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RESEARCH PAPER

Glucose oxidase probe as a surface-enhanced Raman scattering sensor for glucose

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Abstract Glucose oxidase (GOx) possessing a Raman-active chromophore (flavin adenine dinucleotide) is used as a signal reporter for constructing a highly specific "turn off" surface-enhanced Raman scattering (SERS) sensor for glucose. This sensing chip is made by the electrostatic assembly of GOx over silver nanoparticle (Ag NP)-functionalized SERS substrate through a positively charged polyelectrolyte linker under the pH of 6.86. To trace glucose in blood serum, owing to the reduced pH value caused by the production of gluconic acid in the GOx-catalyzed oxidation reaction, the bonding force between GOx and polyelectrolyte weakens, making GOx drop off from the sensing chip. As a result, the SERS intensity of GOx on the chip decreases along with the concentration of glucose. This glucose SERS sensor exhibits excellent selectivity based on the specific GOx/glucose catalysis reaction and high sensitivity to 1.0 μM. The linear sensing range is 2.0–14.0 mM, which also meets the requirement on the working range of the human blood glucose detection. Using GOx as a probe shows superiority over other organic probes because GOx almost has no toxicity to the biological system. This sensing mechanism can be applied for intracellular in vivo SERS monitoring of glucose in the future.

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Introduction

Glucose is an indispensable material in life activities, which can be directly involved in the metabolic process of the human body. With the improvement of living standards, the incidence of diabetes continues to increase, which has already become a major disease to endanger human health. The detection of blood glucose is a topic of concern [1–4]. Nowadays, researchers have designed many methods for blood glucose measurements and detection ways including surface plasmon resonance [5–7], fluorescence [2, 8], and electrochemistry [4, 9]. The electrochemistry has been widely applied into detection for glucose. However, this method has some disadvantages, such as the complexity of the electrode preparation and the stability of the acquisition signal. Moreover, the electrodes may also be inactivated by the generated H_2O_2. Therefore, it is significant to develop a new method to detect glucose sensitively and selectively.

Surface-enhanced Raman scattering (SERS) as one of highly sensitive analytical methods [10–12] that can provide rich and clear fingerprint information to pinpoint the structures of molecules has been applied for glucose sensing in direct [11, 12] or indirect [3, 12–15] ways. However, it is extremely difficult to trace glucose directly by Raman spectroscopy because of its inherent weak Raman activity. Even with SERS enhancement, the weak surface adsorption ability of glucose causes a relatively low SERS signal. Yonzon et al. [11] and Shafer-Peltier et al. [12] exploited a decanethiol and mercaptohexanol self-assembled monolayer to capture and enrich glucose to silver nanostructure's surfaces for a desired sensitivity. However, this physical adsorption-based method lacks of selectivity toward glucose.

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Hence, Raman labeling strategies have been proposed for the detection of glucose, in which the Raman reporters (or Raman tags) that have been bonded to the metal nanoparticles (NPs) or SERS substrates can support stronger and more distinguishable SERS signal than glucose can [16–22]. By tracing the SERS signals of these extrinsic probes, the determination of glucose can be achieved in indirect ways. So far, many small molecules have been used as signal reporters in these indirect glucose sensors, such as 4-mercaptopyridine (4-MPY) [23], 4-mercaptophenylboronic acid (4-MPBA) [15], and *p*-aminothiophenol (PATP) [3]. However, the toxicity of these reporters is still unknown, if they are used for the in vivo purpose.

Glucose oxidase (GOx) as a cheap and widely used enzyme is an indispensable building block in the construction of a glucose sensor due to its high specificity for glucose. However, in the reported SERS sensors for glucose, none adopts GOx as a Raman reporter and glucose SERS sensing hardly refers to the SERS bands of GOx. As an expectation, the SERS spectrum of GOx would be indistinguishable and undetectable. However, in the present study, we found that GOx can support the acceptable SERS signal [24]. Therefore, we design a novel SERS sensor for glucose in the blood serum by monitoring the SERS signal of GOx. Not only the specificity of this sensor can be guaranteed, but also the sensor structure can be simplified because of no extrinsic probes used in this system. To the best of our knowledge, this is the first report to trace glucose based on the SERS signal of GOx.

Experimental section

Materials and methods

GOx was obtained from the Shanghai Yuanye Biotechnology Co., Ltd. A 0.4 wt% concentration of GOx in 0.1 M PBS solution was prepared for the next static assembly based on the related literatures [25]. Glucose, fructose, sucrose, galactose, and mannose were purchased from the Beijing Chemicals Reagent Company. Horseradish peroxidase (HRP) was purchased from the Beijing Dingguo Changsheng Biotechnology Co., Ltd. Poly(dimethyldiallyl ammonium chloride) (PDDA) was bought from Sigma-Aldrich. Silver nitrate (reagent grade) was from the Shanghai Chemical Company. Phosphate-buffered saline (PBS) solution was obtained from the Beijing Chemical Company. The deionized water used throughout the experiments was purified by a Millipore system. The glucose in fetal bovine serum from Gibco was freshly prepared each time. Different amounts of glucose powders were respectively dissolved in the blood serum (1.0 wt %). The pH value of the blood serum solution was kept to 6.86.

A Shimadzu UV-3600 spectrophotometer was used to record ultraviolet-visible (UV-vis) spectra. X-ray photoelectron spectroscopy (XPS) was carried out using a VG ESCALAB MK II electron spectrometer; the excitation source was Mg Kα X-rays ($h\nu$ = 1253.6 eV). Raman spectra under a 532-nm laser excitation were recorded by a portable B&W Tek Raman spectrometer. The laser power was 5.76 mW, while the 5 s integration time period and two accumulations were set. The surface morphologies of the samples (see Electronic Supplementary Material, ESM) were investigated using a scanning electron microscope (SEM, Hitachi SU8020).

Preparation of an Ag NP-assembled film

The Ag NP-assembled film was constructed by assembling Ag NPs over a glass/quartz slide by the static action of PDDA. Ag colloid was first synthesized using Lee's method as described previously [26]. The synthesized Ag colloid has the maximum UV-vis absorption peak at 434 nm and displays mostly spherical Ag NPs as shown in a TEM image (see ESM Fig. S1). Owing to the stabilization of citrate, these Ag NPs show negative charges [27, 28].

Glass slides (0.5 cm × 0.5 cm) were cleaned sequentially in ethanol and deionized water by 10 min ultrasonication. Then, they were heated for no bubbles in a piranha solution (H_2SO_4 and H_2O_2 mixture with a volume ratio of 7:3) for surface hydroxylation. The slides were dried using nitrogen after hydroxylation. Next, they were dipped into 2.0 mg/mL PDDA-PBS solution (0.1 M, pH = 6.86) for 40 min. After being cleaned by PBS solution and dried by nitrogen, these positively charged slides were dipped into the Ag NP colloid for 12 h, forming an Ag NP-self-assembled film on the glass slide through PDDA as a linker [28]. The obtained Ag NP-assembled films were characterized by UV-vis spectroscopy, XPS, and SEM.

Adsorption kinetics of GOx on the Ag NP-assembled chip

To achieve the SERS sensing chips, we also employed the layer-by-layer method for the immobilization of GOx. PDDA (marked by circled plus, 2 mg/mL, 20 min) and GOx (marked by circled dash, 0.4 wt% in 0.1 M PBS solution, 4 h) under the pH of 6.86 were step-by-step assembled on the Ag NP-self-assembled film [27]. It should be noted that this pH value is higher than the isoelectric point of GOx of 4.9. Under this condition, GOx presents negative potential values (Table S1 in ESM). A saturated density of GOx on the Ag NP-self-assembled film was adopted to insure the detection range of this sensing chip (see ESM Fig. S2). Each assembly step was followed with three times PBS solution washing and nitrogen drying. As we have known, the concentration of GOx on the Ag NPs was different with the different assembled time periods. Figure S2 (see ESM) shows that the SERS intensity of the GOx on the substrate becomes unchanged when the assembled time is over 4 h, indicating the saturated adsorption

of GOx. It has been reported that the saturated density of the GOx assembled by the PDDA as a linker is 1.65 μg/cm^2, which is equal to 8.85×10^{-12} mol/cm^2 [28–30]. The GOx SERS sensing chip was kept at 4 °C for further use [31].

Glucose SERS biosensing

The SERS spectra of the GOx SERS sensing chips were first measured by a portable B&W Tek Raman spectrometer under the 532-nm excitation wavelength, and the SERS band intensity at 1342 cm^{-1} was chosen as a contrast I_0. Then, they were immersed into 1.0 mL of different concentrations of glucose in the blood serum from 30.0 mM to 1.0 μM (PBS, 0.1 M, pH = 6.86), involving 20 μL of HRP solution (0.2 wt%, 0.1 M PBS with pH = 6.86). The sensing chips were incubated in the blood serum glucose solutions at 40 °C for 20 min, and they were cleaned by PBS solution three times and dried for SERS measurements. We defined the SERS intensity at 1342 cm^{-1} of the GOx SERS sensing chips after the glucose sensing reaction as I. The working curve is shown by plotting the concentration of glucose in the blood serum with $(I_0–I)/I_0$.

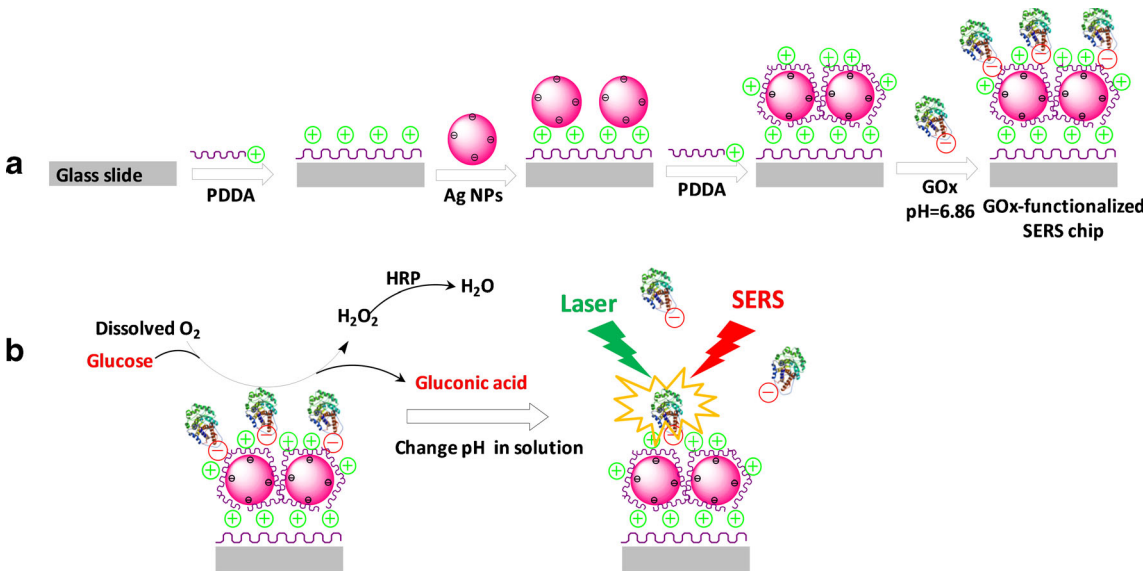
Results and discussion

Glucose sensing mechanism

Scheme 1 shows the preparation of this glucose SERS sensor and the mechanism of SERS sensing for glucose in the blood serum. This SERS sensing chip was prepared by immobilizing GOx on the Ag NP-assembled film under the pH of 6.86 (Scheme 1A). Since this pH condition is larger than the GOx's isoelectric point (4.9), [30] GOx is a negatively charged protein (ESM Table S1). So, we adopted a positively charged polyelectrolyte (PDDA) as a linker to assist the static assembly of GOx.

For the glucose sensing in the blood serum (Scheme 1B), owing to the decrease of the pH value caused by different amounts of the produced gluconic acid in the GOx-catalyzed oxidation reaction [32], the negatively charged GOx approaches to its isoelectric point (no charges). The electric quantity of GOx declines, which weakens the Coulomb force between GOx and PDDA. GOx molecules start to drop off from the substrate. As a result, the SERS signal of GOx would be decreased along with the reduced density of GOx on the slide. So, we can trace the concentration of glucose in the blood serum based on the decreasing SERS intensity of GOx.

It should be noted that another product, hydrogen peroxide (H_2O_2), can be fully decomposed by HRP (0.2 wt% in 0.1 M PBS with pH = 6.86) to form water, which can avoid the etching effect on Ag NPs [6, 23] (Scheme 1B, Fig. 1). In our previous studies [23], it has been reported that H_2O_2 can etch Ag NPs to a smaller size. It would be a problem on the SERS activity of this Ag NP-assembled SERS substrate and further affect the reproducibility of SERS detections in the present strategy. So, HRP was used in the reaction to solve this problem. To prove that all the produced hydrogen peroxides have been decomposed by HRP and cannot etch the Ag NPs, the SEM images of the Ag NP-assembled film, the PDDA decorated on the Ag NP-assembled film, and the GOx immobilized on the Ag NP-assembled film before and after the GOx catalytic reaction were taken and compared (Fig. 1a–d). The statistical size distributions show that the mean sizes are 73.7, 75.6, 76.2, and 77.5 nm for Fig. 1a–d, respectively. The Ag NP sizes have no obvious difference in all these assembly steps, and the GOx-catalyzed oxidation reaction illustrates that



Scheme 1 (**A**, **B**) The preparation of GOx-functionalized SERS chip and the sensing mechanism for glucose in the blood serum

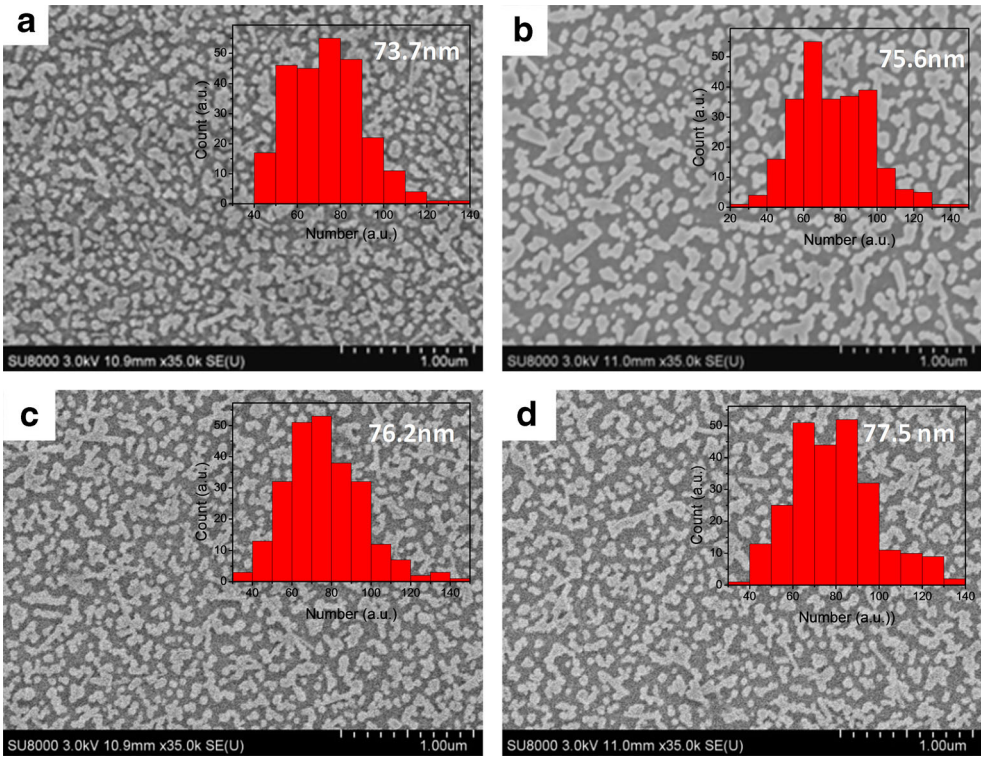


Fig. 1 SEM images and particle size statistics of different substrates: the Ag NP-assembled film (**a**), the PDDA-Ag NP-assembled film (**b**), and the GOx-PDDA-Ag NP-assembled film before (**c**) and after (**d**) the GOx-catalyzed oxidation reaction, respectively

produced H_2O_2 has been completely decomposed and the persistent SERS activity of the Ag NP-assembled film remained.

The UV-vis spectra of the chips at each assembly step and the chips after dipping into the glucose solution were recorded (Fig. 2). From curve a–c, red shifts in plasmon resonance peak by 12–28 nm are revealed, which is because the layer-by-layer immobilized substances change the local refractive index around Ag NPs [32]. The peak of maximum absorption of the Ag NP-assembled film is located at 388 nm, and the color

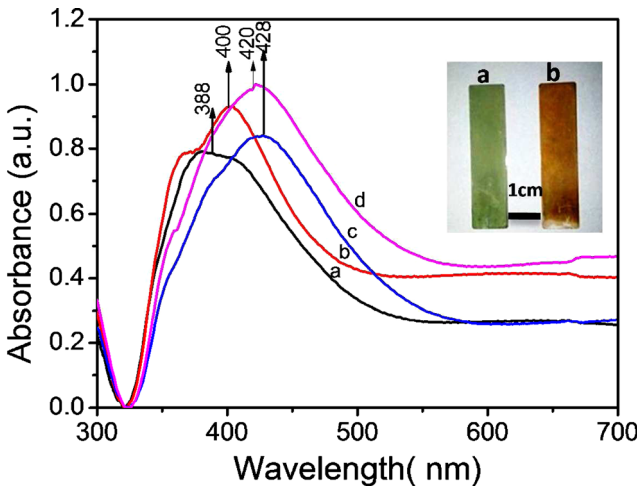


Fig. 2 UV-vis spectra of the Ag NP-assembled film (**a**), the PDDA-Ag NP-assembled film (**b**), and the GOx-functionalized SERS chips before (**c**) and after (**d**) the GOx-catalyzed oxidation reaction, respectively. The assembly time for GOx was 4 h. The photos show the Ag NP-assembled film (**a**) and the GOx-PDDA-Ag NP-assembled film (**b**) on quartz slides

of the Ag NP-assembled film is grayish green (Fig. 2(a)). When the PDDA and GOx were successively decorated on the Ag NP-assembled films, the UV-vis spectra obviously were red shift to 400 and 428 nm, respectively. The slide displays a brown color eventually (Fig. 1b), which indicates that the GOx had been assembled successfully on the Ag NP-assembled film. When the GOx-functionalized SERS chip was immersed into the blood serum glucose solution (10 mM), the maximum of the plasmonic band assigned to Ag NPs, previously lying at 428 nm, has a slight blue shift to 420 nm due to the local refractive index change, which indicates that a certain amount of GOx departed from the SERS chip [33].

To further prove that the glucose sensing mechanism is successful, the XPS spectra were used to record respectively the assembly process of glucose oxidase on the Ag NP-assembled film and the GOx-functionalized SERS chip after immersing into the glucose. Figure 3a, b shows the XPS spectra of nitrogen (N 1*s*) and carbon (C 1*s*) for the Ag NP-assembled film, the PDDA-Ag NP-assembled film, and the GOx-PDDA-Ag NP-assembled film and the GOx-functionalized SERS chip after the glucose sensing reaction, respectively. We can find that both C and N contents obviously increase with the GOx assembly (blue), especially when the band of C 1*s* becomes three peaks in a higher energy range, indicating the complicated protein components of GOx. When the sensing chip was involved in the GOx-catalyzed reaction between the glucose and dissolved oxygen because the potential of the GOx reduced due to the produced glucose acid that

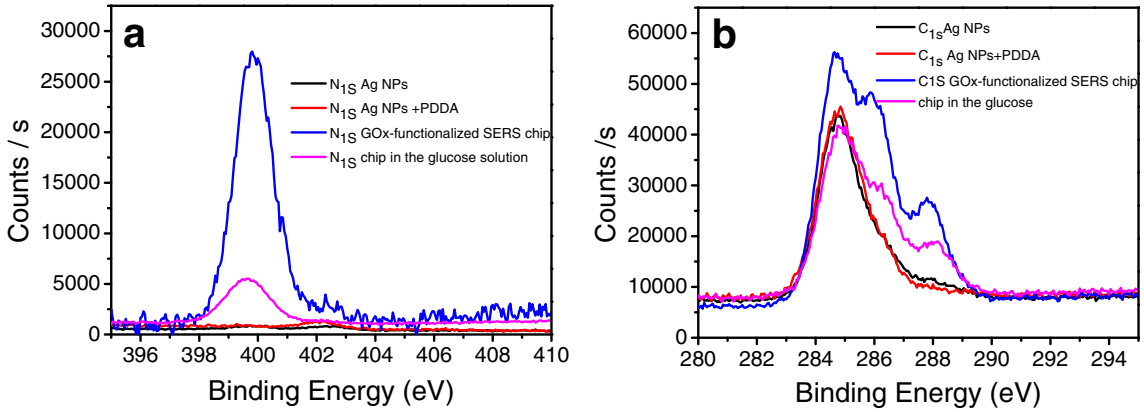


Fig. 3 XPS spectra of N 1*s* and C 1*s* on the chips of Ag NP-assembled film (*black*) and PDDA-Ag NP-assembled film (*red*), GOx-functionalized SERS chip (*blue*), and the sensing chip in response for 1.0 mM of glucose (*purple*)

can weaken the electrostatic force between GOx and PDDA, GOx molecules dropped off from the sensing chip. So, the contents of N and C obviously were decreased (purple).

Glucose SERS biosensing

Figure 4 shows the SERS spectrum of the GOx-modified SERS substrate (curve c). The SERS signal of GOx is mainly stemmed from flavin adenine dinucleotide (FAD), which is a chromophoric cofactor of GOx [24]. Table 1 lists the assignments of SERS bands according to the literature [34]. Moreover, from the SERS signals of the Ag NPs and PDDA-Ag NPs in Fig. 4 (curves a and b), we can clearly observe that they have no interference to the final glucose detection. Before glucose sensing, we first checked the effect of components in the blood serum on the SERS signal. It can be found from curve d that there are almost no additional bands except the bands of GOx compared with curve c.

The different concentrations of glucose in the blood serum from 1.0 μM to 30 mM were detected using our method (in ESM Fig. S3). From Fig. S3, the lowest concentration of our method for glucose was 1.0 μM, which can indicate that the sensor for glucose has high sensitivity. According to a previous report [34], the blood glucose range in a healthy person is 3.0–8.0 mM. Therefore, the glucose concentration range from 2.0 to 14.0 mM is of practical relevance from the physiological perspective. Figure 5a presents the glucose sensing results in the blood serum by using the GOx-functionalized SERS chips, measured at 40 °C and 20 min reaction time period. Figure 5b shows the change ratio of SERS intensity ($R = (I_0 - I)/I_0$) varying with the concentration of glucose in the blood serum, where I_0 and I are the SERS intensities at 1342 cm^{-1} before and after the glucose sensing reaction. A linear relationship is achieved, and the fitting equation is $Y = 0.0251 \cdot X + 0.516$ with a linear correlation coefficient of 0.992. From Fig. 5b, we can find that our method has a good linear relationship from 2 to 14 mM, which meets the requirement of the clinical application level of blood glucose.

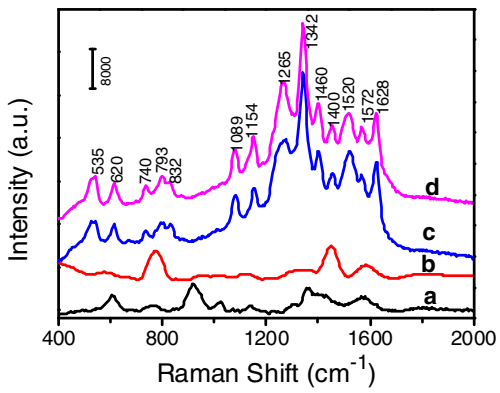


Fig. 4 SERS spectra of the Ag NP-assembled film (**a**), the PDDA-Ag NP-assembled film (**b**), the GOx-functionalized SERS chips (**c**), and the GOx-functionalized SERS chip dipped in 0 M glucose in the blood serum (**d**)

Table 1 Assignments of Raman vibrations modes of GOx

Wave number (cm^{-1})	Vibrational assignments
1628	ν C–C–C
1572	ν C=N
1520	ν C=N
1460	ν C=C + δ CH_3
1400	ν N–C=O + ν C=C + ν C–C
1342	ν C–C=N + ν C=C + δ CH_3
1265	δ CH_3 + δ N–H
1154	ν C–C + ν C–CH_3 + ν C–N + δCH_3
1089	β C–H + ν C–N
832	γ C–H
793	β C–C–C
740	ω NH_2 + γ C–C–C
620	β C–C–C
535	γ C–C–C

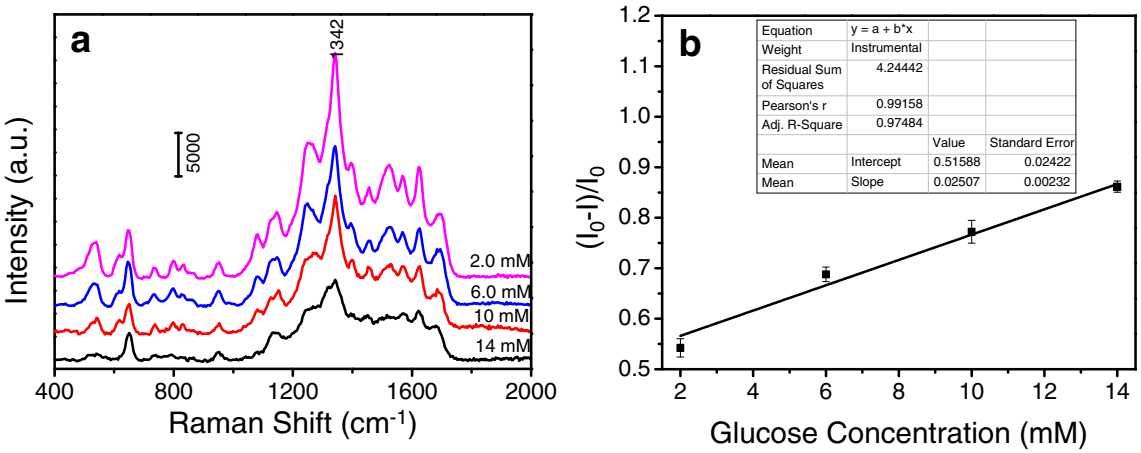


Fig. 5 (**a**) SERS spectra of GOx-assembled SERS chip for glucose sensing for the physiological perspective. (**b**) The relationship between the glucose concentration and the normalized intensity by I_0, which is SERS intensity at 1342 cm^{-1} on the GOx-decorated sensing chip before glucose was added. *Each point* represents an average of three measurements

We also have discussed the reproducibility of our designed sensor in glucose SERS detection on both the same chip and different chips (Fig. 6). Two peaks at 1342 and 1620 cm^{-1} were chosen to evaluate their reproducibility, and we found that the relative standard deviations (RSDs) of Raman signals are calculated as 5.75 and 9.04 % (Fig. 6a, b), which can meet the requirement on the RSD of less than 20 % [36, 37]. For the different slide reproducibilities, each spectrum represents an average of three measurements. The reproducibilities of different chips are shown in Fig. 6c, d, which shows the SERS intensities at 1342 and 1620 cm^{-1}, and the RSDs of these two bands are calculated as 6.06 and 10.6 %, respectively, which also meet the standard [36, 37]. These data indicate that our sensor presents good reproducibility and it can be used for clinical blood glucose detection.

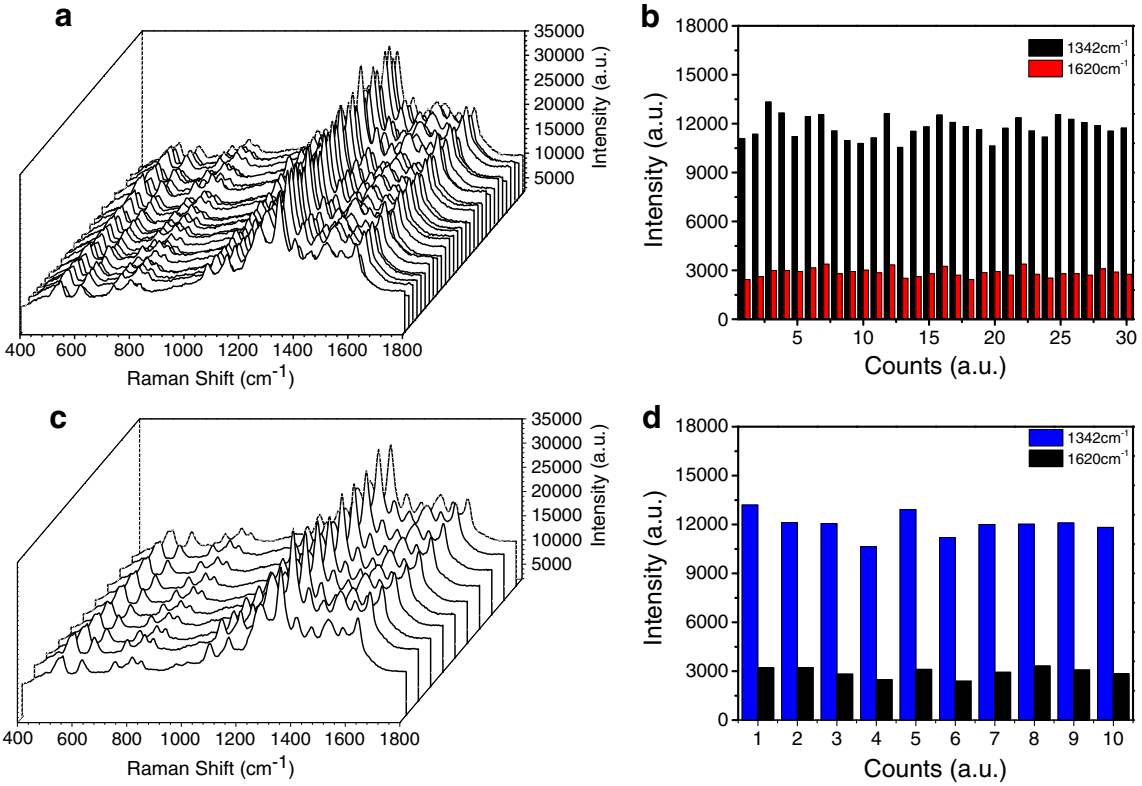


Fig. 6 (**a**) SERS spectra from randomly selected from 30 points. (**b**) The intensities of two different peaks at 30 points on the same sample. (**c**) Mean SERS spectra from randomly selected 10 trials, while each mean spectrum is from three spectra of the same sample. (**d**) The intensities of SERS bands at 1342 and 1620 cm^{-1} in different trials

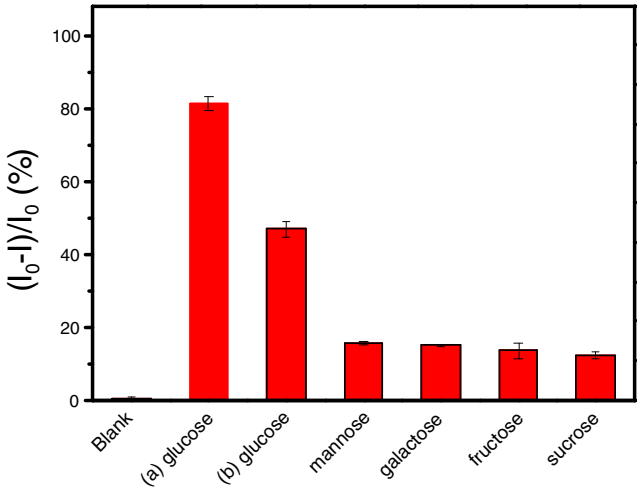


Fig. 7 Variations of SERS intensities at 1342 cm^{-1} of GOx in response to other saccharides, including mannose (0.1 M), galactose (0.1 M), fructose (0.1 M), and sucrose (0.1 M) in the blood serum, compared with 0.02 M (**a**) and 0.001 M (**b**) of glucose. The *blank* stands for a sensing chip in the blood serum without any sugar. The *error bars* are from the three trials

To test the selectivity of detection of glucose, the control experiments were carried out by using a blank blood serum solution and other saccharides (mannose, galactose, fructose, and sucrose) in the blood serum, whose concentrations are 0.1 M. As shown in Fig. 7, the changed SERS intensities of GOx at 1342 cm^{-1} show remarkable decreases when meeting glucose (Fig. 7(a, b)), which are much larger than the signal changes for other sugars under the same experiment conditions. Thus, these data prove that other saccharides do not interfere to the glucose detection in the blood serum. In essence, the developed method shows high selectivity toward glucose.

Conclusions

In summary, a practicable and simple glucose SERS sensor was developed based on the decreasing signal of GOx on the Ag NP-assembled SERS-active chip. This is the first report to adopt GOx as a Raman-active probe for glucose SERS sensing, which is beyond other probes because GOx is indispensable to glucose sensors. The dual role of GOx in specificity toward glucose and signal reporter obviously simplifies the sensor configuration. This sensing chip has an acceptable sensitivity, and the lowest concentration of glucose in the blood serum is 1.0×10^{-6} M. Owing to the highly selective reaction of GOx between dissolved oxygen and glucose solution, other sugars have little interference on this sensor. Our sensing chip is stable and can be stored in the refrigerator (at 4 °C) over half a year for using (ESM Fig. S4). Since we used the instinct Raman features of GOx and no additional Raman tags were induced in this system, the influence of excess Raman reporters on live cells and bio tissues was avoided. This GOx-based glucose SERS sensor is a promising diagnostic tool for the blood glucose detection. It is also a reference for the design of a multifunctional nanosensor for the sorting of tumorous and healthy cells.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no competing interests.

Human and animal rights and informed consent This work does not contain any studies with human participants or animals performed by any of the authors.

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