Microfluidic-SERS devices for one shot limit-of-detection†

Donghyuk Kim,‡a Antonio R. Campos,‡a Ashish Datt, a Zhe Gao,a Matthew Rycenga, b Nathan D. Burrows,c Nathan G. Greenelch,b Chad A. Mirkin,b Catherine J. Murphy,c Richard P. Van Duyneb and Christy L. Haynes*a

Microfluidic sensing platforms facilitate parallel, low sample volume detection using various optical signal transduction mechanisms. Herein, we introduce a simple mixing microfluidic device, enabling serial dilution of introduced analyte solution that terminates in five discrete sensing elements. We demonstrate the utility of this device with on-chip fluorescence and surface-enhanced Raman scattering (SERS) detection of analytes, and we demonstrate device use both when combined with a traditional inflexible SERS substrate and with SERS-active nanoparticles that are directly incorporated into microfluidic channels to create a flexible SERS platform. The results indicate, with varying sensitivities, that either flexible or inflexible devices can be easily used to create a calibration curve and perform a limit of detection study with a single experiment.

Introduction

Microfluidics is an often-used technique for sample manipulation in bioanalytical and biomedical sciences because the devices are largely biocompatible, require small (viz., nanoliter) sample volumes, create small volumes of biohazard waste, and enable faster analyses and higher throughput than many benchtop techniques. These advantages make microfluidics especially promising for biological applications and bioanalytical sensor developments, particularly when interrogated with optical detection schemes. Among the various optical methods that can be used in conjunction with microfluidic platforms, Raman spectroscopy is particularly interesting for bioanalytical applications because it yields an intrinsic vibrational fingerprint for detected analytes, and its performance is not compromised by water interference in aqueous samples. Normal Raman spectroscopy has inherently small scattering cross-sections, yielding poor analyte sensitivities; however, surface-enhanced Raman scattering (SERS) provides opportunities to enhance detection sensitivity significantly.1-4 This enhancement is attributable to the large molecular dipole moment induced when a Raman-active molecule experiences the electromagnetic fields generated at the surface of nanostructured plasmonic noble metals. Practically speaking, the SERS limit of detection can reach the single-molecule detection realm, but nanomolar and picomolar analyte concentration detection is routinely observed with high quality plasmonic substrates.5-9 Accordingly, SERS has been employed in microfluidic platforms to identify chemical moieties in bioanalyte systems including cells, viruses, bacteria, organelles, sub-organelles, DNA, proteins, drugs, and cellular communication mediators.8-15

Colloidal noble metal nanoparticles are the most commonly used SERS-active substrates within microfluidic devices.1,14-18 In general, the SERS-active nanoparticles are injected through a microfluidic channel where they encounter analyte species at a specified physical location within the device. The primary challenge with this type of approaches is that it is difficult to achieve large and consistent signal enhancement44-48 without controlled colloidal nanoparticle aggregation.5,18,49 It has been reported that the best SERS signal enhancement for gold nanoparticles can be achieved when nanoparticles are in contact, or at least separated by not more than 1–2 nm;5,18,49 thus, the challenge of controlling nanoparticle aggregation presents persistent experimental roadblocks related to stability, sensitivity, and reproducibility of the obtained signal both in and out of microfluidic devices. Previous work also reports unexpected loss of nanoparticles or defects in their aggregation/arrangement due to nanoparticle interactions with channel surfaces or the flow profile.19 To avoid these difficulties, there have been several reported systems where a SERS-active substrate is incorporated into a microfluidic device.20,21 In these reports, SERS-active substrates were largely fabricated either on
glass or silicon using high-end lithography techniques, aligned, and bound to a layer containing the microfluidic channel geometries. These finely tuned SERS-active substrates, such as nanoholes or nanogaps, have very high signal enhancements compared to simple colloidal nanoparticles; however, fabrication can be prohibitively expensive and requires access to specialized instrumentation for time- and labor-intensive fabrication protocols.

Herein, we present two types of proof-of-concept microfluidic-SERS sensing platforms with potential to address the aforementioned challenges: a microfluidic gold film-over-nanospheres (AuFON) platform and a flexible SERS sensor platform with nanoparticles incorporated directly into the microfluidic polymer layer. Gold was chosen over silver as the plasmonic material, despite its lower signal enhancement with added analytical strengths. In the proof-of-concept realization of a portable, durable SERS sensing platform employing PDMS-based microfluidic-SERS sensor platforms presented here, microfluidic channels are designed to enable easy limit-of-detection (LOD) or limit-of-quantification (LOQ) studies. The fundamental principle of the device is based on previously reported microfluidic devices, capable of creating chemical gradients, with a slight modification to achieve simultaneous detection of different concentrations of an analyte. Another advantage of the PDMS-based SERS sensor is that PDMS provides strong Raman-active bands in a 490–700 cm⁻¹ shift region as an internal standard. As our results show, the presented microfluidic-SERS platforms are capable of quantitative, single experiment LOD/LOQ assessment, and demonstrate their potential for multiplexed high-throughput analysis. Further development of these proof-of-concept platforms will facilitate the development of several diagnostic devices for early disease detection and continuous monitoring of patients.

**Methods and experimental setup**

**AuFON fabrication**

After silicon immersion in a base bath with 10 : 1 : 1 water: ammonium hydroxide (30%): hydrogen peroxide (30%) for an hour, 13 μL of 600 nm-diameter silica nanospheres (Bangs Laboratories, Fishers, IN) were drop cast onto the clean silicon wafer. The silica nanospheres were distributed on the silicon wafer until there were no visible mixing lines, and then the wafer was allowed to air dry. After nanosphere self-assembly and drying, 200 nm of Au (99.999% Au Kurt J Lesker, Clairton, PA) was deposited onto the nanosphere template under vacuum, as measured by a quartz crystal microbalance (Denton Vacuum, Moorestown, NJ). The localized surface plasmon resonance (LSPR) of the substrate was measured to be $\lambda_{\text{max}} = 790$ nm using a fiber optic probe (Ocean Optics, Dunedin, Florida) with a flat gold film as the reflective standard, and the AuFONs were stored in a closed petri dish until use.

**Au concave nanocube (AuNC) synthesis**

Gold concave nanocubes (AuNCs, 53 ± 10 nm in edge length [n = 30], 4 nM as synthesized) were fabricated in a synthesis adapted from Zhang et al. In brief, Au seeds were prepared by quickly injecting 0.60 mL of ice-cold, freshly prepared NaBH₄ (10 mM) into a rapidly stirring solution containing 0.25 mL of HAuCl₄ (10 mM) and 10.0 mL of cetyltrimethylammonium chloride (CTAC, 100 mM). The seed solution was stirred for 1 minute and then left undisturbed for 2 hours. A growth solution was prepared by consecutively adding 0.50 mL of HAuCl₄ (10 mM), 100 μL of AgNO₃ (10 mM), 0.20 mL of HCl (1.0 M), then 0.10 mL of ascorbic acid (100 mM) into 10.0 mL of 0.1 M CTAC. The seed particles were serially diluted in 100 mM CTAC to generate a solution 1/1000 the concentration of the original seed solution. Particle growth was initiated by adding 0.1 mL of the diluted seeds to the growth solution. The reaction was swirled immediately after the addition of the seeds and then left undisturbed on the bench top overnight. The in-solution LSPR $\lambda_{\text{max}}$ was 618 nm.
Au nanorod (AuNR) synthesis

Gold nanorods (AuNRs, \(48 \pm 11 \times 13 \pm 2 \text{ nm} \quad (n = 30)\), 5 nM after washing) were prepared on a two-liter scale in a millifluidic flow reactor following previously published procedures\(^\text{37}\) based on a seeded growth approach.\(^\text{40-42}\) Briefly summarized, two solutions were prepared, labeled “growth” and “seed.” For the growth solution, 98.55 mL of HAuCl\(_4\) (0.01 M), 12.0–18.3 mL of AgNO\(_3\) (0.01 M), and 10.84 mL of ascorbic acid (0.1 M) were added to 0.1 M CTAB (cetyltrimethylammonium bromide) with a final volume of 1 L. For the seed solution, 2.365 mL of gold nanoparticle seeds prepared following previously established methods\(^4\) was added to CTAB (0.1 M) with a final volume of 1 L. Then, these solutions were combined \(\text{via}\) peristaltic pump (Cole-Palmer Masterflex L/S) in a millifluidic reactor (Tygon polyvinyl tubing, i.d. = 2.79 mm) with: (1) polyethylene Y-mixer and joints, (2) a flow rate of approximately 8.0 mL min\(^{-1}\), and (3) a residence time of 20 minutes. Gold nanorod suspensions were eluted from the reactor into an aqua regia-cleaned two-liter Erlenmeyer flask with magnetic stirring and held for 2–3 hours prior to purification, concentration, and characterization.

Gold nanorods were concentrated and purified by washing with centrifugation. The 2 liters of suspension was divided into 50 mL centrifuge tubes and centrifuged at 11 000 \(\times g\) for 15 minutes. The supernatant was syphoned off, and the pellets were redispersed in 1 mL of nanopure water, each, and combined into eight centrifuge tubes filled to 40 mL with nanopure water. These were then centrifuged at 5000 \(\times g\) for 25 minutes, syphoned, and dispersed in nanopure water. This process was repeated twice more with CTAB (800 \(\mu\text{M}\)) for dispersing the pellet. The suspension was then centrifuged one last time at 5000 \(\times g\) for 25 minutes with the pellets combined into one centrifuge tube and dispersed in CTAB (800 \(\mu\text{M}\)). The resulting suspension was then characterized using UV-Vis-NIR spectroscopy, DLS, PALS, and a bromide ion-selective electrode. The in-solution LSPR \(\lambda_{\text{max}}\) values were 526 nm and 760 nm, and the resulting nanorod concentration was 5 nM.

Nanoparticle characterization

These colloidal nanoparticles were used in the synthesis of flexible SERS sensor platforms—detailed below—and likely retain some CTAB/CTAC moieties on their surface.\(^\text{25,26}\) Characterization of these nanoparticles was performed by transmission electron microscopy (TEM, FEI Tecnai T12 electron microscope operating at 120 kV) and UV-Vis extinction (Ocean Optics, Dunedin, Florida).

Microfluidic-AuFON device fabrication

Standard photolithography procedures described in a previous paper were followed for device fabrication.\(^\text{33}\) Briefly, the device design (Fig. 1), printed onto a transparent film (CAD/Art Services Inc., Bandon, OR), was transferred to a blank chrome mask plate (Nanofilms, Westlake Village, CA). Then, using the mask, the design was transferred to a SU-8 photoresist layer (Microchem, Newton, MA) on a silicon wafer. Then, de-gassed 10 : 1 weight ratio of Sylgard 184 resin and curing agent mixture (Ellsworth Adhesives, Germantown, WI) was cast onto the master and cured at 65 °C overnight to complete the PDMS channel layer. Channel dimensions were 100 \(\mu\text{m}\) wide and 100 \(\mu\text{m}\) high. For practical purposes, the terminal channels where measurements were performed had 1000 \(\mu\text{m}\) width. Bonding of the PDMS layer to the AuFON was done \(\text{via}\) oxygen plasma treatment at 100 W for 10 seconds after inlets and outlets were punched. All fabrication steps were performed in the Minnesota Nano Center (MNC) at the University of Minnesota.

Flexible microfluidic-SERS sensor device fabrication

Flexible SERS sensors were fabricated using the same SU-8 mold used for the microfluidic-AuFON devices. Nanoparticle solutions (1 mL of 5 nM AuNRs or 4 nM AuNCs in water) were centrifuged at 10 000 \(\times g\) for 10 minutes, and the supernatants were removed using a micropipette. Then, the nanoparticles were re-suspended into 100 \(\mu\text{L}\) of the curing agent component of Sylgard 184, mixed with 900 \(\mu\text{L}\) Sylgard 184 resin, de-gassed, and finally poured onto the terminal channel array area of the SU-8 mold. After 30 minutes of curing on a 65 °C hot plate, 10 : 1 resin : curing agent mixture of Sylgard 184 was poured onto the mold, covering the entire device design, and cured overnight. Then, the device layer was peeled, cut, and punched for inlets and outlets. At this stage in device fabrication, SERS measurement on the microfluidic platform was possible but often not successful, likely because a large majority of the nanoparticles were completely incased in PDMS (i.e. not exposed to the in-channel stream of analyte). To enhance nanoparticle/analyte interaction, the PDMS layer was dry etched \(\text{via}\) reactive ion etching (75% CF\(_4\) and 25% O\(_2\), 100 W, one hour) and then this layer was bound to another clean and flat PDMS layer \(\text{via}\) oxygen plasma treatment.

Analyte solution preparation

10 mM trans-1,2-bis(4-pyridyl)ethylene (BPE, Sigma Aldrich) was prepared in ethanol, followed by dilution to 10 nM with MilliQ water (Millipore, Billerica, MA). 50 \(\mu\text{M}\) rhodamine 6G (R6G, Sigma-Aldrich, St. Louis, MO) stock solution was also prepared.
in ethanol, and the final 1 μM R6G solution was prepared by diluting the stock with MilliQ water.

**Fluorescence microscopy**

An inverted microscope with a 20× objective (Nikon, Melville, NY) and a CCD camera (QuantEM, Photometric, Tucson, AZ) was used to collect on-chip fluorescence images in three replicates. Metamorph Ver. 7.7.5 was used as the imaging software. Images of each channel were acquired with 10 ms exposure times. Once collected, the maximum fluorescence intensity, in arbitrary units (AU$_{\text{max}}$), in the region was recorded from each channel.

**SERS measurements**

The prepared microfluidic-AuFON device substrate was attached to the xyz stage (Thor Labs, Newton, NJ), and SERS spectra were measured with a SnRI ORS system ($\lambda_{\text{ex}} = 785$ nm, Snowy Range Instruments, Laramie, WY). The LSPR $\lambda_{\text{max}}$ values the SERS substrates were 790 nm for the AuFON, 760 nm for the embedded AuNRs, and 618 nm for the embedded AuNCs; thus, the SnRI ORS system excitation wavelength is most appropriate for the AuFON and AuNR substrates. An xyz micromanipulator stage was used to achieve fine control over the measurement spot locations and focus throughout the experiment. Measurements were made across all five channels at five different positions within each channel. An averaged spectrum was collected (three replicates for 1 second each) at an incident laser power of 3 mW for each position. SERS measurements were conducted after 10 minutes flow through the device to ensure that the gold surface was equilibrated to the solution-phase analyte concentration so that the measurement was not biased with time.

To be noted, a sharp Raman peak was frequently obtained at $\sim 520$ cm$^{-1}$ shift in the flexible SERS sensors. In the literature, several studies have observed this peak during SERS measurements in a PDMS device; the most convincing identity of this peak is mono- or poly-crystalline silicon. For SERS measurements in the flexible SERS sensor, a silicon wafer was always present underneath the flexible SERS devices during measurements to better visualize the channels, which may have led to the sharp Raman peak. Another possibility is that the reactive ion etching chamber is frequently used for silicon etching, and a silicon wafer was present in the chamber during etching of the flexible SERS PDMS layer; as such, the Au nanoparticles may have been exposed to silicon during the etching process. This 520 cm$^{-1}$ shift band was not considered when assessing the performance of these devices.

**Results and discussion**

**Device operation/simulation**

The microfluidic device used herein was designed to establish a concentration gradient of injected solutions so that a range of discrete concentrations are presented to each detection element. Once solution 1 and 2 are injected through inlets 1 and 2, respectively, the solutions repeatedly mix and split while passing through serpentine channels (denoted as mixing channels, Fig. 2). The original millifluidic design combines all branches at the end so that a linear concentration gradient of the solution is established in one wide channel downstream of the mixing channels, but herein, all outcome branches are separated so that the analyte coming out of each channel can be individually monitored. To achieve the desired results, complete mixing is required within each mixing channel. Computational fluid dynamics (CFD) calculations assuming a 3-dimensional single laminar flow model were performed using COMSOL Multiphysics 4.3 to assess the mixing process for the given channel geometry (Fig. 2). Channel dimensions were modeled as fabricated except that the channel height was set as 50 μm with symmetry to shorten computing time. As such, in this simulation, incompressible flow and the no slip boundary condition were used with user-defined diffusion coefficients, ranging from $0.5 \times 10^{-5}$ cm$^2$ s$^{-1}$ to $1.0 \times 10^{-5}$ cm$^2$ s$^{-1}$, and flow rates of 5, 10, 20, and 30 μL per minute. Fig. 2 shows the microfluidic device design with a representative simulation data plot. The simulation results confirm that, in all given conditions, each mixing channel achieves complete mixing (i.e., the device operates as desired). In the experiments described below, a flow rate 10 μL per minute was used.

**Fluorescence imaging**

Before performing SERS measurements, device performance was experimentally evaluated by fluorescence imaging. Fig. 3a shows the actual device bound to a clean glass substrate and fluorescence images from each location marked using red boxes. By visual inspection, the achieved fluorescence images showed the expected behavior, and thus, the obtained data were further analyzed quantitatively. Fig. 3b summarizes fluorescence intensity data (maximum fluorescence intensity in arbitrary units, AU$_{\text{max}}$) for R6G introduced into 3 representative devices. In total, seven devices were tested for linearity of fluorescence response from the channel arrays, and the average $R^2$ value was 0.94 ± 0.02 (mean ± standard error of mean). This linear response was further evaluated by obtaining measurements from 3 vertical locations in each of the five terminal channels of a device (Fig. S1†). For this assessment, fluorescence intensity from the array of five channels was obtained.
SERS assessment of the microfluidic-AuFON device

Having achieved the desired performance of the microfluidic portion of our sensing platform, we next evaluated SERS performance of our microfluidic-AuFON platform. As PDMS does not bind well to gold surfaces, the AuFON was intentionally removed at preferred device binding locations to expose the silicon surface, which does bind to PDMS. Then, oxygen plasma treatment was used to induce permanent bonding between the PDMS device and AuFON substrate. Once assembled as shown in Fig. 1, a BPE solution was introduced into the device following the same procedure used for fluorescence imaging: media without BPE into one inlet and BPE solution into the other inlet using a 10 µL per minute flow rate. We started with a high concentration of BPE (10 mM). BPE is known to adsorb onto noble-metal surfaces, so the channels were rinsed with water before SERS measurements. The LSPR $\lambda_{\text{max}}$ of the in-device AuFON was 790 nm, a good plasmonic match for the SERS excitation wavelength of 785 nm. The SERS spectrum of the AuFON, the device showed linear response to linear concentration gradients of BPE. Even though measuring BPE concentrations lower than 1 nM was not successful every time, the difference between the 0 nM channel and the 1 nM channel was always clear, and LOD evaluation by extrapolation (Fig. 4c) yields different LOD/LOQs in the nM range (see Table 1 for a complete listing of LOD/LOQ values for all devices) for the microfluidic-AuFON devices. On a few occasions, the first channel, which should present no analyte, showed a low intensity BPE signal. This is due to an imperfection at the beginning of the device operation where BPE solution reached the detection terminal as bubbles were removed from the device, which can be easily corrected in future work.

Interestingly, different BPE Raman bands result in differing slopes in linear regression analysis (Fig. 5). This result is

<table>
<thead>
<tr>
<th>Device</th>
<th>Fluorescence (M, AuFON)</th>
<th>Flexible SERS sensor</th>
</tr>
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<tbody>
<tr>
<td></td>
<td>0.30/0.90</td>
<td>0.69/2.09 0.86/2.61</td>
</tr>
<tr>
<td>Device 2</td>
<td>0.30/0.88</td>
<td>0.55/1.65 0.53/1.62</td>
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<tr>
<td>Device 3</td>
<td>0.50/1.50</td>
<td>0.44/1.33 0.42/1.27</td>
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Fig. 5 SERS response analysis a microfluidic-AuFON platform with 10 mM BPE.
interesting because the peak heights are the product of the substrate enhancement factor (EF), Raman scattering cross-section, and concentration of the analyte. Assuming a constant EF with a known concentration of analyte in the channel, the slopes from all bands would be similar if the vibrational cross-sections were similar. Another potential explanation for this variation in slope could be due to the data processing and analysis routine where the presented data is obtained after baseline subtraction using an in-house algorithm. The algorithm is imperfect at choosing good baseline values, especially when the spectrum is crowded, and this could contribute to the variation in our linear regression analysis. Further analysis will be needed to delineate whether this is an artifact of analysis or a true reflection of scattering cross-section differences among vibrational modes.

**SERS assessment of the flexible microfluidic-SERS sensor device**

The performance of the flexible SERS device was assessed using the same experimental system detailed above. The device performance was assessed in a step-by-step fashion to characterize the performance of the Au nanoparticles embedded within the PDMS layer. As a preliminary experiment, a prototype straight channel microfluidic device was fabricated (Fig. 6) with channel dimensions of 2000 μm (width) × 50 μm (height) × 25 000 μm (length) with incorporated citrate-capped gold nanospheres (AuNSs). Without dry etching, a small SERS signal was recorded, indicating that at least some of the AuNSs were extruding out of PDMS surface to make contact with the in-channel analyte. However, the success rate of obtaining high quality SERS spectra was significantly lower than that achieved with devices that underwent reactive ion etching (Fig. S3†).

Scanning electron microscopy (SEM) assessment of nanoparticle-embedded PDMS, after reactive ion etching, clearly demonstrates nanoparticles protruding from the PDMS surface. SERS spectra of 1 mM BPE and 1 mM benzenethiol, both well-known SERS probes, were successfully obtained using the preliminary flexible AuNS SERS platform (Fig. 6c and d). All characteristic SERS bands for analytes were observed from both BPE and benzenethiol, and the enhancement factor was estimated to be between $5.9 \times 10^4$ and $4.1 \times 10^7$ (see ESI† for assumptions and calculation). This enhancement factor range includes values higher than that achieved with the nanoparticles in solution, likely because embedded nanoparticles are no longer stabilized by citrate ligands and may occur in small aggregates.

With these preliminary data, we proceeded with well-characterized, high enhancement factor-producing AuNCs and AuNRs, both shown in Fig. 7. All attempts to obtain LSPR measurements from the completed device were only marginally successful (Fig. S4†). This is likely due to the small number density of nanoparticles in these experiments, but we could observe a slight LSPR $\lambda_{\text{max}}$ peak shift from the nanoparticles in a completed device when compared to the colloidal nanoparticles before incorporation into PDMS. The shift is probably due to formation of small nanoparticle aggregates within the PDMS media and the increased matrix refractive index by embedding at least a portion of the nanoparticle in PDMS. Using the same microfluidic platform described for the microfluidic-AuFON sensor, AuNRs or AuNCs were directly embedded into the terminal channel array portion of the PDMS. 1 mM BPE was used as the analyte for this assessment; and as such, the expected concentrations for the five terminals were 0, 0.125, 0.5, 0.875, and 1 mM BPE. A linearity assessment was performed, comparing the intensity of BPE’s 1640 cm$^{-1}$ shift band to PDMS’s 490 cm$^{-1}$ shift band (acting as an internal standard). While the LOD was higher than the microfluidic-AuFON platform, the flexible SERS sensor with
both AuNRs and AuNCs also showed the expected linear response to BPE analyte (Fig. 8). Using a PDMS peak as an internal standard yielded a moderate improvement in linearity for the AuNR devices (0.93 ± 0.01, mean ± standard error of the mean, compared to 0.90 ± 0.03). The $R^2$ value for AuNC devices was improved significantly (0.89 ± 0.03, mean ± standard error of the mean, compared to 0.69 ± 0.05) with this internal standard (Fig. S3†). Spatial variation in SERS responses within each terminal channel was also evaluated at 3 discrete, randomly chosen locations. SERS BPE band energies were similar; however, band intensities were somewhat variable. This is likely due to random NC dispersion in the PDMS or formation of localized electromagnetic hot spots. Together, these results demonstrate the utility of the embedded AuNR- and AuNC-based microfluidic-SERS sensors.

There are many opportunities for further optimization of these flexible devices during the fabrication process. For example, the exact amount of gold nanoparticles added to and protruding from the PDMS layer has not been optimized. It is already clear, as observed under dark-field microscopy (data not shown), that a thinner nanoparticle-containing PDMS layer will lead to more uniform presentation of nanoparticles on the surface of PDMS while also requiring a smaller number of nanoparticles. This will present an opportunity for more reproducible, and potentially more sensitive, SERS measurements. Furthermore, many groups are working to optimize SERS enhancement factors by controlling gaps between nanoparticles (e.g., controlled fabrication of nanoparticle dimers or trimers). In the flexible SERS sensor platform, nanoparticles are embedded and fixed with, presumably, only a portion of the nanoparticle protruding into the microfluidic channel. This may allow, for example, nanoparticle dimer formation with a reduced degree of freedom and enable extraordinarily sensitive SERS sensing.

Conclusions

Herein, we explored the use of two microfluidic SERS sensor platforms, a microfluidic-AuFON and a flexible microfluidic-SERS sensor, for on-line high enhancement factor, low volume SERS measurements. The microfluidics portion of the sensor platforms provides desired control over the sample fluids, as simulated theoretically and verified experimentally, and varied concentrations of analyte for simultaneous assessment of LOD/LOQ by SERS measurements. While the dimension of the entire devices presented herein is relatively large (2.5 cm × 7.0 cm), because the aim here was to match the size of a standard microscope slide, the overall size can be easily adjusted as required by application or substrate dimensions. The material used for SERS detection is gold, a noble metal presenting minimum reactivity and toxicity to biological systems. Furthermore, the ease of surface functionalization of gold makes microfluidics-SERS approaches well suited for applications where it is necessary to introduce biological functionalities (e.g., antibodies, aptamers, enzymes, nucleic acids, proteins, or small molecules).

Once incorporated with such surface functionalities, simultaneous detection of multiple analytes with high throughput should be easily achieved. Live cell imaging is another potential application for the presented sensor platforms as the flexible SERS sensor approach may provide an opportunity to allow membrane-specific SERS imaging. Further developments of our proof-of-concept microfluidic SERS sensor platforms will provide unique advantages to researchers in the bioanalytical sciences and bring significant impact in biomedical applications by providing opportunities for wearable sensors or on-site (portable) point-of-care devices.

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Notes and references


