based on long-term use of hypoglycemic drugs to ensure that blood sugar levels of patients are maintained within a reasonable range. Failure of controlling the blood sugar levels of patients with hyperglycemia would lead to serious complications, such as diabetic hypertension, hyperosmotic coma, lactic acidosis, ketoacidosis, diabetic heart disease, and diabetic cerebrovascular disease, among others. These blood sugar states would directly affect the health and life safety of diabetic patients. Therefore, accurate, reliable, convenient, and quick blood glucose detection methods...
are important for the control over blood glucose levels of diabetic patients [3,4]. With the continuous development and advancement of medical technology, blood glucose testing methods characterized as invasive, minimally invasive, and non-invasive have continuously emerged [5,6]. However, the glucose level in intravenous serum is still used as the standard measurement route by the medical profession. Therefore, invasive blood glucose detection methods are still being used in clinical biochemical testing to ensure high accuracy of the blood glucose detection.

The main currently employed methods for the detection of glucose in serum are based on glucose oxidase (GOD-POD) [7] and hexokinase (HK) [8] methods. In the first concept, glucose oxidase (GOD) is used to oxidize glucose into gluconic acid and release hydrogen peroxide. The Trinder reaction is then utilized to calculate the blood glucose content by Uv-Visible absorbance spectrometry. This GOD method is advantageous in terms of simple operation and low-cost. However, the specificity of peroxidase is poor, and species like uric acid, vitamin C and bilirubin could compete with the chromogenic substances of hydrogen peroxide, leading to inhibition of the reaction and poor detection. Besides, this method based on GOD also suffers from a narrow linear detection range.

The second route is based on hexokinase consisting of six-carbon sugar phosphorylase [9]. This enzyme promotes changes of glucose from stable to active states, and transforms phosphorylate glucose and ATP into glucose-6-phosphate (G-6-P) and ADP. G-6-P is dehydrogenated under the catalysis of glucose-6-phosphate dehydrogenase (G6PD) to generate 6-phosphogluconate (6-GP), while reducing NADP to NADPH. Since the rate of NADPH production is directly proportional to the glucose level, monitoring the increasing rate of absorbance at the wavelength of 340nm will allow the determination of the glucose concentration in serum. The hexokinase route is advantageous in terms of accurate determination of glucose samples containing mild hemolysis, lipemia, jaundice, vitamin C, sodium fluoride, heparin, EDTA, and oxalate. However, the hexokinase method is limited by the release of substances from red blood cells organophosphates, as well as the consumption of NADP by some enzymes. Therefore, both methods based on GOD and hexokinase could well complete the detection of glucose content in serum but might lead to errors. Therefore, the development of novel and accurate blood glucose detection methods is highly desirable to eliminate such errors.

Various optical detection methods have so far been proposed in the field of biomolecule detection, including absorbance, immunofluorescence effect [9], chemiluminescence, interference measurement, Raman scattering [10,11], surface plasmon resonance [12], and polarization [13,14]. Meanwhile, the glucose molecule with chirality and specific rotation of +52.2° can be employed for the detection of glucose levels in serum by constructing optical rotation detection sensors. The weak measurement technology has attracted increasing attention since reported a few decades ago [15–18]. For instance, the weak measurement sensor proposed in our previous work exhibited broad prospects in biological detection due to its high sensitivity, elevated resolution, fast response, low interference, simple design, and easy operation [19–21]. In particular, the optical rotation measurement sensors are effective for the detection of amino acids and proteins [22–24]. There have been some previous studies about glucose or chiroptical sensors based on weak measurement that have shown promising results [25–29]. However, current optical detection methods suffer from specificity since glucose is not the only chiral molecule in human serum but others, such as peptides, amino acids, nucleic acids are also chiral. Under non-specific detection conditions, the presence of such chiral molecules would affect the detection of glucose levels, leading to errors. Therefore, finding specific detection methods for chiral molecules is of great significance for glucose detection.

In this work, a novel sensor based on a weak measurement scheme was developed for the specific detection of glucose for the first time. The change in specific optical rotation of glucose before and after the specific oxidation by GOD was used to realize specific detection by combining with the high-resolution optical weak measurement scheme. The method consisted of
first analyzing the change in specific rotation of glucose and its products under the action of GOD. The feasibility, detection range, and resolution of glucose detection were then determined by the optical rotation weak measurement sensor. Next, the specificity of the proposed method toward glucose detection was verified. Finally, the proposed method was compared to the commercial route based on a glucose determination kit to verify the feasibility of the proposed optically weak measurement sensor. The results revealed that the proposed weak measurement sensor did not only provide high accuracy, resolution, simplicity, and rapidity toward the detection of blood glucose but also was feasible for studying the interaction of other chiral molecules.

2. Experimental

2.1. Materials

The employed materials included D- (+)-Glucose (C₆H₁₂O₆ Molecular Weight (MW): 180.16 g/mol, assay: ≥ 99.5% (GC), optical activity: [α]20/D +52.2° in water), GOD (from Aspergillus niger), potassium hydroxide (KOH assay: ≥ 85%), L-proline (C₅H₉NO₂, Molecular Weight (MW): 115.13 g/mol, assay: ≥ 99.5% (NT), optical activity: [α]20/D −85.0°), sodium chloride (NaCl), and glucose kit (GOD method, linear range [0.4, 4.5] g/L, linear correlation coefficient R-square > 0.990).

2.2. Methods and theories

The structural diagram of the sensor is shown in Fig. 1. The measuring sensor consisted of a Superluminent Laser Diode, a set of coupling lens, a pre-selective polarizer, a Sample Cell (SC), an Optical Rotation Plate (OP), a post-selective polarizer, and a spectrometer.

![Fig. 1. Structure diagram of weak measurement sensor consisted of the superluminescent diode (SLD, IPSDD0804, 840 nm, 5 mW, Inphenix), collimating and coupling lens (L1, L2, Thorlabs Inc.), pre-polarizer and post-polarizer (P1, P2, Thorlabs Inc., LPVIS050-MP, extinction ratio of 100000:1), sample cell (SC, length 4 cm), optical rotation plate (OP, Union Optic), and spectrometer (HR4000, OCEANVIEW).](image)

In this study, the OCEAN VIEW HR4000 spectrometer was used to collect the spectral data, which then were processed by a self-made program to obtain information related to the center wavelengths.

The Hamiltonian interaction with a measuring device can be expressed according to von Neumann [15]:

\[ \hat{H} = -g(t)P\hat{A} \]  

(1)

where \( g(t) \) is a normalized function with compact support near the time of the measurement, \( P \) represents the momentum of a photon, and \( \hat{A} \) is the measuring operator. The measured physical quantities will be amplified by the weak value of \( \hat{A} \) (\( A_w \)) to achieve the effect of weak value amplification (WVA).

The initial momentum state of system is prepared to be a normalized Gaussian wave function which is supposed to center at 0.

\[ \varphi(P) = e^{-\frac{P^2}{2\Delta^2}} \]  

(2)

The measured physical quantity consisted of the optical rotation of a liquid chiral molecule, which can be regarded as circular birefringence. This would imply a small phase difference
between the left and right-handed circular polarization. Here, \(|-\rangle\) (for left-handed circular polarization) and \(|+\rangle\) (for right-handed circular polarization) were used as the orthogonal vectors of the measuring sensor states. The relationship between the circular polarization and linear polarization (H for horizontal and V for vertical) can be given by Eq. (3):

\[
\begin{align*}
|H\rangle &= \frac{\sqrt{2}}{2} (|-\rangle + |+\rangle) \\
|V\rangle &= \frac{\sqrt{2}}{2} (|-\rangle - |+\rangle)
\end{align*}
\]

The pre- and post-selective polarizers were adjusted to set the initial and final polarization states of light. The polarized axis of the pre-selective polarizer was approximately parallel (in the angle of \(\beta\)) to the vertical direction, and the polarized axis of the post-selective polarizer was parallel to the horizontal direction. Thus, the initial and final states can be expressed by Eq. (4):

\[
\begin{align*}
|\psi_{in}\rangle &= \cos \beta |H\rangle + \sin \beta |V\rangle = \frac{\sqrt{2}}{2} (e^{-i\beta} |+\rangle + e^{i\beta} |-) \\
|\psi_{out}\rangle &= |V\rangle = \frac{\sqrt{2}}{2} (|+\rangle - |-\rangle)
\end{align*}
\]

After passing through the pre-selective polarization, the light would then pass through a Sample Cell and an Optical Rotation Plate (OP). The OP can be described by an operator of the circular polarization states (Eq. (5)):

\[
\hat{P} = e^{-i\alpha_0 P} |+\rangle \langle + | + e^{i\alpha_0 P} |-\rangle \langle - |
\]

where \(\alpha_0\) is the tiny optical rotation angle of OP, which could be modulated in the experiment to obtain high sensitivity. Due to the rotatory dispersion effect of OP, we use the normalized parameter \(P\) to represent the dispersion (here we suppose the initial central momentum to be 0). The coefficient coupling during the OP provides the coefficient of \(\alpha_0\) between momentum \(P\) and measuring operator \(\hat{A}\). According to [30], the coefficient factor \(\alpha_0\) decides the amplification factor of weak value \(A_\omega\).

The states of photons at the post-selective polarizer can be represented by applying the operator to the post-selected polarizer according to Eq. (6):

\[
|\psi_{out}\rangle = e^{-i\alpha} \sin \frac{\pi}{4} |+\rangle + e^{-i\alpha} \cos \frac{\pi}{4} |-\rangle
\]

where \(\alpha\) is the rotation angle of liquid in the sample cell. After post-selection, the final state of system is written as

\[
\phi (P) = \langle \psi_{out} | \psi_i \rangle e^{i\alpha_0 P} \langle \varphi | = \sin (\alpha_0 P - \alpha) e^{-\frac{P}{2\Delta}}
\]

So the momentum probability distribution is

\[
\Phi (P) = |\phi (P)|^2 = \sin^2 (\alpha_0 P - \alpha) e^{-\frac{P^2}{\Delta^2}}
\]

Thus we can obtain the momentum shift of

\[
\delta P = \frac{2\alpha_0 \alpha \Delta^2}{\alpha_0^2 \Delta^2 + 2\alpha^2}
\]

and therefore the shift of center wavelength

\[
\delta \lambda = \delta (2\pi / P) \approx \frac{2\pi}{\lambda_0} \cdot \frac{2\alpha_0 \alpha}{\alpha_0^2 + 2\alpha^2 \Delta^2}
\]

where \(\lambda_0\) represent the initial central wavelength and \(\Delta\) represent the width of spectrum.
Note that the center wavelength was only related to the optical rotation, and had no relationship with the channels of different spatial positions.

The Optical Rotation (OR), which could give rise to the rotation of the polarization plane of the incident light beam, would dominate the hallmark of chiral molecules.

\[
\alpha = \frac{100\alpha}{\ell \cdot C}
\]

where the optical activity ([\alpha]) and concentration (C) are inherent features of liquid samples composed of chiral molecules, and \(\ell\) presents the interaction length between the light and sample.

Depending on Eq. (10), the weak measurement would be appropriate for the detection of chirality by measuring the OR angle.

The change in the probability distribution of photons with wavelength after measurement would allow calculating the central expectation value of the spectrum, thereby obtaining the optical rotation value. The measurement based on the center wavelength was employed to indirectly measure the optical rotation angle of the substance, as well as further measure the concentration of the substance. In our previous work, weak-amplitude measurement results were achieved when the spectrum exhibited a bimodal state. Hence, the measurement range was also adjusted to the sensitive region of the double peaks.

3. Results and discussion

3.1. Change in specific optical rotation before and after glucose specific oxidation

As shown in Fig. 2(a), deionized water was first placed in the sample cell followed by adjusting the weak measurement sensor to the bimodal state. Next, 2 g/L glucose solution (left to stand for 24 hours after preparation) was added to the sample cell. Finally, GOD was added to the sample cell under magnetic stirring. The data were recorded each time the solution in the sample cell became stable.

As shown in chemical reaction formula (i) in Fig. 2(b), glucose was specifically oxidized to gluconolactone at the initial specific rotation of \(+61.7^\circ\) under GOD catalysis. Gluconolactone was unstable in aqueous solution, thereby gradually hydrolyzed into a balanced sensor mixed solution of gluconic acid, glucono-\(\delta\)-lactone, and glucono-\(\gamma\)-lactone at the specific rotation of mixed solution of \(+11.2^\circ\) (Fig. 2(a)). Therefore, the center wavelength of the sensor first increased after adding GOD (relative to glucose), and then gradually decreased over time of several hours before reaching stability.

The excessively long hydrolysis time of gluconolactone was unsuitable for detection but can be accelerated by adding OH\(^-\) (Fig. 2(b)-(ii)). The above experimental steps were then repeated (Fig. 2(a)). After adding GOD to fully oxidize the glucose, OH\(^-\) ions were added to accelerate the hydrolysis of gluconolactone and changes in the center wavelength of the sensor were recorded during the whole process. The results revealed that the presence of OH\(^-\) greatly reduced the detection time due to the accelerated hydrolysis of gluconolactone. But the addition of an OH\(^-\) solution without optical activity will result in a lower measurement result of the concentration of the product, resulting in a higher measurement result of glucose. Therefore, the volume of the added OH\(^-\) solution should be controlled as much as possible to reduce the error.

Therefore, the specific detection of glucose levels can be completed by using the optical rotation weak measurement sensor to quickly obtain the changes in the optical rotation before and after glucose specific oxidation and hydrolysis.

3.2. Range and resolution of glucose detection by an optical rotation weak measurement sensor

Glucose solutions with different concentrations of 0, 2, 4, 6, 8, 10, and 15g/L were prepared and let to rest for 24h. As shown in Fig. 3(a), the optical rotation measurement sensor was
Fig. 2. (a) Real-time changes in the central wavelength of the sensor during hydrolysis of the product after specific oxidation of glucose by GOD. The inset shows the change in the central wavelength of the sensor when the oxidation product is rapidly hydrolyzed under OH\(^-\) conditions. (b) (i) and (ii) Reaction equations of the specific oxidation of glucose under GOD conditions and rapid hydrolysis of products under alkaline conditions, respectively.
used to record the center wavelengths before and after the glucose-specific reactions for all concentrations, represented by the blue and orange lines, respectively. The relationships between the center wavelengths differences before and after the oxidative hydrolysis of different glucose concentrations were then fitted as a function of the corresponding concentrations. As shown in Fig. 3(b), linear relationships were obtained with a correlation coefficient estimated to $R^2_{0-10g/L}=0.9997$ and $R^2_{0-15g/L}=0.9761$, respectively. Therefore, a good linear relationship between the change in the optical rotation before and after the oxidative hydrolysis of different concentrations of glucose was obtained. As a result, the proposed optical rotation measurement sensor can linearly express different glucose levels through the shifts in center wavelengths.

We choose the data of 0–10g/L glucose solution to calculate the resolution of glucose detection by the system. Compared with the 0g/L glucose solution, the center wavelength of the 10g/L glucose solution before and after specific oxidation changes to 12.559nm. Therefore, the sensitivity of the system to the glucose detection can be calculated as $S_{glu} = \delta \lambda / \delta C = 1.256 \text{nm/(g/L)}$ ($\lambda$ – center wavelength, $C$ – concentration). Meanwhile, fluctuations in the sensor center wavelength were recorded at different concentration gradient glucose solutions and corresponding reaction product solutions within 500s. These fluctuations were utilized to calculate the standard deviation after averaging the data per second and the result was estimated to $\sigma_{SO} = 1.14 \times 10^{-3} \text{nm}$. Based on the formula $\sigma_{glu} = 3\sigma_{SO}/S_{glu}$, a resolution of $2.71 \times 10^{-3} \text{g/L} (1.50 \times 10^{-2} \text{mmol/L}$) was obtained for the glucose of the sensor.

The variation in optical rotation of the sample cell was simulated by rotating the front selection polarizer in the sensor (Fig. 1). As the optical rotation raised, the center wavelength of the sensor first declined slowly, followed by a rapid increase and then a slow decrease (Fig. 4). A region with good linearity (linear regression function of $\text{CW} = 76.59 \text{OR} + 831.9$, CW-central wavelength OR-optical rotation, $r^2 > 0.9995$) was noticed for the rapid increase in center wavelength of the sensor with the optical rotation. This region with the range area of 0.2310° can be regarded as the working area of the sensor. Meanwhile, fluctuations in the sensor center wavelength were recorded at three points (a, b, and c) in the linear region within 500s. These fluctuations were utilized to calculate the standard deviation after averaging the data per second and the result
was estimated to $\sigma_{SO} = 3.12 \times 10^{-4}$ nm. The change in the sensor center wavelength at 0.2310° was calculated as 17.851 nm, thereby the sensor sensitivity to the optical rotation detection was $S_R = 77.277$ nm/degree. Based on the formula $\sigma_R = 3\sigma_{SO}/S_R$, a resolution of $1.21 \times 10^{-5}$° was obtained for the optical rotation of the sensor. Also, the specific detection resolution and detection area range of the sensor toward glucose were calculated according to the length of the sample pool in the sensor of 0.4 dm. Since the specific optical rotation of glucose is +52.2°, according to the formula $[\alpha] = 100\alpha/l\cdot C$, the optical rotation of 1g/L glucose solution in the system can be calculated to be 0.02088°. Therefore, it can be seen that the maximum linear detection range of the system for glucose is about $R_{glu} = 0.2310/0.02088 \approx 11$g/L.

![Fig. 4. Schematic diagram showing the use of the sensor linear detection of the working area, along with the spectrum situation in and around the area.]

### 3.3 Specificity of the weak measurement sensor toward glucose detection.

The specificity of the proposed glucose sensor was verified by preparing three samples 1, 2 and 3 based on (1 g/L glucose solution), (1 g/L glucose, 0.5 g/L proline, and 0.5 g/L NaCl mixed solution) and (0.5 g/L L-proline and 0.5 g/L NaCl mixed solution), respectively. Also, 1 g/L glucose was used as a standard and all prepared samples are listed in the description of Fig. 5.

As shown in Fig. 5, no significant changes in the sensor center wavelengths were noticed for sample 1 and sample 3 before and after treatment. By comparison, the sensor center wavelengths of sample 2 and the standard product changed significantly after treatment, and the changing range looked the same. Therefore, specific glucose detection can be achieved by the proposed optical weak measurement sensor through the specific oxidation of glucose by GOD.

### 3.3. Comparison with existing detection methods

Glucose solutions with concentrations of 0, 0.3, 0.75, 0.9, 1.0 and 1.5 g/L (normal blood glucose range of 0.7–1.1 g/L) were prepared for testing along with 1 g/L glucose solution as standard. The samples were tested by the commercial glucose determination kit (GOD) and the
as-prepared sensor based on weak measurement. The results are gathered in Table 1, where $A$ is the absorbance, CCDK represents the converted concentration determined by the kit, CWD is the center wavelength difference, and CCWM denotes the converted concentration of the weak measurement sensor.

| Sample       | Sample 1 | Sample 2 | Sample 3 | Sample 4 | Sample 5 | Sample 6 | Standard |
|--------------|----------|----------|----------|----------|----------|----------|----------|
| CCDK (g/L)   | 0        | 0.280    | 0.772    | 0.901    | 1.012    | 1.497    | 1        |
| CCWM (g/L)   | 0        | 0.301    | 0.765    | 0.901    | 1.001    | 1.506    | 1        |

A comparison of the two methods showed that the as-prepared sensor delivered almost the same as the detection results as those obtained by the commercial kit, confirming the high feasibility of the proposed sensing scheme. At the same time, compared with the commercial glucose detection kit, the detection method proposed in this study has advantages in detection resolution and detection range, and also has higher adjustability. Because the detection resolution and detection range of the weak measurement system for glucose are related to the length of the sample cell. As the length of the sample cell increases, the detection sensitivity and resolution of the system gradually increase, and the detection range of the system gradually decreases. Therefore, sample cells of different lengths can be selected according to different detection scenarios to better complete the detection.
4. Conclusions

A novel sensor based on an optically weak measurement scheme was successfully developed for the specific detection of glucose. The change in specific rotation of glucose after oxidation with GOD was used to complete the quantitative analysis of glucose by the proposed optical rotation measurement sensor. The experiments successfully revealed differences in the detectable optical rotations before and after the specific oxidation of glucose under GOD conditions. The optical rotation weak measurement sensor showed linear detection of glucose in the range of 0–11 g/L (0–61 mmol/L) with a specific resolution of 2.71×10^{-3} g/L (1.50×10^{-2} mmol/L). The sensor was also shown to be better than some commonly used glucose-specific detection methods in terms of specificity. Besides, a comparison between the as-prepared sensor and the commercial glucose detection kit revealed good detection of glucose in samples near human physiological blood glucose, showing the high feasibility of the proposed sensor. On the other hand, the high sensitivity, good resolution, and elevated linear range of the proposed optical rotation weak measurement sensor would be suitable for studying other chemical reactions and intermolecular interactions prone to variation in optical rotations, such as proteins, nucleic acids, amino acids, and polysaccharides. In sum, the proposed sensor looks very promising for specific detection of glucose and can be extended to the construction of other weak measurement sensors.

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Data availability. The data used to support the findings of this study are available from the corresponding author upon request.

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