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Review

Glucose detection through surface-enhanced Raman spectroscopy: A review

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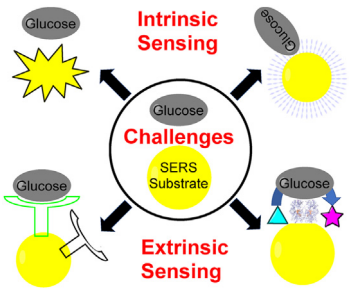
HIGHLIGHTS

- Challenges and rational design of SERS based glucose detection.
- Intrinsic and extrinsic glucose sensing.
- SERS active platform and partition layer functionalized surface.
- Boronic acid and enzymatic reaction based sensors.

GRAPHICAL ABSTRACT



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ABSTRACT

Glucose detection is of vital importance to diabetes diagnosis and treatment. Optical approaches in glucose sensing have received much attention in recent years due to the relatively low cost, portable, and mini-invasive or non-invasive potentials. Surface enhanced Raman spectroscopy (SERS) endows the benefits of extremely high sensitivity because of enhanced signals and specificity due to the fingerprint of molecules of interest. However, the direct detection of glucose through SERS was challenging because of poor adsorption of glucose on bare metals and low cross section of glucose. In order to address these challenges, several approaches were proposed and utilized for glucose detection through SERS. This review article mainly focuses on the development of surface enhanced Raman scattering based glucose sensors in recent 10 years. The sensing mechanisms, rational design and sensing properties to glucose are reviewed. Two strategies are summarized as intrinsic sensing and extrinsic sensing. Four general categories for glucose sensing through SERS are discussed including SERS active platform, partition layer functionalized surface, boronic acid based sensors, and enzymatic reaction based biosensors. Finally, the challenges and outlook for SERS based glucose sensors are also presented.

Contents

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1. Introduction

Diabetes, a metabolic disorder, affects over 420 million people globally and causes more than 3.2 million deaths every year [1]. It is one of leading fatal diseases worldwide, but if detected on time, it can be prevented [2,3]. The chronic metabolic disorder is found to have a direct association with blood glucose level [4]. For blood glucose monitoring, electrochemical based test strips and meter systems are the common methods [5,6]. The approach relies on indirect detection of enzymatic byproducts by glucose oxidation, and monitors blood glucose frequently using finger sticks and blood samples [7]. Using microneedles for blood extraction or monitoring glucose in sweat or the interstitial fluid of skin has been proposed as less painful approaches than that of finger sticks or blood samples. The approaches may cause accuracy issues, because the small size or much lower glucose concentrations in interstitial fluid or sweat compared to blood used [4]. However, the disease not detected on time or not appropriately monitored are still the main causes of death. A faster, easier, and less painful method for frequently measuring glucose levels with lower cost is thus highly necessary for the interests of patients, clinics and the society. In addition, continuous monitoring of blood glucose would help diagnosis and treatment of the disease.

Due to the importance of the task, numerous analytical methods have been utilized to achieve sensitive and selective detection of glucose based on mass spectrometry [8], electrochemistry [9], chemi-luminescence [10], fluorescence [11], colorimetric methods [12] over the years. Optical approaches have been investigated extensively due to their benefits such as minimally invasive or noninvasive potentials, portability, relatively low cost, sensitivity and selectivity. Several optical techniques have been exploited for the detection of glucose, such as infrared absorption, laser polarimetry, fluorescence modification of dyes, bio-impedance spectroscopy, and thermal emission spectroscopy. Most of these techniques are not molecular specific and can yield similar results with structurally similar molecules [13].

Raman scattering is an inelastic process where incident photons either lose energy to or gain energy from the vibrational and rotational motion of an analyte molecule [14]. The resulting Raman spectra consist of bands specific to the molecular structure, and therefore give rise to chemical fingerprints that are unique to molecules. In addition, Raman peaks typically have 10–100 times narrower spectral widths than fluorescence/absorption ones, and thus increase multiplex capability. However, Raman scattering signal is very weak, with only about 1 in 10^6–10^{10} photons being scattered inelastically, which limits its utility for chemical analysis. This changed until 1970s when surface enhanced Raman spectroscopy (SERS) was discovered [15,16]. SERS inherits all the benefits of normal Raman spectroscopy such as unique fingerprints spectra and narrow band peaks, but overcomes the inherent limitations of weak signals and poor sensitivity [17]. The discovery has thus led to a new field in biosensing for a variety of analytes [18–21]. For example, SERS shows the potentials to detection of multiple pathogen bacteria [20], identification of fungi diseases [22], as well as monitoring biomarkers for cancer detection [18]. Very recently, SERS was even utilized to combat the global pandemic for the COVID-19 virus detection efficiently and sensitively [23].

Several good reviews exist on SERS based glucose detection published 10 years ago [24,25]. Considering the rapid development in this field, I summarize and present the recent progress of SERS based glucose sensing, with an emphasis on the recent 10 years. Although there are also quite a few excellent reviews on SERS based biosensing [18,26–28], a different perspective in this work is presented. After a basic introduction, SERS mechanisms and the rational design and strategy, I discuss the glucose sensing comprehensively including SERS substrates design and sensing performance. Four different categories are summarized for SERS based glucose detection for the first time. Finally, I extensively present the conclusions and outlook of this topic, as well as pros/cons of SERS based glucose detection. It is hoped that this review will guide and inspire researchers and biomedical companies towards the development of glucose sensors through SERS, and further give insights to the exploration of sensors on other analytes.

2. SERS mechanisms

It is generally believed that electromagnetic enhancement (EM) and chemical enhancement (CE) are the two mechanisms responsible for the enhanced Raman signals [17,29–31]. EM mechanism contributes dominantly to the total SERS enhancement with 4–11 orders of magnitude. The collective oscillation of free electrons on the metal surface excited by incident light causes selective absorption and scattering and is known as localized surface plasmon resonance (SPR), which results in strong field enhancement, famously known as the electromagnetic enhancement. This light concentration occurs preferentially at hot spots, generally the gaps, crevices, or sharp features of plasmonic materials (e.g., Ag, Au, and Cu), because they show strong SPR in the visible to near-infrared region. Since the strength of local electric field depends on the distance between molecules and the surface, the SERS enhancement decreases with increase of the distance. CE is in the range of 10^1 to 10^3 times enhancement, due to the chemical interaction between molecules and the nanostructured surface in the ground state. This chemical interaction leads to the formation of a charge-transfer state between the surface and molecules. The charge transfer state can be resonantly excited leading to a resonance Raman enhancement and is highly molecular specific.

The total enhancement factor (EF) comprises the contribution of EM and CE mechanisms. One popular way to simply obtain EF experimentally is using the following equation,

$$EF = \frac{I_{SERS} / N_{Surf}}{I_{NR} / N_{Vol}} \quad (1)$$

where, I_{SERS} and I_{NR} are the intensities of the Raman spectra obtained from the SERS and normal Raman approaches, N_{Surf} and N_{Vol} refer to the average number of molecules in the scattering volume for SERS and normal Raman experiments.

3. Challenges and rational design of SERS based glucose detection

Two challenges exist when SERS is used to detect glucose: the low Raman cross-section of glucose, and poor adsorption of glucose on bare metal surface such as gold or silver [32]. The Raman cross-section of polarizability of glucose is 5.6×10^{-30} $cm^2 \cdot molecule^{-1} \cdot sr^{-1}$, which is much smaller than that of some Raman dyes, and even smaller compared to fluorescent molecules. Very recently, Van Duyne et al. verified differential Raman scattering cross section of glucose with a range of $5.0–8.9 \times 10^{-30}$ $cm^2 \cdot molcule^{-1} \cdot sr^{-1}$ [33]. While benzene, a strong Raman scatter, has a cross section of 2.8×10^{-28} $cm^2 \cdot molcule^{-1} \cdot sr^{-1}$. The resulting glucose Raman emission is thus easily overshadowed by strong background noises from the surrounding environment [4]. On the other hand, as a carbohydrate molecule, glucose, has low binding affinity onto bare metal surfaces. Glucose is different from molecules with thiol groups, which bind strongly onto Au/Ag surfaces via covalent metal-thiol bonds. Considering the above-mentioned challenges, several approaches were proposed.

While small molecule detection with SERS has been predominantly accomplished with the intrinsic strategy in the early period, glucose sensing through SERS has been achieved with both intrinsic and extrinsic sensing approaches recently. For the intrinsic format, also called as direct detection or label-free detection, Raman spectra with fingerprint peaks, unique to the analyte (e.g., glucose) are obtained. The simplest strategy is to develop efficient plasmonic materials with improved hot spots or to optimize enhanced Raman technique, which could enlarge the enhancement factor, thus glucose Raman signals could be visualized directly. The other strategy for intrinsic sensing is aimed to increasing glucose binding affinity with Raman substrates, decreasing the distance between glucose and the surface, and correspondingly enlarging the Raman signals. A partition layer on the substrates surface to preconcentrate glucose molecules into a thin layer of SERS active area was proposed and explored [32]. No chemical interactions are involved in almost all the studies of SERS based glucose detection through intrinsic sensing.

Although most of early studies took advantage of intrinsic sensing strategy, the extrinsic approach has been investigated extensively in recent years. Extrinsic (also known as indirect) sensing approaches employ a Raman-active “probe” molecule which chemically reacts or interacts with the analyte of interest, and the probe is attached to the plasmonic surface. Analyte-induced chemical changes of the probe molecules result in measurable Raman signal differences for some or all of the vibrational modes. Glucose analyte leads to interactions with the dye molecule and the formation of a new molecule, which has corresponding variation of Raman signals. Two general methods are summarized. Firstly, applying the boronic acid based recognition molecules functionalized surface, glucose forms boronate ester reversibly, and is captured on the surface. In this way, boronic acid molecules are used as both glucose recognition structures and Raman active molecules. The other approach is the utilization of enzymatic reactions, in which the product (e.g., hydrogen peroxide) affects Raman signals of probes. For example, formation of hydrogen peroxide converted the Raman-caged molecule to the Raman-active product, which induced signal changes for efficient glucose monitoring [34]. Researchers also studied enzymatic reactions for etching the Ag SERS substrates, which changed the probe's Raman signals with varied glucose concentrations [35].

4. SERS based glucose detection

According to the rational design to address challenges of glucose detection through SERS, four general categories are summarized, including SERS active platform, partition layer functionalized surface, boronic acid based sensors, and enzymatic reaction based biosensors.

4.1. SERS active platform

One of the difficulties for SERS based glucose sensing is the low cross-section of glucose molecules, to develop active SERS substrates with enlarged enhancement factor is one feasible strategy. Mrozek et al. demonstrated detection and characterization of carbohydrates through SERS for the first time [36]. They injected saccharide solution onto a roughened silver substrate, with subsequent deposition of silver colloid, and obtained spectral fingerprints for seven monosaccharides. However, collecting reproducible and reliable SERS signals for glucose detection with high sensitivity and selectivity is still challenging. Following the study, many researchers worked on the designing, developing and optimizing SERS active substrates for glucose detection, mainly aiming to enlarge the enhancement factor, and/or to improve signal reproducibility and reliability.

Core-shell materials, one kind of novel materials, have become potential SERS substrates, as random colloidal particle based substrates suffer poor signal reproducibility and data reliability. Hwang et al. investigated Au@SiO_2 core/shell nanoparticles assemblage as SERS substrates (Fig. 1A) for glucose detection successfully [37]. The signal intensities representing glucose concentrations for the bands at 935 and 1345 cm^{-1} (Fig. 1B) demonstrate the potential detection of glucose for a wide range ($10^{-12} - 10^{-3}$ M). The probe stability

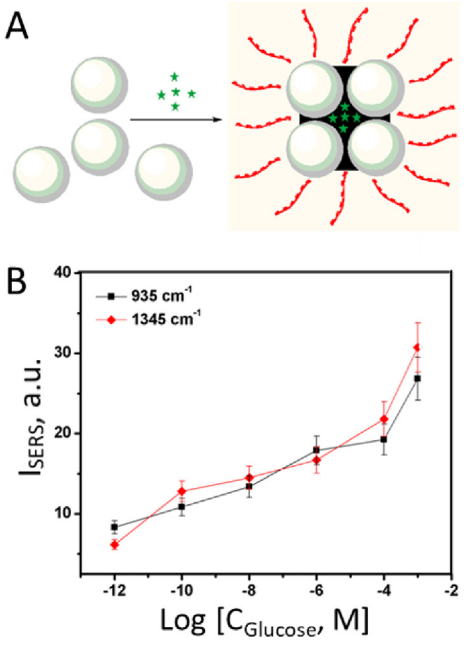

Fig. 1. A) Schematic illustration of Au@SiO_2 NPs and generated Raman active contents in solution between ends of adjacent Au@SiO_2 NPs in the presence of glucose. B) A logarithmic plot of glucose concentration vs. corresponding signal intensity (from 532 nm excited SERS spectra of glucose on Au@SiO_2 NPs) for the bands at 935 and 1345 cm^{-1}, respectively. Reprinted with permission from Ref. [37], Copyright 2013 Wiley.

studies presented that the glucose spectral band position did not change obviously for 3 days. Radziuk and the group fabricated one SERS-active, thin plasmonic nanofilm by preformed silver NPs in the matrix of poly (vinyl alcohol) adsorbed on silica microparticles for several analytes detection, and a greater amount of glucose was monitored in time [38]. One sustained and cost-effective substrate using silver nanoparticles protected by nitrogen doped graphene quantum dots was proposed by Liu and others, stronger Raman enhancement and improved stability compared to pure silver particles substrates were achieved, as well as detection in both aqueous solutions and blood samples [39].

Optimizing the substrate platform presents one way to enhance the Raman signals. Zhang et al. proposed a well-controlled armrest Ag nanorods@Al_2O_3 structure SERS substrates that could detect glucose through SERS as low as 0.1 μM, by enhancing hot spots and tuning resonance between Ag nanopillars and Ag nanorods [40]. Choi and others designed a smart SERS platform using nano-plasmonic wells for glucose detection as shown in Fig. 2A [41]. The SERS signal was easily maximized at the center near the bottom of the well due to spherical feature of the fabricated wells and electromagnetic field enhancement by the metallic nanoparticles (e.g., Au or Ag) integrated on their surfaces. Concentration dependent SERS spectra of glucose and intrinsic signals of glucose at as low as 0.1 mg/mL was observed (Fig. 2B). In addition, this smart design improves the reproducibility and allows dual mode sensing via plasmon resonance energy transfer strategy (PRET) besides SERS [42].

Besides the popular plasmonic metals, two-dimensional materials (such as graphene) have also been proposed as SERS substrates with enhanced signals due to their special electronic and optical properties [13,43,44]. Chattopadhyay and the group produced graphene on copper substrates for glucose detection [13]. Fractional charge transfer between glucose and graphene aided by a possible π-π interaction contributed to the graphene enhanced Raman signals. The intensity ratio of the 1122 cm^{-1} peak of glucose to the 2D peak of graphene varied linearly with the glucose concentrations for detection of glucose in physiological concentrations. Recently, monolayer Janus transition metal dichalcogenide served as an efficient, two-dimensional material based SERS substrate due to dipole interactions, charge redistribution and enhanced Raman signals [44]. The substrates were achieved for glucose detection in the range of 1–10 mM through utilizing changes of C–C stretching Raman peak around 1360 cm^{-1}.

Exploitation of novel Raman techniques for enhanced Raman signals is also a viable approach [45–48]. Through the proposed photo-induced enhanced Raman spectroscopy (PIERS), monitoring 1 nM glucose concentration was demonstrated (Fig. 3A) by Parkin and others [45]. The combination of plasmonic nanoparticles with a photo-activated substrate gives rise to large signal enhancement owing to chemical enhancement due to increased electron density at the noble-metal surfaces. Using the novel design, enhancement factor of an order of magnitude was achieved over traditional SERS spectra, especially for low Raman cross-section analytes such as glucose. Rice and others applied semiconductor-graphene oxide substrates and enabled chemical SERS enhancement by the application of an electric field (10–25 V/mm) to aligned semiconducting peptide nanotube-graphene oxide composite structures (Fig. 3B) [46]. The technique allows nanomolar detection sensitivity of glucose with up to 10-fold signal enhancement compared to metal-based substrates, and the increased Raman scattering was attributed to enhanced charge-transfer resonance enabled by work function lowering of the peptide nanotubes. The group later combined piezoelectric peptide nanotubes, Ag NPs and flexed substrates for signal enhancement through combination of piezoelectric peptide nanotubes and Ag NPs and the flexed substrates [47]. The novel design of flexed substrates played a role in enhancement, attributed to piezoelectric induced charge via mechanically activated bending.

Admittedly, several research groups proposed glucose detection just through the optimization of SERS platform, but glucose Raman signals with this strategy are relatively weak, and easily overshadowed by other interferences. The limitations of this strategy are still involved with the two widely accepted challenges when SERS is used for glucose detection, as this strategy does not fundamentally resolve the issues of adsorption of glucose on bare metal surfaces or cross sections of glucose.

4.2. Partition layer functionalized surface

In order to address the adsorption issue of glucose on metal surfaces, Van Duyne's group has conducted extensive studies. In a pioneering work, they proposed the partition layer strategy for

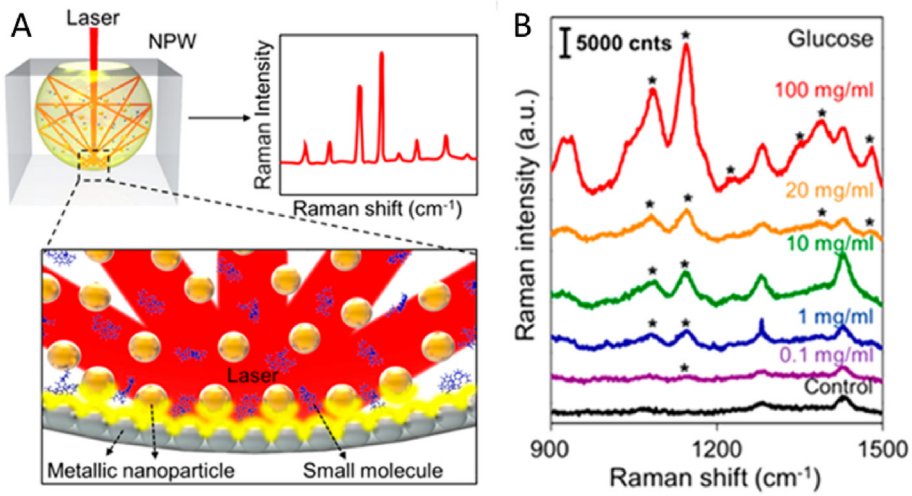

Fig. 2. A) Schematic illustration of the solution-state SERS maximized by using a spherical nano-plasmonic well (NPW) with the expected enhanced Raman spectrum signals. B) Concentration-dependent intrinsic SERS spectra of glucose from the label-free SERS measurement in the NPW. Adapted with permission from Ref. [41], Copyright 2018 American Chemical Society.

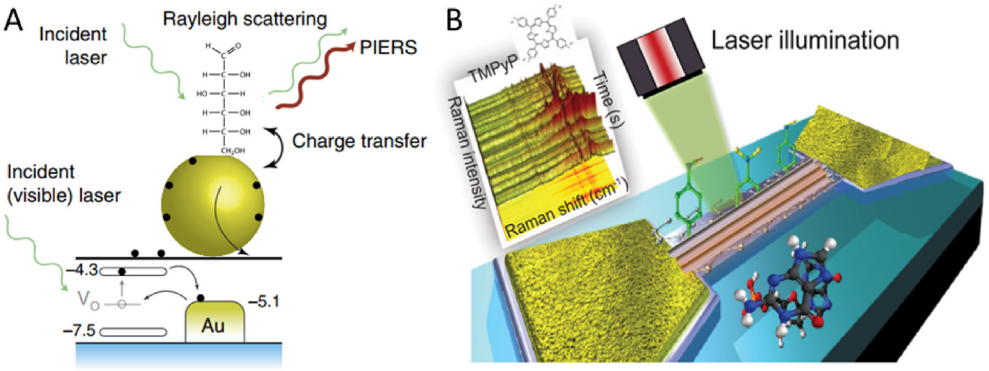

Fig. 3. A) Sensitive molecular detections glucose via charged particles through photo-induced enhanced Raman spectroscopy (PIERS). Modified with permission from Ref. [45], Copyright 2016 Nature Research. B) Schematic illustration of the substrate design with the inset shows Raman spectra from the analyte molecule TMPyP at a relatively low concentration on the FF-PNT/GO template with an applied electric field of 25 V/mm. Modified with permission from Ref. [46], Copyright 2019 American Chemical Society.

direct detection of glucose using surface-enhanced Raman spectroscopy [32]. An alkanethiol monolayer as the partition layer functionalized on silver film over nanosphere (AgFON) was applied to bring glucose within the 0–4 nm thick zone of electromagnetic field enhancement. With the partial layer, glucose Raman signals at 1064, 1123 cm^{-1} were observed; otherwise, no glucose was visualized. Due to the protein resistant properties, the Van Duyne group switched to an ethylene glycol terminated self-assembled monolayer (SAM) as the partition layer [49]. Exposure to bovine serum albumin (BSA, a model protein interferant) did not affect glucose detection with the (1-mercaptoundeca-11-yl)tri(ethylene glycol) (EG3) partition layer. A real-time, quantitative and biocompatible glucose sensor with reversibility, reusability, and stability (for 3 days) was achieved.

To further optimize the surface to preconcentrate glucose, mixed decanethiol (DT)/mercaptohexanol (MH) partition layer was applied for real-time and *in vivo* sensing as shown in Fig. 4A [50–52]. The mixed monolayer provided appropriate balance between hydrophobic and hydrophilic groups and showed temporal stability for at least 10 days in bovine plasma. The new layer also presented quantitative analysis of glucose in a mixture of interfering analytes. Compared with previous EG3 SAM partition layer, this study had less calibration error. The reversibility of the sensor was studied through exposure to cycles of 0 and 100 mM aqueous glucose solutions without flushing the sensor between measurements, and presented a completely reversible sensing surface for optimal partitioning and de-partitioning of glucose in less than 1 min (as shown in Fig. 4B). The quick response indicated the high potential for real-time continuous sensing. In order to provide a more stable surface, to improve chemometric analysis, to shift SERS resonances to near-IR wavelengths, and to facilitate the use of lower cost lasers, the group applied AuFON and a shorter chain length version of EGs as the partition layer [53]. In addition, switching to Au surfaces decreased biological autofluorescence, demonstrated better chemometric results with improved calibration, validation over a range of 0.5–44 mM, and stability for 11 days.

Building on the success in the field, Van Duyne and co-workers advanced into *in vivo* glucose detection on rat models [50]. For the subcutaneous implantation, an incision was made in the skin of a rat and a pocket was blunt dissected into the subcutaneous space for implanting DT/MH @AgFON substate. They thus achieved the first quantitative, *in vivo* and transcutaneous glucose measurements through spatially offset SERS [54]. The sensor performed continuous monitoring accurately for multiple rats, and over 17 days after implantation [55].

Other groups also exploited the partition layer strategy and worked towards glucose detection [56–61]. Xia and others utilized

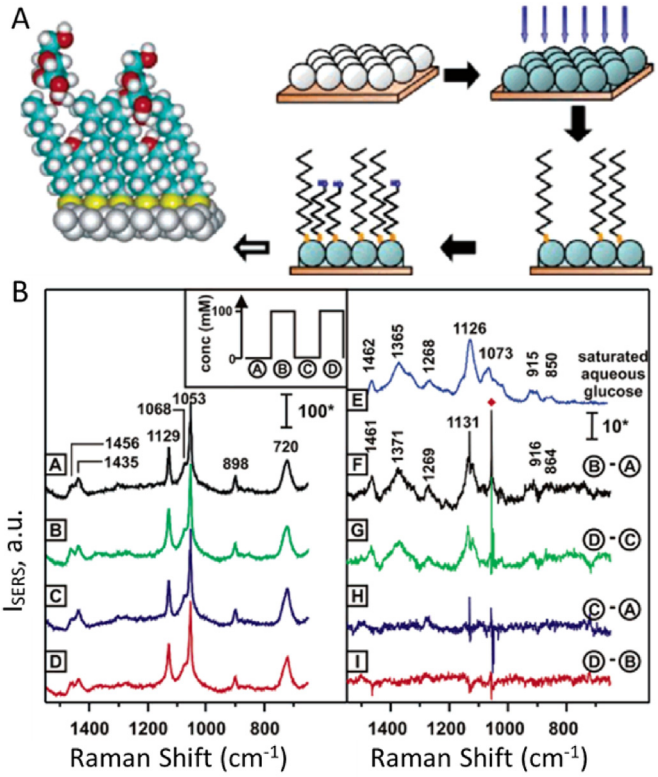

Fig. 4. Partition layer strategy for glucose detection. A) Sensor preparation with AgFON depositing metal through a mask of self-assembled nanospheres, functionalization by successive immersions in ethanolic solutions of DT and MH, and glucose partition in to and out of the DT/MH layer. Adapted with permission from Ref. [50] Copyright 2006, American Chemical Society. B) Glucose pulsing sequence on the SAM-modified AgFON surface (inset). SERS spectra of the sample cycled between 0 and 100 mM aqueous glucose solutions (left), Normal Raman spectrum and glucose aqueous solution and difference spectra showing partitioning/departitioning of glucose (Right). Adapted with permission from Ref. [51] Copyright 2005 American Chemical Society.

dodecanethiol functionalized Ag nanocubes for glucose detection [56]. They explored SAM's response to glucose, observed conformational changes in the alkanethiolate SAMs, and proposed no penetration for glucose molecules into the monolayers. Olivo et al. fabricated 2-naphthalene thiol-functionalized nanogap metallic surfaces by deep UV lithography for glucose detection [57]. The substrates demonstrated improved reproducibility and less relative standard deviation. Very recently, Liu and others demonstrated the capability of 1-decanethiol coated silver needle array as SERS

substrates for *in situ* intradermal detection of glucose [60]. In addition, the probe achieves *in vivo* quantification of glucose in a mouse model of diabetes, and provides potentials in painless glucose monitoring.

Besides the small molecules, functional proteins were creatively developed as a partition layer [62]. Albumin coated star-like gold nanoparticles (Fig. 5A) endows the detection of glucose at 10^{-9} M with EF of 10^{11} (Fig. 5B), which presented performance-enhancing substrates compared without albumin functionalization. The formation of peptide bonds due to the interaction of glucose with albumin and the appropriate separation distance between the NPs and glucose. Galectin-1 was later designed as both a stabilizer or a nano-biosystem and an active biomolecular probe for glucose detection, and the Galectin-1/AuNPs showed ability to bind glucose and concentration response SERS signals (100 pM–10 mM) [63].

The partition layer strategy has increased extensive attention, and glucose detection (even with *in vivo* studies) was achieved through utilizing direct glucose Raman signals. However, the glucose signals are easily overshadowed by strong background noises from the surrounding environment. The approach may also endure poor selectivity over other sugars and slow sensing response. These disadvantages also arise when glucose detection through development of SERS active platform, which generally utilizes direct glucose detection approach (intrinsic sensing) as well. Considering these challenges, indirect glucose detection has been proposed and developed through boronic acid interactions or enzymatic reactions in recent years.

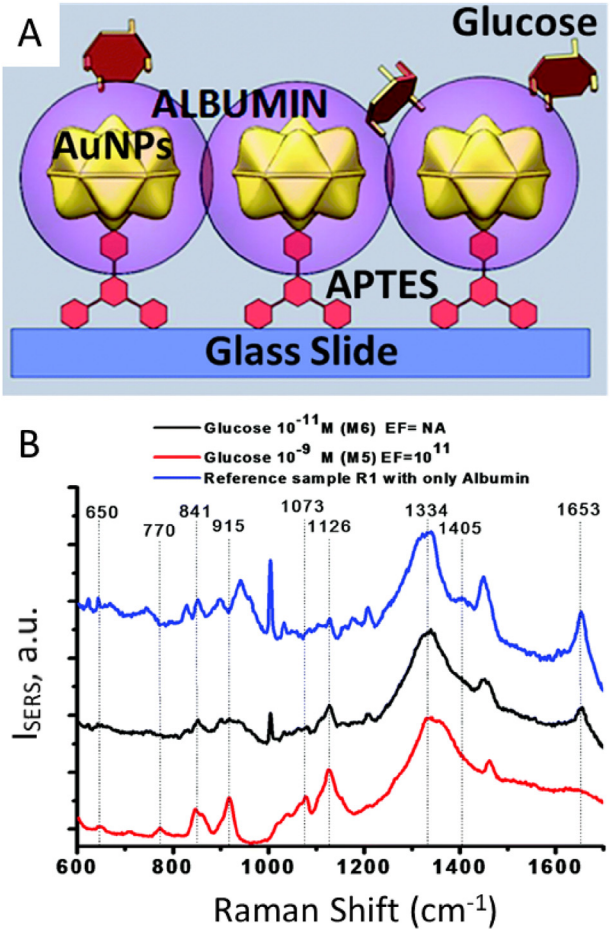

Fig. 5. A) Schematic illustration of SERS substrates: albumin coated starlike Au NPs functionalized on the glass slide surface. B) M5 (10^{-11} M glucose, Red), M6 (10^{-9} M glucose, Black) spectra obtained using albumin coated Au NPs substrates and the reference substrate R1 (glass/Au NPs without albumin functionalization) and the detection of 10^{-11} M glucose. Modified with permission from Ref. [62]. Copyright 2016 Royal Society of Chemistry. (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

4.3. Boronic acid based sensors

A molecular recognition agent, phenylboronic acid, represents an ideal synthetic molecular receptor, due to its ability to recognize the *cis*-diol configuration in saccharides and to form reversible covalent complexes with saccharides in aqueous media [64–66]. Many researchers thus have adapted boronic acids for glucose sensing in combination with fluorescence, colorimetry, surface plasmon resonance, electrochemistry, etc. Li and the group introduced the boronic-acid strategy for SERS based glucose sensing for the first time, and prepared 3,3′-boronic benzyl viologen functionalized gold nanoparticle-coated zinc oxide nanowires and silver nanoparticles as two substrates [67]. The electrostatic interaction between the substrate and the boronic structure was proposed to play important roles in glucose response signals.

Building on the initial success, extensive studies on boronic acid based glucose sensing through SERS have been widely proposed in recent years, and are summarized in Table 1. It is found that 4-mercaptophenyl boronic acid (4-MPBA) is the most popular boronic acid for glucose determination through SERS, possibly due to its strong binding ability to both metallic surface and glucose, and unique Raman properties. Various researchers produced 4-MPBA-functionalized substrates and observed increasing Raman signals with glucose concentrations [68–73]. Lei and others designed and developed 4-MPBA functionalized silver nanorod arrays as SERS substrates for glucose detection [68], and proposed that orientation effects and charge transfer effects, resulted from the binding of glucose with the boronic acid motif, both of which affected SERS signals of boron-carbon and phenyl ring in MPBA. Raman intensities of several peaks from 4-MPBA increased with glucose concentrations, and quantitative detection in a clinically relevant concentration range was realized. Recently, the group progressed into a minimal invasive system for long term monitoring (over a period of 60 days) of glucose via SERS using 4-MPBA functionalized Au NPs [69]. Both *in vitro* and *ex vivo* detection showed glucose-concentration dependent Raman signals. Taking advantage of the boronic acid – glucose interactions, recently Jiang and others proposed graphene oxide nanoribbon (GONR) – gold nanoparticles for glucose detection with recovered Raman signals [73]. With addition of 4-MPBA, the catalytic efficiency of GONR to form gold nanoparticles and further the Raman enhancement were decreased. Addition of glucose promoted the formation of MPBA–glucose complex, recovered GONR's catalytic efficiency and increased the SERS peak intensity.

Modifying the substrate platform, different sensing phenomena were observed. For example, Gupta et al. configured a glucose biosensor based on 4-MPBA terminated Ag @AuNPs/graphene oxide substrates [74]. The SERS peaks of B–O stretch at 1070 cm^{-1} was decreased with increasing glucose concentrations. In order to obtain enhanced, stable, and reproducible signals, Lu and the group built a novel substrate by employing *p*-aminothiophenol (PATP) which resided inside Au@Ag structure as a linkage agent and an internal standard, and by utilizing 4-MPBA functionalization for recognition of glucose molecules [75]. Signals at 1177 cm^{-1} of B–OH stretch decreased with increasing glucose concentrations, and the specific peaks of the employed internal standard was used as a benchmark, and glucose detection in urine as low as 0.1 mM in the presence of other interferents was realized. To further increase the binding ability and to preconcentrate glucose, the combination of a 1-decanethiol partition layer and the boronic acid recognition

Table 1
Summarized boronic acid based glucose sensing using SERS and their corresponding sensing performance in recent years.

Ref.	Substrates	Functionalized molecules	Limit of detection	Detection range
[67]	AuNPs-ZnONWs, Ag NPs	BBV	0.25 mM	0.9–30 mM
[68]	Ag Nanorods	4-MPBA	/	0–20 mM
[69]	Au NPs	4-MPBA	/	0–20 mM
[70]	GO@SiO_2@Ag NPs	4-MPBA	/	2–20 mM
[71]	Ag – hydrogel microparticles	4-MPBA	/	/
[72]	Au nanoaggregate on mirror structure	4-MPBA	0.05 mM	0.1–15 mM
[73]	Graphene oxide nanoribbon – Au NPs	4-MPBA	0.13 nM	0.33–5.33 nM
[74]	Ag@AuNPs-GO	4-MPBA	0.33 mM	2–6 mM
[75]	Au@Ag	4-MPBA	0.1 mM	0.1–6 mM
[76]	Au nanorod-Au surface	2-MPBA/1-DT	0.5 mM	2–16 mM
[77]	Ag NPs	4-MPBA	/	0.05–5 mM
[4]	Au nano clusters	4-MPBA	/	0.1–30 mM
[1]	AuFON	1,1 bisboronic acid	/	1–10 mM
[78]	Bimetallic film over nanospheres	4-MPBA/Os-BA	0.1 mM	0.1–10 mM
[79]	BMFON	4-MPBA/Alkyne-PBA	0.1 mM	/
[80]	Au@Ag NRs	4-MPBA/4-CPBA	10 nM	10 nM-10 mM
[81]	Ag nanodendrites	4-MPBA/4-CPBA	5 μM	0.05–5 mM
[83]	Ag NPs-Au slide	4-MPBA/PATP	0.01 mM	0.03–20 mM
[84]	Au nanodisks-Ag NPs	4-MPBA/PATP	/	1–40 mM
[82]	Au nanopillar	MPBA/Os-BA	/	7–392 μM

molecules were proposed by Tamer and the group [76]. The determination of glucose under clinical relevant concentrations in presence of interferents and in plasma samples were realized through applying paper-based substrates.

Besides Raman intensity on/off response for sensing, ratiometric and peak-shifted phenomena could be utilized as well. Zheng and others investigated 4-MPBA functionalized Ag NPs for glucose detection by taking advantage of the difference in the kinetics of dissociation of the OH^- associated MPBA and glucose associated MPBA species, and utilized ratiometric signals [77]. Recently, Choo and co-workers made use of 4-MPBA functionalized Au nanomaterials for glucose binding (Fig. 6A) and found that binding of glucose to MPBA suppressed the "breathing" mode of MPBA at 1071 cm^{-1} and energized the constrained bending mode at 1084 cm^{-1}, leading to the dominant peak shift from 1071 to 1084 cm^{-1} with both experimental and DFT simulation evidences, as shown in Fig. 6B [4]. In addition, reversibility of MPBA-glucose bonding allowed continuous tracking of ambient glucose concentrations, and MPBA-coated substrates showed very stable performance over a 30 day period. They further demonstrated intraocular glucose measurements in *ex vivo* rabbit eyes accurately. The miniaturized SERS implant and Raman irradiation of IR light especially demonstrates the implantable devices with potential biomedical applications.

Optimization of the recognizing boronic acid is necessary to improve the sensing performance, Van Duyne and his group designed and tested multiple bisboronic acid derivatives on AuFON substrates for increased sensitivity with SERS [1]. The combination of selectivity in bisboronic acid receptors and spectral resolution in the SERS data endowed the sensors to resolve glucose even in high backgrounds of fructose, to detect glucose accurately in the 1–10 mM range with multivariate statistical analysis, and further to provide increased evidence with distinction of the spectra into hypoglycemic, normal, and hyperglycemic ranges (Fig. 7A). Especially, the Raman peak intensity of 1070 cm^{-1} (from glucose directly) showed glucose concentration dependent properties (Fig. 7B). Different from other boronic acid based glucose sensing through SERS, this work, to the best of my knowledge, uniquely applied direct glucose Raman signals for detection; at the same time, the limitations of intrinsic glucose sensing might appear.

Although glucose detection was achieved using Raman signal changes of boronic acid recognition molecules or glucose, the

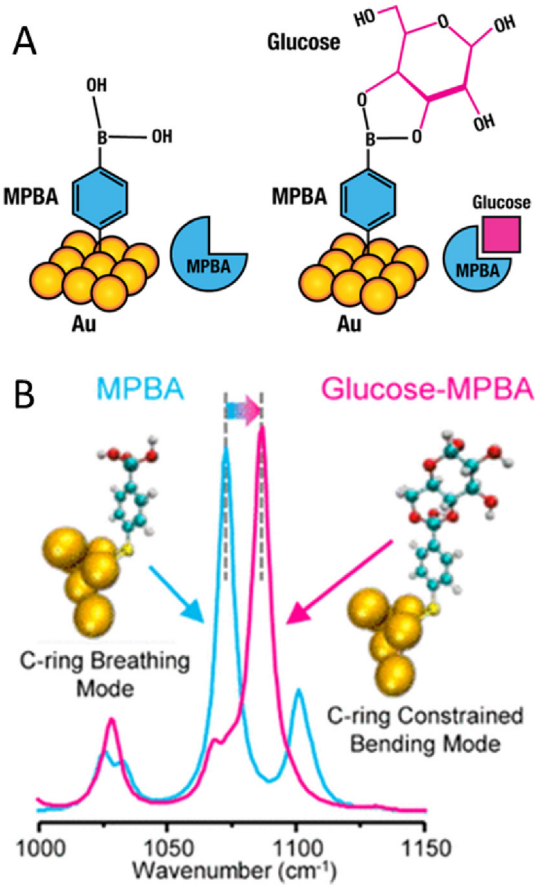

Fig. 6. Indirect glucose detection using boronic acid based sensors. A) Schematic illustrations of MPBA (left) and glucose-bound MPBA (right), B) MPBA's Raman-peak-shifting before and after glucose binding and the DFT-simulation geometries. Adapted with permission from Ref. [4], Copyright 2018 American Chemical Society.

interference from several functional groups of biomolecules in the conventional imaging range (600-1800 cm^{-1}) may hamper the glucose sensing applications. A biological silent region (1800-2800 cm^{-1}) was thus proposed and utilized, offering specific sensing of glucose, without the interference from other endogenous molecules. Olivio et al. proposed a seminal glucose detection

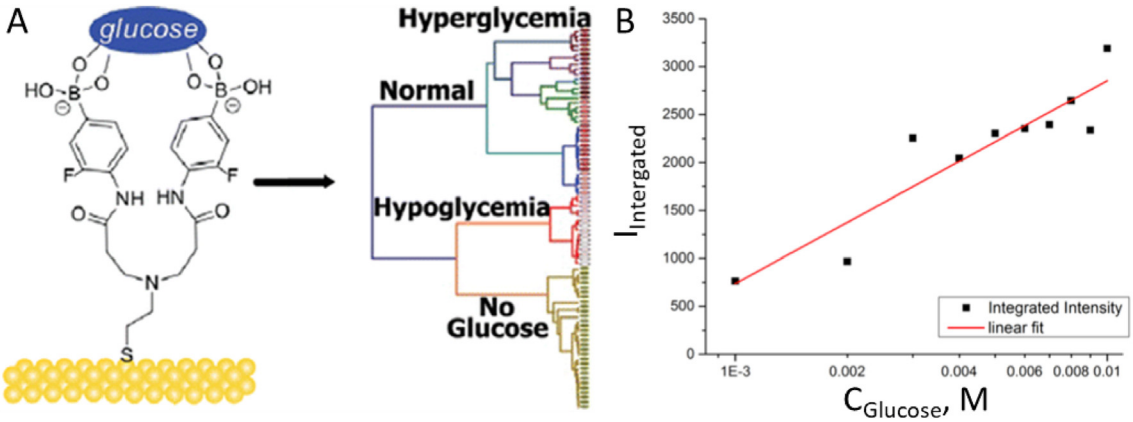

Fig. 7. A) Glucose binding with bisboronic acid functionalized Au surface and the distinguishing between hypoglycemia (1–3 mM), normal (4–8 mM), and hyperglycemia (>8 mM). B) Log scale glucose concentration (1–10 mM) versus integrated SERS intensity of the 1070 cm^{-1} peak from concentration dependent SERS difference spectra. Reprinted with permission from Ref. [1], Copyright 2016 American Chemical Society.

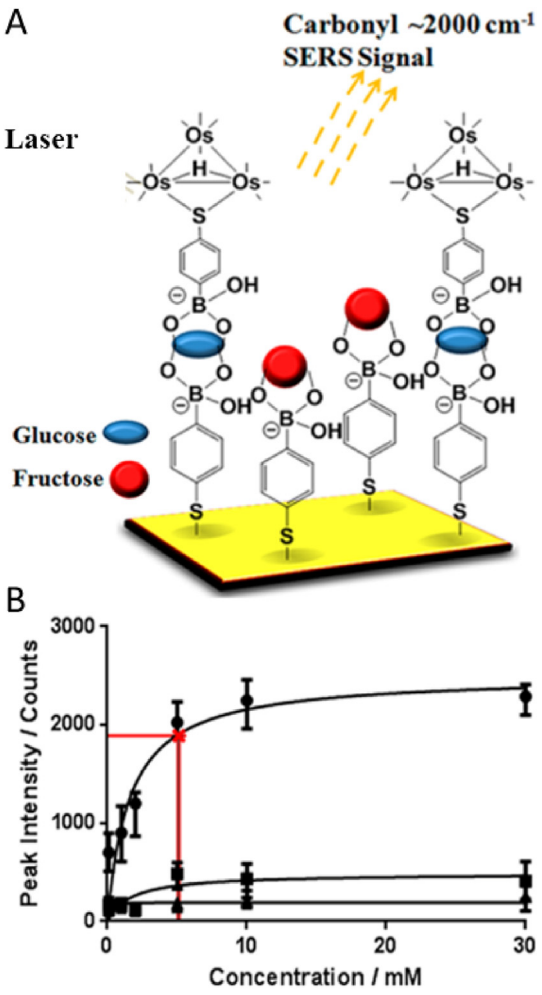

Fig. 8. A) Schematic illustration of the two acceptor strategy for glucose sensing in the biological silent region, and a glucose molecule brings Os-BA to the substrate selectively via formation of a bidentate complex. B) Plot represents the intensity of CO stretching frequency (at 2111 cm^{-1}) versus different concentrations of (●) glucose, (▲) fructose, and (■) galactose, with the interpolated value for the spiked urine sample shown in red. The first data points are at 0.1 mM. Modified with permission from Ref. [78], Copyright 2013 American Chemical Society. (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

approach using a smart design of two carbohydrate receptors (Fig. 8A) [78]. The first primary receptor comprised 4-MPBA anchored onto a SERS substrate, and the second carbohydrate receptor was a 4-MPBA-triosmium carbonyl cluster conjugate (Os-BA) which was used as a mid-IR probe for determination of glucose through SERS mode. Glucose was first captured by the primary carbohydrate receptor, following the labeling by the Os-BA. The work showed concentration-response signals at 2111 cm^{-1} (CO stretching) and high specificity for glucose compared with other sugars (Fig. 8B). The spectroscopic handle for glucose quantification is in a window (1800-2200 cm^{-1}), which relatively devoid of interference from any functional groups of biomolecules. This group later did a similar work, where alkyne structures featured as a secondary receptor with a distinct Raman peak at 1996 cm^{-1} [79].

Inspired by the strategy, Chen. et al. [80], Yin. et al. [81] applied 4-MPBA and 4-Cyanophenylboronic acid (4-CPBA) as primary and secondary receptors, respectively. Using the Raman peak at 2226 cm^{-1} of the cyano group as a signal reporter, a LOD of 10 nM was achieved [80]. Very recently, the strategy was proposed for differentiating different saccharides with varied boronic acid indicator molecules [82]. To further increase the Raman signals, two receptors and photo-coupling transformation of *p*-aminothiophenol (PATP) to 4,4′-dimercaptoazobenzene (DMAB) were integrated and glucose assay with broad detection range, good sensitivity and selectivity was realized [83,84]. Although several factors such as the complicated procedure and long incubation time need to be paid attention, the smart two acceptor strategy could improve signals and prevent interference of groups from other biomolecules.

4.4. Enzymatic reaction based biosensors

The glucose oxidase (GOx) specifically catalyzes glucose oxidation in the presence of oxygen to produce gluconic acid and hydrogen peroxide (H_2O_2) as shown in Equation (2). The product H_2O_2 could further catalyze a reactant A to form a product B (as Equation (3)), which results in measurable Raman spectral changes for the vibrational modes.

$$\text{Glucose} + O_2 + H_2O \xrightarrow{GOx} \text{Gluconic acid} + H_2O_2 \quad (2)$$

$$A \xrightarrow{H_2O_2/Cat.} B \quad (3)$$

These two-step catalytic reactions for glucose sensing through SERS were proposed by Shen et al. for the first time [85]. They

fabricated a SERS glucose sensor through gold colloids–bienzyme conjugates (Fig. 9A). Gold colloids modified by horseradish peroxidase and glucose oxidase (HRP/GOD-gold colloids) were added to the mixture of o-phenylenediamine and glucose, following the formation of hydrogen peroxide (H_2O_2) upon the enzymatic reaction. Then, o-phenylenediamine was oxidized in the presence of horseradish peroxidase, resulting in the liberation of azoaniline, a compound with strong Raman scattering signals. Two characteristic Raman peaks at 1438 and 1582 cm^{-1} due to N=N and C=C stretching modes respectively were observed relating with glucose concentrations (Fig. 9B), indicating the liberation of the oxidation product from the reaction and utilizing for glucose determination. Qian et al. later configured the starch coated gold nanoshells as enhancement substrates and methylene blue as a Raman dye. Glucose was oxidized in the presence of glucose oxidase to produce H_2O_2, which was converted to free radicals. The radicals could quench Raman signals of methylene blue [86].

With the two-step approach, a variety of molecules (A in Equation (3)) were exploited such as Leucomalachite green (LMG) [34,87], 3-MPBA [88–90], 4-MPBA [91] 4-mercaptobenzoic acid [92], PATP [35,93,94], 3,3′5,5′-tetramethylbenzidine (TMB) [95,96], Osmium clusters [97,98], 2-mercaptohydroquinone (2-MHQ) [99]. These molecules are generally oxidized by H_2O_2, yielding from glucose enzymatic reactions (Eq. (2)), producing corresponding products (B) (Equation (3)), which resulted in measurable Raman signal changes. The corresponding substrates, catalysts, sensing properties and performance are summarized in Table 2. The approach presents indirect sensing by employing a Raman-active "probe" molecule which chemically reacts or interacts with the analyte of interest, and the probe is attached to the plasmonic surface. Generally, this approach demonstrates great sensitivity and selectivity over other sugars, and some even were tested in blood or urine samples. However, the stability of used enzyme and the presence of oxygen concentrations in the samples may cause reliability concerns during their applications.

Following the work, the two-step reaction strategy was modified by Jung's group for glucose detection through silver ion guided Raman signals and PATP molecules on the gold wafer surface, which acted not only as Raman tags but also as linkage agents [35]. Ag^+ ions were obtained by using glucose oxidase to catalyze the oxidation of glucose and producing hydrogen peroxide (H_2O_2) to etch the AgNPs. Therefore, they recorded the SERS intensity of PATP (Raman tags and linkage agents) to determine the concentration of glucose as low as 0.1 mM. Similarly, glucose induced enzymatic reaction generated H_2O_2, which etched silver nanoparticles and further caused changes of PATP [93,94] and 4-mercaptobenzoic acid [100] signals.

The one-step enzymatic catalytic reaction (Equation (2)) was also harnessed for glucose sensing without additional Raman dyes [101–103]. Al-Ogaidi et al. synthesized Au nanostar@silica core-shell nanoparticles conjugated with GOx enzyme molecules for SERS based glucose detection [101]. Glucose concentration from 0.025 mM to 25 mM was quantitatively detected with a LOD of 16 μM. In this work, no additional dye was introduced, as Raman peaks from H_2O_2 and gluconic acid through enzymatic reaction were applied. Building on the enzymatic reaction, Xu and others employed electrostatic assembly of glucose oxidase (GOx) over Ag nanoparticle-functionalized SERS substrate through a positively charged polyelectrolyte linker [102]. 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 weakened, making GOx drop off from the sensing chip and leading to measurable changes of GOx Raman signals at 1342 cm^{-1} (shown as Fig. 10). The SERS signal of GOx is mainly stemmed from flavin adenine dinucleotide (FAD), which is a chromophoric cofactor. The study achieved high sensitivity (with LOD of 1 μM) and selectivity over glucose.

The cost and stability of used enzymes are pushing researchers to provide other options. With saccharide-oxidase and/or peroxidase like properties, several groups introduced nanozymes into the SERS based glucose detection due to their inexpensiveness, reasonable stability and mass production. AuNPs/Cu-TCPP(Fe) nanosheets demonstrated tandem enzyme of glucose oxidase and peroxidase like properties [104]. Gold nanoparticles with glucose oxidase mimicking performance induce catalysis reaction to convert glucose into hydrogen peroxide in the presence of oxygen (similar to Equation (2)); Cu-TCPP(Fe) nanosheets contribute peroxidase-like activity for catalysis of caged Leucomalachite green (LMG) to activated malachite green (MG) molecules (similar to Equation (3)), and the illustration is shown in Fig. 11A. Au NPs also served as substrates for enhanced Raman scattering signals. The SERS assay showed sensitivity to glucose detection, and Raman signals with different glucose concentrations from 0.16 to 0.80 mM were shown (Fig. 11 B). In addition, the probe demonstrated selective detection of glucose over other saccharides, and determination of salivary glucose in a non-invasive way. AuNPs@MIL-101@enzymes [87], Ag@polyaniline composites [105] and Co_3O_4 nanoparticles [106] were also presented saccharide-oxidase, peroxidase like properties for catalytic oxidation, and worked as enhanced Raman substrates.

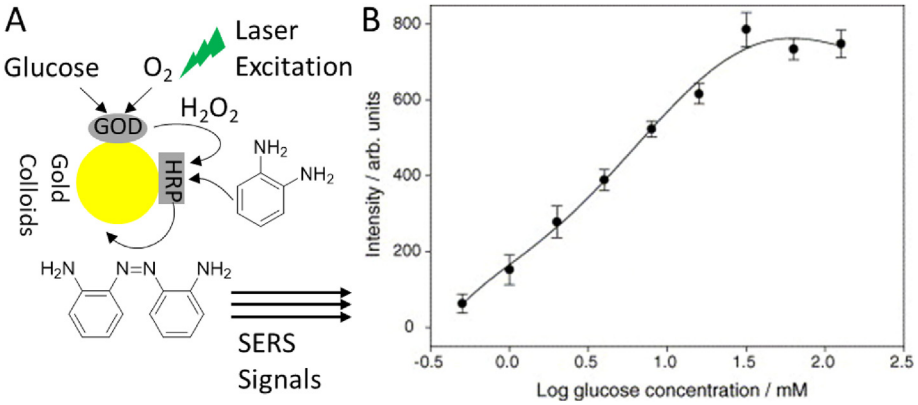

Fig. 9. A) Oxidation of *o*-phenylenediamines catalyzed by GOD/HRP bienzymatic system and principle of the indirect detection of glucose. B) Intensity change of the peak at 1438 cm^{-1} vs. the logarithm of the glucose concentrations. Error bars represent the standard deviation of five measurements. Modified with permission from Ref. [85] Copyright 2006 Elsevier.

Table 2
Summarized enzymatic catalytic based glucose biosensors using SERS and their corresponding sensing performance in recent years.

Ref.	Substrates	Catalysts	Functionalized molecules/Sensing targets	Limit of detection	Detection range
[85]	Au colloids	GOx/HRP	o-phenylenediamine	0.46 mM	0.5–32 mM
[86]	Au nanoshells	GOx/Au nanoshells	Methylene blue	/	0.1–100 mM
[34]	Citrate-Au NPs	GOx/peroxidase	LMG	/	0–200 mM
[87]	Au NPs@MIL	GOx/Au NPs@MIL	LMG	4.2 μM	10–200 μM
[88]	Au NPs	GOx	3-MPBA	/	0.5–10 mM
[89]	Au NPs	GOx	3-MPBA	/	10–500 μM
[90]	MOSF@GNPs	GOx	3-MPBA	/	/
[91]	SiO_2@Au@Ag	GOx/SiO_2@Au@Ag	4-MPBA	0.15 mM	0.5–8.0 mM
[92]	Ag NPs	GOx/HRP	4-MBA	1 μM	1 μM-0.1 M
[35]	Ag NPs-Au wafers	GOx	PATP	0.1 mM	0.5–8 mM
[93]	Au@Ag NPs	GOx	PATP	0.02 μM	0.5–400 μM
[94]	Ag nanotriangles	GOx	PATP	0.4 nM	/
[95]	Ag NPs	GOx/Ag NPs	TMB	35 nM	0.33–6.67 μM
[96]	Ag– Cu_2O/rGO	GOx/Ag–Cu_2O/rGO	TMB	10 nM	10 nM- 10 mM
[97]	Au @ $(PAH\text{-}Os)_4$ NPs	GOx/peroxidase	Os(III) complex	/	1–7 mM
[98]	TERS tip and gold NPs cantilever	GOx/Au	Triosmium carbonyl cluster	0.21 mM	0.5–5 mM
[99]	Au NPs	GOx	2-MHQ	0.159 μM	0.1–10 mM
[100]	Au@Ag	GOx	4-mercaptobenzoic acid	1 μM	1 μM-0.1 M
[101]	Au nanostar @silica NPs	GOx	Gluconic acid H_2O_2	16 μM	25 μM-25 mM
[102]	Ag NPs assembled film	GOx	FAD	1 μM	1 μM-30 mM
[103]	Au NPs-MCs hydrogels	GOx	pH	/	/
[104]	Au NPs	AuNPs/Cu-TCPP(Fe)	LMG	3.9 μM	0.16–8.0 mM
[105]	Ag@polyaniline	Ag@polyaniline	TMB	0.1 nM	0.1 nM-10 μM
[106]	Co_3O_4	Co_3O_4	TMB	0.1 nM	0.1 nM-10 mM

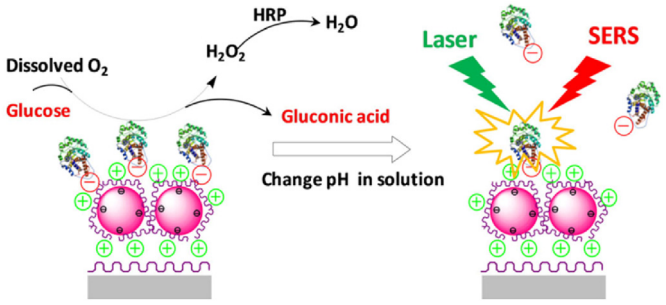

Fig. 10. Illustration of sensing mechanisms for glucose detection using GOx-assembled SERS chips with the one-step reaction. Under the enzymatic reaction, the formation of gluconic acid decreased the solution pH, GOx molecules started to drop off from the substrate glucose oxidase, and led to decline of GOx SERS signals. Adapted with permission from Ref. [102], Copyright 2016 Springer.

5. Conclusions and outlook

Great success has been made by using SERS for the sensitive and specific detection of glucose. Both intrinsic and extrinsic sensing strategies have been utilized for glucose detection. Popular in the early years, intrinsic sensing for glucose was realized through developing more efficient plasmonic substrates, enhanced-Raman techniques, or through functionalized partition layer strategy. The electrostatic and hydrophobic interactions were used as partition layer for glucose sensing. The resulting glucose Raman signals are generally weak, and easily overshadowed by the strong background noises from the surrounding environment. This strategy generally lacks selectivity over other sugars and the speed necessary for a quick sensing response. The problems could be circumvented by the extrinsic sensing strategy, where a Raman-active probe is used. Interactions of probe-analyte result in detectable Raman signal changes. As summarized, boronic acid and enzymatic reactions are two popular viable ways. The extrinsic sensing strategy could be further extended into analysis of other targets (especially with low Raman cross-section) through exploiting of host-guest interactions, biomolecular recognitions for selective detection. Considering interference, another promising direction for glucose detection is to introduce Raman-responsive signals at biological silent region such as through using two acceptor boronic acids or tailor-made Raman probes. It helps prevent interference or decrease noises in Raman spectra.

The Raman signal off/on approach is the most widely applied for glucose detection, alternatives have appeared to show potentials

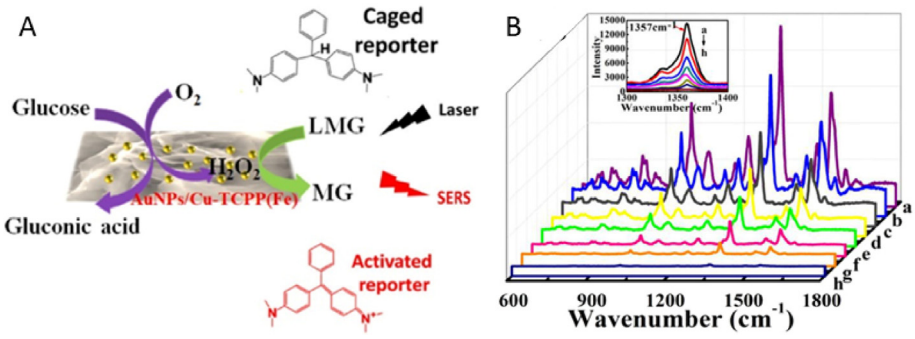

Fig. 11. A) Schematic illustration of the enzyme-free tandem reaction strategy for SERS detection of glucose. B) The glucose concentrations from (a–h) are 0.16, 0.32, 0.64, 1.25, 2.5, 5.0, 6.0, and 8.0 mmol/L, and the inset is the enlarged range from 1300 to 1400 cm^{-1}. Reproduced with permission from Ref. [104] Copyright 2020 American Chemical Society.

for broader biomedical sensing, such as peak shift, ratiometric signals, multimodal sensing, etc. For example, multichannel sensing was recently proposed to improve the reliability of sensors [107]. In addition, to address the noisy and weak Raman signals, advanced data processing (e.g., robust optimization model [108] and principal component analysis [1]) have already been studied, and will play bigger roles in future. The combination of machine learning and SERS optophysiology allowed to observe the gradients of multiple metabolites in the extracellular environment of a series of cells [109].

Until now, most of SERS based analytical methods or sensors are still limited to research laboratories, as challenges still exist in this field. Researchers need to pay more attention when quantitative detection is achieved through SERS, as reproducibility and repeatability are always perplexing issues. Raman intensity/enhancement is dependent on hot spots and metallic structures, and large spatial and chip-to-chip fluctuations are present. Reliability is another issue that needs to be overcome. The reliability of SERS relies on the rational design of SERS substrates, appropriate sample preparation, delicate control of the measurement conditions, and adequate data analysis. Especially, it is noticed the Raman response signals by glucose analyte from different research groups are different (e.g., Raman intensity on, off and peak shift have been observed with increasing of glucose concentrations using 4-MPBA functionalized metallic surfaces as SERS substrates in Section 4.3), possibly due to the different adsorption orientations, effect of laser wavelength, or enhancement mechanisms, which may bewilder new incoming researchers.

While the glucose sensing technique and principles through SERS are growing gradually mature in *ex vivo* conditions, the trend for glucose sensing would progress to *in vivo* applications, cells to clinics. The corresponding substrates, optical parts, and data collection would be the key points. With further refinements in the system, such as instrumentation, optics, and surface, the SERS based glucose sensor through portable Raman devices could provide the prospect to be used in painless glucose monitoring of diabetic patients in future and serve as potential alternatives/supplements to conventional personal and point-of-care assays.

There is still work to be done in the field before SERS can be fully implemented in practice in order to answer the significant biomedical questions. Technology transfer from laboratory into practical applications needs to meet the demands of economic viability and operational simplicity. The further commercial production of tailor-made substrates and industrial application of SERS for sensing various targets would be not far away. In addition, it is necessary to develop SERS substrates based on lab-on-chip devices with compatible properties which take advantage of microchip systems, data display, separation and detection of targets, and thus to realize the sensing areas in chemical, medical and environmental fields.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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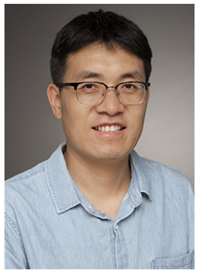

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