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Review

Rich variety of substrates for surface enhanced Raman spectroscopy

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Abstract

The efficiency of the application of surface enhanced Raman spectroscopy (SERS) technique to each specified purpose significantly depends on the choice of the SERS substrate with an appropriate structure as well as on its performance. Until the present time a rich variety of SERS substrates was fabricated. They can be classified according to their structures. The present work is a review of main types of SERS substrates for using in the trace analysis application. They can be classified into 4 groups: (1) Substrates using gold nanoparticles (AuNPs) with spherical shape such as colloidal AuNPs, AuNPs fabricated by pulsed laser deposition, by sputtering or by capillary force assembly (CFA), substrates fabricated by electrospinning technique, substrates using metallic nanoparticle arrays fabricated by electron beam lithography combined with CFA method, substrates using silver nanoparticle (AgNP) arrays grain by chemical seeded method, substrates with tunable surface plasmon resonance, substrates based on precies subnanometer plasmonic junctions within AuNP assemblies, substrates fabricated by simultaneously immobilizing both AuNPs and AgNPs on the same glass sides etc. (2) Substrates using nanostructures with non-spherical shapes such as gold nanowire (NW), or highly anisotropic nickel NW together with large area, free-standing carpets, substrates with obviously angular, quasi-vertically aligned cuboid-shaped TiO₂ NW arrays decorated with AgNPs, substrates using gold nanoprisrn monolayer films, substrates using silver nanocube dimmers or monodisperse close-packed gold nanotriangle monolayers. (3) Substrates using multiparticle complex nanostructure such as nanoparticle cluster arrays, gold nanoflowers and nanodendrites. (4) Flexible substrate such as paper-based swab with gold nanorods, adhesive polymer tapes fabricated by inkjet printing method and flexible and adhesive SERS tapes fabricated by decorating AuNPs via the conventional drop-dry method.

Keywords: substrate, SERS, nanoparticle, nanowire, nanoflower, nanodendrite
Classification numbers: 4.00, 4.02, 4.08

1. Introduction

Surface-enhanced Raman spectroscopy (SERS) was discovered since about four decades ago [1] and was explained as the result of the excitation of surface plasmons [2]. Soon
after this discovery the research on SERS achieved very promising successes, which were presented in a comprehensive review of Moskovits [3]. Subsequently it was demonstrated that under favorable conditions intense SERS emissions can be recorded with extremely high sensitivity to be able to detect single molecules [4, 5].

A decade ago Moskovits wrote an interesting retrospective on the development of SERS [6]. Subsequently a fundamental collection of topical reviews on SERS research and application with the contributions of a large numbers of experts was published [7]. Recently a new collection of topical reviews on main modern problems of SERS was also published [8].

From the contents of above-mentioned reviews and monographs it was evident that the efficiency of the application of SERS technique in analytical, biophysical and life science applications significantly depends on the characteristics of the used SERS substrates.

There were various methods of preparing substrates for SERS. In an early work of Maya et al [9] sputtered gold films in a pure form or as nanocomposites in silica or silicon nitride were screened for SERS activity using rhodamine 6G as a probe. The films were prepared by sputtering pure gold or solidified Au–Si alloys in plasmas generated in a dc glow discharge apparatus. The plasmas were produced with argon, nitrogen, or argon–oxygen as the sputtering gas to directly deposit gold films or in the latter case a gold oxide intermediate. The alloys produce nanocomposite films in a silicon nitride or silica matrix depending on the plasma gas. SERS activity was detected in some of the films thus leading to a search for the critical parameters that controlled this phenomenon. The films were characterized by profilometry, x-ray diffraction (XRD), and atomic force microscopy (AFM). SERS activity was found to be correlated to crystallite size in the 10–25 nm range and to roughness larger than 15 nm, and it was independent of film thickness. Sputtered gold films, particularly those containing the gold as a nanocomposite in silica are attractive media for SERS because of excellent adherence, ruggedness, and simplicity in preparation.

SERS reproducible substrate using nanostructured gold surfaces were prepared by Materny et al [10]. In a Raman spectroscopy experiment although the unique identification of molecules is possible via their vibrational lines, high concentrations (mmol 1−1) are needed for their nonresonant excitation owing to their low scattering cross section. The intensity of the Raman spectra is amplified by the use of the SERS technique. While the use of silver sols results only in a limited reproducibility of the Raman line intensities, lithographically designed, nanostructured gold surfaces used as SERS-active substrates should, in principle, combine the high sensitivity with better reproducibility. For this purpose, we have produced gratings of gold dots on Si(001) surfaces by means of electron beam lithography (EBL). Qualitative and quantitative investigations of crystal violet (CV) performed using nanostructured surfaces give high reproducibility and enhancement of the Raman lines. The substrates are reusable after cleaning; all results presented could be obtained from a single SERS substrate. For the experiments very low laser powers were used.

This work is a review of a rich variety of SERS substrates. In section 2 we present the structures of substrates using different gold nanoparticles (AuNPs) with spherical shape. Many types of substrates using various nanostructures with non-spherical shapes are considered in section 3. Substrates using multiparticle complex nanostructures are presented in section 4, and recently invented flexible substrates are introduced in section 5. Conclusion and discussion are presented in section 6.

2. Substrates using metallic nanoparticles with spherical shape

The simplest method to fabricate a SERS substrate of this type is to immobilize gold colloidal nanoparticles upon a glass substrate. Probing the enhancement mechanisms of SERS with p-aminophenol molecules absorbed on self-assembled gold colloidal nanoparticles was performed by Baia et al [11]. In this work gold colloidal nanoparticles were immobilized upon a glass substrate and their morphology and optical properties are analyzed with TEM and UV–vis absorption spectroscopy. The substrate suitability for SERS in visible and near-infrared spectral region is demonstrated with four excitation lines using p-aminophenol. The SERS spectra of probing molecules exhibit a clear signature of electromagnetic and charge-transfer enhancement mechanisms, which critically depend on the laser lines. The large tunability of surface plasmon excitation combined with the advantage of highly chemical affinity to gold of probe molecules recommends this SERS-active system as a useful model for probing the mechanisms of Raman enhancement.

Fabrication of SERS substrates by pulsed laser deposition (PLD) of gold nanoparticles (AuNPs) was performed by Sanchez-Cortes et al [12]. The authors fabricate AuNPs supported on glass and CaF2 substrates by PLD [13–15], and investigated their potential for providing enhanced Raman and infrared spectra using one of the dithiocarbamate funcides, thiram, as a test molecule. The advantage of these substrates in their stability against the degradation after illumination with the visible (633 nm) laser employed in SERS analysis. The substrates were held at room temperature. The in-plane AuNP morphology was determined by transmission electron microscopy (TEM). TEM images were digitally processed. Au are of at least 200 × 200 nm2 was analyzed in order to obtain meaningful statistical data. The optical extinction spectra of the sample deposited on both glass and CaF2 substrates were determined in the range 350–800 nm as ln(1/T), where T is the transmission coefficient measured at normal incidence.

The Au content of the pulsed laser deposited samples was found to be [Au] = (11 ± 1) × 1015 atoms cm−2. The average values of the length (along the long dimension) and the breadth (the in-plane dimension perpendicular to the length) of AuNPs are (7 ± 1) nm and (5 ± 1) nm, respectively. Since glass substrate is amorphous, there is no preferential
nucleation center. On the contrary, CaF₂ is an ionic crystal and therefore, the existence of preferential nucleation centers was observed. For both substrates, a broad absorption band was seen that was related to the surface plasmon resonance (SPR) of AuNPs, thus confirming the formation of AuNPs also on CaF₂ substrates. The SPR relate to AuNPs produced on glass substrates has a peak at 595 nm with a full width at half maximum close to $\Delta \lambda \approx 150$ nm, while the SPR associated to AuNPs produced on CaF₂ in red-shifted (with a peak at 645 nm) and broader ($\Delta \lambda \approx 240$ nm). The extinction spectra showed that both samples are suitable for SERS measurements at 633 nm.

The authors conclude that AuNPs manufactured by a versatile and clean method such as PLD can be considered extremely efficient tunable plasmonic nanoparticles. The optical properties of these AuNPs can be easily controlled by the experimental macroscopic parameters used in their fabrication, leading to very efficient substrates for SERS spectroscopy. The additional advantages attained by PLD in comparison to evaporated Au films are (i) the fabrication of thinner metal films, with the subsequent use of a lower amount of metal, (ii) the great effectiveness of the fabricated films due to the hight proportion of hot spots, (iii) a lower adsorbate degradation under the laser illumination employed for SERS, and (iv) the absence of impurities.

Highly efficient and reproducible SERS substrates based on sputtered gold nanoparticles (AuNPs) were demonstrated by Merlen et al [16]. The main advantage of this approach is that it offers an extremely efficient and easy way to control the plasmon band. AuNPs were deposited directly on glass plates by sputtering. Substrates appear blue for short time deposition and become more golden with increasing deposition time. Whatever the deposition time, prepared substrates appear extremely rough and are thus good candidates for electromagnetic enhancement.

The ultraviolet-visible spectra of the substrates were recorded. For the substrates with low deposition time, a single broad absorption band was observed around 530 nm. While increasing the deposition time and the nanoparticle size, this band progressively shifted towards higher wavelengths and became broader. This is the typical behavior of the plasmon absorption band of AuNPs [17].

Using those substrates, typical SERS of methylene blue (in a solution of $10^{-4}$ mol l⁻¹) at different wavelengths and gold deposition times were determined SERS spectra could be easily observed with concentration down to $10^{-6}$ mol l⁻¹. For short (< 20 s) or long (> 50 s) gold deposition times, the signal was very weak, whatever the wavelength. This suggested that a typical AuNP size of around 20 nm is necessary for a strong enhancement [6].

Using a 458 nm wavelength excitation, no signal was observed whatever the gold deposition time, which was not surprising in so far as AuNPs do not show any plasmon absorption such a wavelength. Another interesting feature of prepared substrates is the control of the plasmon absorption band. By choosing the gold deposition time, it is possible to control the plasmon band position, from 530 nm up to near infrared. The electromagnetic enhancement theory suggests that this absorption band position should have a strong influence on the enhancement for a given wavelength. The condition for maximum enhancement should occur when the surface plasmon absorption band is located between the corresponding wavelengths of the laser excitation and the Raman scattered photon. This is exactly what took place: for the substrate obtained with 20 s deposition time, the plasmon absorption is stronger at 514.5 nm than at 785 nm, in agreement with experimental data. On the contrary, for the substrates with 50 s deposition time, the absorption is now in the infrared region, and actually the authors observed that SERS intensity was higher at 785 nm than at 514.5 nm.

A novel approach using capillary force assembly (CFA) method for fabricating highly efficient SERS substrates was demonstrated by Cerf et al [18]. CFA has already shown its potentiality to create gold nanoparticle (AuNP) assemblies with single particle resolution [19–21]. In the present work the authors showed how the combination of CFA with soft lithography can be used as a much more straight forward and affordable procedure to generate in a controlled ad regular manner the electromagnetic hot spots with high coverage rate. Previously the authors have shown that through thin methodology they were able to precisely position AuNPs a long a periodic 2D matrix [22]. In the present work the authors demonstrated the efficiency of such an arrangement as a SERS substrate.

By means of Raman spectroscopy, the authors have evidenced that the greatest local electric field enhancement is provoked by aggregates of particle provokes only a relatively small enhancement. Dimers also exhibit high enhancements, but their SERS efficiency depends on their orientation: a perpendicular orientation of dimmers with respect to the analytic switches the SERS effect off. This kind of substrate can easily be fabricated with prefucionized metallic particles and could be coupled with other selective and automatized decomposition method [23]. One could late imagine evolving toward a label-free biochip with optical readout by coupling, for example, SERS substrates with biological molecules or cells for high-sensitivity monitoring of specific interactions.

In [24] Yu et al presented a new class of highly sensitive, reproducible, stable, portable, large-scale, and inexpensive SERS substrates fabricated by electrospinning technique. At the beginning, nearly monodisperse silver nanoparticles (AgNPs) were synthesized in large quantities via a microwave-assisted method. The poly(vinylalcohol) (PVA), a nontoxic, biocompatible polymer, a popular material used in electrospinning, was employed, not only as the host matrix, but also as an organic additive inducing the aggregation of individual AgNPs. Subsequently, the resulting SERS-active aggregates were assembled in PVA nanofibers by electrospinning process, and at the same time, the aggregation of AgNPs ‘froze up’. The coating polymer can provide protection for the active Ag aggregates from the surrounding environment. Under a moderate solvent, the coating polymer would slightly swell and the small target molecules would permeate into the polymer and access the hot spots easily. Thus, the obtained substrates possess an extremely long lifetimes and high sensitivity. On the other hand, the obtained
substrate is completely free-standing and can be tailored freely due to the flexibility of polymer. Moreover, both the fabrication of high sensitivity Ag aggregates and the electrospinning process are low-cost and high-throughput.

TEM image of AgNPs synthesized by microwave irradiation confirmed the generation of highly crystalline nanoparticles with a nearly spherical shape. The XRD pattern of AgNPs showed a face-centered cubic silver crystal structure. The UV–vis spectra of monodispersed AgNPs synthesized by microwave displayed a strong extinction band with a maximum at 403 nm, which was a characteristic plasmon resonance band of isolated spherical AgNPs [25]. When the PVA solution was introduced, the Ag colloids exhibited two absorption bands. One was near 403 nm, indicating the uncoupled AgNPs, and the other absorbance band red-shifted with the increase of the Ag/PVA molar ratio. The appearance of this long-wavelength plasmon band is a clear indication of the formation of aggregated nanostructures [26, 27]. Electrospinning [28, 29] the Ag/PVA solution with different molar ratios Ag/PVA resulted in a series of various AgNP aggregates assembled within PVA nanofibers. Thus various arrays of AgNP aggregates in PVA fibers would be obtained via electrospinning technique by adjusting the quantity of AgNPs which were added in PVA solution.

Thus the authors have demonstrated a facile and new method to fabricate free-standing and flexible SERS substrates, where high SERS-active Ag dimer or aligned aggregates are assembled within PVA nanofibers with chain-like arrays by adjusting the quantity of AgNPs dispersed in PVA solution in the electrospinning process. The results demonstrated that the degree of aggregation of AgNPs in PVA nanofibers and the electrospinning time are two key factors determining the magnitude of SERS signal enhancement and the sensitivity of detection. The dimer and short chain-like structure of AgNP aggregates have been demonstrated the best optimized system for achieving possibly the highest enhancement.

High-performance SERS substrates using plasmonic nanoparticle arrays with nanometer separations was demonstrated by Cronin et al [30]. In this work the authors fabricated arrays of metal nanoparticles with separations on the order of 1 nm using EBL combined with evaporation technique. They applied the methods of previous research using controlled tunnel junctions to form single electron transistors [31] and spintronic devices [32]. The authors used EBL system to write 25 sets of nanoparticle arrays, each of them contains slightly different nanoparticle geometry (i.e. size, shape, separation). After fabrication, the silver nanoparticle samples were coated with a non-Raman-resonant dye molecule, p-aminothiophenol (p-ATP).

Thus the authors successfully fabricated SERS substrates using plasmonic nanoparticle array with nanometer separations. A significant increase in the Raman intensity was observed when the polarization is matched to the angle-evaporated nanometer size gaps, demonstrating the electric filed enhancement of the plasmonically coupled nanoparticles. Numerical simulation of the electromagnetic response of these nanoparticles showed significant enhancements in the calculated electric field and SERS signal, which depend strongly on the polarization of the incident light. On the basis of the $10^7$–$10^{10}$ SERS enhancement factor, these substrates could be used in devices approaching chemical detection at the single molecule level.

In [33] Liz-Marzán et al demonstrated the fabrication of reproducible SERS substrates using silver nanoparticle (AgNP) arrays grown by chemical seeded method. The fabrication based on the design of a novel highly efficient and uniform SERS substrates and taken the advantages of the block copolymer micelle nanolithography concept for making well-ordered and uniformly spaced Au nanodot assemblies, which were subsequently used as seed substrates for chemical growth, thereby yielding AgNP arrays containing a high density of hotspots, which render these concentrated island films ideal substrates for reproducible SERS detection.

Self-assembled SERS substrates with tunable SPRs were fabricated by Briber, Rabin et al [34]. These substrates are optimized for use with specific laser wavelength-analyte combinations. In order to achieve large signal enhancement, temporal stability, and reproducibility over large substrate areas at low cost, only self-assembly and templating processes are employed. The resulting substrates consist of arrays of gold nanospheres with controlled diameter and spacing, properties that dictate the optical response of the structure. Tunability of the extended SPR is observed in the range of 520–1000 nm. It is demonstrated that the enhancement factor is maximized when the SPR is red-shifted with respect to the SERS instrument laser line. Despite relying on self-organization, site-to-site enhancement factor variations smaller than 10% are obtained.

SERS substrates based on precise subnanometer plasmonic junctions within gold nanoparticle assemblies using cucurbit[7]uril (CB[n]) ‘glue’ were fabricated by Mahajan et al [35]. CB[n] are macrocyclic host molecules with subnanometer dimensions capable of binding to gold surfaces. Aggregation of gold nanoparticles with CB[n] produces a repeatable, fixed, and rigid interparticle separation of 0.9 nm, and thus such assemblies possess distinct and exquisitely sensitive plasmonics. Understanding the plasmonic evolution is the key to their use as powerful SERS substrates. Furthermore, this unique spatial control permits fast nanoscale probing of the plasmonics of the aggregates ‘glued’ together by CBs within different kinetic regimes using simultaneous extinction and SERS measurements. The kinetic rates determine the topology of the aggregates including the constituent structural motifs and allow the identification of discrete plasmon modes which are attributed to disordered chains of increasing lengths by theoretical simulations. The CBs directly report the near-field strength of the nanojunctions they create via their own SERS, allowing calibration of the enhancement. Owing to the unique barrel-shaped geometry of CB[n] and their ability to bind ‘guest’ molecules, the aggregates afford a new type of in situ self-calibrated and reliable SERS substrate where molecules can be selectively trapped by the CB[n] and exposed to the nanojunction plasmonic field. Using this concept, a powerful molecular-recognition-
based SERS assay is demonstrated by selective CB[n] host–guest complexation.

In [36] Kneipp et al investigated the characteristics of SERS substrates fabricated by simultaneously immobilizing both gold and silver nanoparticles on the same glass slides using 3-aminopropyl-triethoxysilane (APTMS) and 3-aminopropyl-triethoxysilane (APTES). For the mixed gold/silver surfaces, the silanized substrates were immersed in the mixtures of gold and silver nanoparticle solution with different amounts of gold and silver nanoparticle. Silver nanoparticles of different size distribution and plasmonic properties were prepared by bottom-up reduction with citrate [37] and hydroxylamine [38], as well as by the top-down process by laser ablation from bulk silver [39]. Gold nanoparticles were prepared by citrate reduction [40]. The extinction spectra of different types of nanoparticles immobilized with APTMS and APTES were recorded. They exhibit the plasmon bands of silver nanoparticles around 400 nm and gold nanoparticles around 520 nm. That was also observed before the immobilization. Spectra of immobilized nanoparticles showed a pronounced broad extended plasmon band, typical for nanoaggregates [41, 42]. The nanostructure of the surfaces was investigated by scanning force microscopy.

The authors found that the highest nanoparticle densities are reached with citrate-reduced gold nanoparticles and with ablated silver nanoparticles and those particle densities by more than a factor of 10. The distribution of SERS enhancement factors was determined at the microscopic level as a function of nanoparticle type and linker molecule. For nanoparticle of similar size, the morphology and types of aggregates on the surface must play a major role in the enhancement. The properties of the aggregates are mainly a result of particle capping and the specific interaction of the nanoparticles with the linker molecules. The differences become most obvious when comparing the extinction spectra of the surface generated with silver nanoparticles fabricated by laser ablation and those of reduction-fabricated silver nanoparticles.

The possibility to use the same linker to immobilize both silver and gold nanoparticles can be employed to combine them on one substrate. The authors determined the SERS enhancement factors for different types of mixed surfaces with gold nanoparticles and hydroxylamine reduced silver nanoparticles. The enhancement factor is on the order of $10^6$ for the gold to silver ratios of ~3 and ~1. This enhancement is similar to that of the surfaces containing is similar to that of the surfaces containing only gold nanoparticles. Using the surface with lower amount of gold nanoparticles, at a gold to silver ratio of ~3 the enhancement factor is about 1 order of magnitude lower, similar to the surface containing only such silver nanoparticles. Thus the authors have characterized a variety of plasmonic nanoparticle monolayers fabricated by immobilizing different types of silver and gold nanoparticles with amino-silane linker regarding their SERS enhancement. It was shown that silver and gold nanoparticles can be immobilized simultaneously using the same linker molecules. Due to different interactions of gold and silver nanoparticles with analyte molecules, mixing of gold and silver nanoparticles can provide the substrates with very high performance.

The substrates with stacked and tunable large-scale plasmonic nanoparticle arrays were demonstrated by Rockstuhl et al [43]. The fabrication of each substrate started with the functionalization of a glass or silicon plate to attach gold nanoparticles (AuNPs), then the functionalized plate was immersed in a solution of spherical AuNPs. Thus by a bottom-up technique based on the electrostatic forces the authors performed the fabrication of a substrate consisting of two amorously arranged arrays of plasmonic AuNPs that are stacked one above the other. This method allow for large-scale samples that can be fabricated in short time and at low cost. Futhermore, the samples allow for an easy tuning of their operation wavelength just by varying the distance between AuNP arrays in the nanometer range. For this purpose the authors used charged monolayers of molecules that act as a reliable spacer.

The performance of fabricated samples was proven for two different molecules and in two configurations. Nile blue and fluorescein were the two selected molecules. Their Raman modes were remarkably enhanced when compared to samples where the molecules have been added ion top of single AuNP arrays. Simulations revealed that the performance of the samples could be predicted by a simple model based on two spheres. Therefore, the presented SERS samples serve as a universal, inexpensive, and easy to produce tool to investigate the Raman modes of a huge class of molecules. Beyond their usage as SERS substrates, the present substrates would find applications in many other functional devices where the interaction of light with matter needs to be intensified at specific wavelength.

The substrates with two-dimensional (2D) silver nanoparticle tetramer (AgNPT) array were demonstrated by Wang, Wu et al [44]. The authors have successfully fabricated a densely packed 2D AgNPT array by electrochemical deposition on the closely packed porous Al template. This 2D structure dramatically enhanced the signal intensity of the SERS spectra and achieved a very high sensitivity of the R6G molecules in solution with a concentration as low as $10^{-15}$ M. Both line shape and feature positron in the SERS spectra were sensitive to the solution concentration, single-molecule adsorption took place. This was further supported by the analysis of the number of molecules in the probe region. Time-evolved SERS spectra showed high signal stability at one spot, characteristic of the single-molecule adsorption behavior, and an intense signal fluctuation in the SERS spectra of the other spot of the same sample surface, indicative of multimolecule adsorption behavior. Both types of adsorption demonstrated that there was the coexistence of single-molecule adsorption behavior in the 2–5 nm nanogaps. The detection limit down to the single-molecule on the prepared sample mainly stemmed from the formation of 2D ‘hotspot lattice’ of the AgNPT array. Such a highly sensitive SERS structure might have wide applications in chemical detection, environmental analysis, medical diagnosis, drug sensing and so on.
3. Substrates using nanostructures with non-spherical shapes

Besides metallic nanoparticles with spherical shape, several types of nanostructures with non-spherical shape were also used for fabricating SERS substrates. One of them is the nanowire (NW). SERS substrates with gold NW arrays were prepared by Lamy de la Chapelle et al [45]. The authors investigated the SERS efficiency of gold NWs arrays elaborated by EBL and lift-off technique efficiency by depositing a molecular probe (BPE)trans-1,2-bis(4-pyridyl) ethylen on the arrays and using an excitation wavelength of 632.8 nm. The observation of the dependence of the Raman enhancement versus the NW length is clearly demonstrated and remarkably a maximum enhancement is observed. For such arrays, we also show clearly that odd multipolar localized surface plasmon modes such arrays, we also show clearly that odd multipolar localized surface plasmon modes such arrays, we also show clearly that odd multipolar localized surface plasmon modes such arrays, we also show clearly that odd multipolar localized surface plasmon modes such arrays, we also show clearly that odd multipolar localized surface plasmon modes such arrays, we also show clearly that odd multipolar localized surface plasmon modes such arrays, we also show clearly that odd multipolar localized surface plasmon modes such arrays, we also show clearly that odd multipolar localized surface plasmon modes such arrays, we also show clearly that odd multipolar localized surface plasmon modes such arrays, we also show clearly that odd multipolar localized surface plasmon modes such arrays, we also show clearly that odd multipolar localized surface plasmon modes such arrays, we also show clearly that odd 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arrangement of the nanoprism monolayers generates large numbers of hot spots in the 2D arrays in the tip-to-tip and edge-to-edge inter-particle regions, giving rise to strong SERS signals. When deposited on an Au mirror film, additional hotspots are created in the 3nd dimension in the gaps between the 2D nanoprismon layers and the Au film. SERS enhancement factors reaching $10^4$ for non-resonant probe molecules are achieved.

In [55] Sepaniak et al demonstrated the fabrication of special nanocomposite SERS substrate by using EBL and nanotransfer printing. In this work an unconventional nano-fabrication approach is used to produce efficient SERS substrates. Metallic nanopatterns of silver disks are transferred from a stamp onto poly(dimethylsiloxane) (PDMS) to create nanocomposite substrates with regular periodic morphologies. The stamp with periodic arrays of square, triangular, and elliptical pillars is created via EBL of ma-N 2403 resist. A modified cyclodextrin is thermally evaporated onto the stamp to overcome the adhesive nature of the EBL resist and to function as a releasing layer. Subsequently, Ag is physically vapor deposited onto the stamp at a controlled rate and thickness and used directly for nanotransfer printing (nTP). Stamps, substrates, and the efficiency of the nTP process were explored by scanning electron microscopy. Transferred Ag nanodisk–PDMS substrates are studied by SERS using Rhodamine 6G as the probe analyte. There are observed optimal conditions involving both Ag and cyclodextrin thickness. The SERS response of metallic nanodisks of various shapes and sizes on the original stamp is compared to the corresponding nTP created substrates with similar trends observed. Limits of detection for CV and mitoxantrone are approximately $10^{-8}$ and $10^{-9}$ M, respectively. As an innovative feature of this approach, we demonstrate that physical manipulation of the PDMS post-nTP can be altered to change morphology, e.g., to change internanodisk spacing. Additionally, stamps are shown to be reusable after the nTP process, adding the potential to scale-up regular morphology substrates by a stamp-and-repeat methodology.

SERS substrates using silver nanocube dimmers were fabricated by Rabin et al [56] using a large set of silver nanocube dimmers programmed to self-assemble in preset locations of a patterned substrate. This SERS substrate made it possible to demonstrate the dependence of the SERS enhancement on the geometry of the silver nanocube dimers and to quantify the dispersion in the SERS enhancement obtained in an ensemble of dimers. In addition to the effects of the gap distance of the dimer and the orientation of the dimer axis relative to the laser polarization on SERS enhancement, the data reveal an interesting dependence of the site-to-site variations of the enhancement on the relative orientation of the nanocubes in the dimer. We observed the highest heterogeneity in the SERS signal intensity with face-to-face dimers and a more robust SERS enhancement with face-to-edge dimers. Numerical calculations indicate that the plasmon resonance frequencies of face-to-face dimers shift considerably with small changes in gap distance. The resonance frequency shifts make it less likely for many of the dimers to satisfy the matching condition between the photon frequencies and the plasmon resonance frequency, offering an explanation for the large site-to-site variations in SERS signal intensity. These results indicate that plasmonic nanostructure designs for SERS substrates for real-world applications should be selected not only to maximize the signal enhancement potential but also to minimize the heterogeneity of the substrate with respect to signal enhancement. The latter criterion poses new challenges to experimentalists and theorists alike.

Since the AuNTs are stable in aqueous solution, surface activity can be obtained through functionalization with polyvinyl pyrrolidone (PVP) [59, 60]. PVP coating of plasmonic nanoparticles allows the formation of single-nanoparticle monolayers at the air–liquid interface extended over large areas reaching square centimeters. Therefore the authors used PVP coating and subsequent self-assembly for fabricating SERS substrates based on AuNTs. The SERS performance of both AuNTs in solution and assemblies was demonstrated through benzenethiol detection, reaching enhancement factor around $10^5$, even for single AuNTs in solution.

4. Substrates using multiparticle complex nanostructures

Recently multiparticle complex nanostructures such as nanoparticle cluster arrays (NCAs), nanoflowers and nanodendrites were also employed for the fabrication of SERS substrates. In [61] Reinhard et al demonstrated engineered SERS substrates with multiscale enhancement using NCAs. The authors remarked that the SERS enhancement by noble metal nanoparticle arrays depends on both the properties of the constitutive building blocks such as shape, size, roughness, composition, as well as the geometric characteristics of the whole array, such as interparticle separation, array side, and geometry [62–64]. Therefore, the key requirements for the success of this methodology in the fabrication of SERS substrates with large and reproducible signal enhancement. In the present work the authors demonstrated that NCAs provide reproducible SERS spectra of different bacteria species including Escherichia coli, Bacillus cereus and Staphylococcus aureus with sufficient quality for potential diagnostic applications. The authors fabricate NCAs by combining top-down nanofabrication and bottom-up self-assembly process [65–68]. This approach provides control over the size of the particle clusters and their spatial location on the nanoscale. The authors used this process to fabricate regular arrays of...
40 nm gold nanoparticle clusters of determined cluster size \( n \) and cluster edge-to-edge separation \( \lambda \). The photonic-plasmonic scattering resonances of the arrays as a function of \( n \) and \( \lambda \) were characterized. The spectra are dominated by the ensemble resonance of the gold film supported nanoparticle clusters at large cluster separation. A systematic variation of \( \lambda \) revealed that the plasmon resonance peak red-shifts with decreasing \( \lambda \) for \( \lambda \leq 200 \) nm, indicating additional intercluster near-field interactions. The red-shift of the plasmon resonance is accompanied by an increase of the SERS enhancements for \( \lambda \leq 200 \) nm, indicating that the net enhancement is the result of the multiscale field enhancement in NCAs. Beside the dependence on \( \lambda \), the SERS signal enhancement also depends on the cluster size \( n \), and the authors investigated the optical response and the SERS enhancement of NCAs as a function of \( n \). The cluster resonances of the arrays strongly red-shift with increasing cluster size \( n \) up to \( n = 4 \).

Overall, the present work revealed that NCAs can be used to engineer SERS substrates whose spectral and field localization properties can be controlled systematically by varying \( n \) and \( \lambda \). The authors found that NCAs offer good compromise between signal enhancement and substrate reproducibility. Moreover, the engineered SERS substrates with NCAs clearly outperformed other substrates in SERS measurements of bacteria.

The role of the building block in multiscale SERS substrates with engineered NCAs for bacterial biosensing was investigated by Reinhard et al. [69]. Noble metal NCAs are a novel class of engineered substrates for SERS, in which the noble metal nanoparticles interact on multiple length scales to create a multiscale \( E \)-field cascade enhancement. In this work the role of the building block for the NCA performance is quantified. Periodic NCAs with constant cluster diameter \( (D = 200 \) nm) but variable nanoparticle diameter \( (d) \) and intercluster separation \( (\lambda) \) were assembled on glass and their optical response and SERS enhancement were systematically characterized as a function of \( D \), \( \Lambda \) and \( d \). An increase of \( d \) from 40 to 80 nm and simultaneous decrease of \( \Lambda \) from 200 to 50 nm led to an improvement of the ensemble averaged SERS enhancement factor by a factor of up to \( \sim 8 \). The coefficient of variation \( (C_v) \) of the enhancement factors \( (G) \) is significantly lower for the \( d = 80 \) nm NCAs than for the \( d = 40 \) nm and \( d = 60 \) nm NCAs. Optimized \((D = 200 \) nm, \( \Lambda = 50 \) nm, \( d = 80 \) nm) NCAs show the overall highest signal reproducibility of all investigated NCAs and random nanoparticle substrates and achieve effective single cell detection sensitivity.

Ultra-high-density array of silver nanoclusters for SERS substrate with high sensitivity and excellent reproducibility was demonstrated by Kim et al. [70]. In this work the authors introduced a simple but robust method to fabricate an ultra-high-density array of silver nanoclusters for a SERS substrate with high sensitivity and excellent reproducibility at a very large area (wafer scale) based on polystyrene-block-poly(4-vinylpyridine) copolymer (PS-b-P4VP) micelles. After silver nitrates were incorporated into the micelle cores (P4VP) followed by the reduction to silver nanoclusters, we systematically controlled the gap distance between two neighboring silver nanoclusters ranging from 8 to 61 nm, while the diameter of each silver nanocluster was kept nearly constant (\( \sim 25 \) nm). To make a silver nanocluster array with a gap distance of 8 nm, the use of crew-cut-type micelles is required. Fabricated SERS substrate with a gap distance of 8 nm showed very high signal intensity with a SERS enhancement factor as high as \( 10^8 \), which is enough to detect a single molecule, and excellent reproducibility (less than \( \pm 5\% \)) of the signal intensity. This is because of the uniform size and gap distance of silver nanoclusters in a large area. The substrate could also be used for label-free immunoassays, biosensing, and nanoscale optical antennas and light sources.

SERS substrates in the form of the tags with gold nanoflowers (AuNFs) for \textit{in vivo} applications were proposed by Lee et al. [71]. The AuNFs are ideal material for preparing SERS substrates because of the abundance of ‘hot’ spots generated by their special surface topography which could result in substantial local electromagnetic field enhancement [72–75]. Applying this enhancement effect the authors used AuNFs to fabricate stable SERS-active tag for living cells.

In a previous work the authors elaborated a ‘green chemistry’ approach using 2-[4-(2-hydroxyethyl-1-piperazinyl)] ethanesulfonic acid (HEPES) as the reducing \textit{cum} shape—directing agent to form gold multipods with one light tips [76]. This method was able to fabricate complex nanoflowers [77–80]. In the present work the authors modified HEPES reduction method to fabricate metallic (Au) nanocrystals with flower-like structures in high field and good size monodispersity.

The average size of AuNFs was tunable by controlling the composition on the initial reaction mixture. The preparation could be easily scaled up to gram-quantity production. The formation of flower-like particle went-through three indentifiable stages:

- Reduction of Au(III) ions to Au primary nanocrystals;
- Agglomeration of the Au primary particles to form intermediate agglomerates;
- Anisotropic growth of the intermediate agglomerates into flower-like extended structures.

The as-synthesize AuNFs exhibited strong SERS effect. They were developed into SERS-active tags by packaging RhB AuNF particles with denatured bovin serum albumin molecules. The application of these SERS-active tags in living cells was demonstrated by using the RAW 264.7 macrophage cell line.

Recently there was a significant progress in the improvement of methods of fabricating flower-like nanostructures [81–83]. The application of the increase of the enhancement efficiency of SERS substrates.

Beside nanoflowers there exits also another form of multiparticle complex nanostructures—the nanodendrites [84–87]. Very recently Long et al. [88] fabricated a silver dendrite-integrated chip for using in the SERS experiments. Subsequently Dao et al. [89, 90] fabricated SERS substrates by depositing silver nanodendrites (AgNDS) on silicon and used them in the trace analysis of a herbicide: the paraquat (PQ) the
AgNDs deposited on silicon have been manufactured by two methods: electroless deposition and electrodeposition, using the same aqueous solution of AgNO₃ and HF, and after that they have been used as SERS-active substrates to detect trace amounts of PQ, a commonly used herbicide. The results showed that the electrodeposited AgNDs have much better ramification. Specifically, on a trunk, the number of branches becomes much greater, the branches are almost of the same length, forming the same angle with the trunk and evenly spaced. Besides, the density of the dendrites also becomes thicker and dendrites arranged together in a better order. Corresponding to the improvement of AgNDs morphology is the improvement of the intensity and resolution of the SERS spectrum of PQ, when the AgNDs with improved morphology were used as SERS substrates. As a result, while the SERS-active substrates made from electrodeposited AgNDs were able to detect PQ with concentration as low as 0.01 ppm, the ones made from electroless deposited AgNDs could only detect the PQ of concentration hundreds of times higher.

5. Flexible substrates

Besides above presented rigid SERS substrates the flexible ones were recently invented. In [91] Singamaneni et al demonstrated the fabrication of highly efficient paper-based SERS substrate in the form of the swab by loading gold nanorods (AuNRs) on filter paper. This SERS substrate can be used by simply swabbing the surface of the object suspected of exposure to a hazardous material. Apart from the large enhancement, the uniform decoration of AuNRs preserves the favorable attributes such as flexibility, conformational nature, and capillarity of the paper.

AuNRs were synthesized by seed-mediated approach using cetyltrimethylammonium bromide (CTAB) as a capping agent [92, 93]. UV–vis extinction spectra of the AuNR solution showed two characteristic peaks at ~530 and 650 nm corresponding to the transverse and longitudinal plasmon resonances of the AuNRs [94]. AuNRs-loaded paper exhibited a similar extinction spectrum with both transverse and longitudinal plasmon resonances slightly blue-shifted compared to the solution. The observed blue-shift can be attribute to the change in the dielectric ambient (from water to air + substrate) with an effective decrease in the refractive index. AFM images revealed a uniform and dense adsorption of AuNRs on the surface of the paper without any sign of large scale aggregation of AuNRs.

One of the distinct advantages of the paper-based SERS substrate is the ability to collect trace amount of analytes from real-world surface by swabbing across the surface.

Thus the authors have demonstrated highly efficient SERS substrate based on common filter paper filled with AuNRs, which exhibited more than 2 orders of magnitude higher SERS enhancement compared to the silicon-based SERS substrate. Numerous favorable traits of the paper such as flexibility, conformability, efficient uptake, and transport of the analytes from liquid and solid media to the surface of metal nanostructures due to hierarchical vasculature and high specific surface area make the paper-based SERS substrates an excellent candidate for trace chemical and biological detection. The paper-based SERS substrates also offer cost-effective platform for SERS detection an open up a new venue for other biological and chemical detection.

A productive method to fabricate SERS substrate on cellulose paper is the inkjet printing method proposed by White et al [95]. In this work the authors demonstrated an ultra low-cost paper-based SERS substrate using inkjet printing as the fabrication method. A high signal-to-noise ratio was achieved even with only 10 femtomoles of analyte molecules in the entire sample volume and with a relatively low power red laser as the excitation source. In addition to the excellent performance, the substrate does not require any complicated or lengthy micro- or nano-fabrication. The SERS substrate can be created in nearly any environment at the moment the user is ready to perform a measurement. Most importantly, this eliminates the problem of the limited shelf-life of SERS substrates because the inkjet printed substrates do not need to be aquired in bulk and stored. Instead, they can be fabricated with unprecendented simplicity and speed at the time and point of use. The extremely low cost and simplicity of fabrication make the paper-based SERS substrates ideal for a number of applications, including routine lab use, as well as use in the field at the point of sample acquisition. Future improvement would include integration with paper-based microfluidides and the use of a simple fiber optic probe to excite the substrate and collect the scattered light when performing measurements.

For the fabrication of SERS substrates in the form of adhesive polymer tapes it is crucial to have a suitable technique to deposit plasmonic metallic nanoparticles (NPs) onto these tapes. In [96] Grzybowski et al proposed a straightforward method of deposition combining mechanochemical activation and soft lithography. In the presented approach the target surface is activated by simple pulling on an adhesive tape. By this route the authors were able to deposit a range of different types of NPs- from antibacterial silver to antifungal copper-on the ‘sticky’ side of the tape or only on its patterned fragments. The tapes covered with NPs retain their adhesive properties while gaining new ones, including increased electrical conductivity or bacteriostaticity.

Flexible and adhesive SERS substrate in the form of the tape for rapid detection of pesticide residues in fruits and vegetables were recently demonstrated by Guo et al [97]. The authors fabricated the flexible and adhesive SERS tape by decorating the commercial tape with gold nanoparticle (AuNPs) via the conventional drop-dry method. AuNPs were prepared according to a modified Frens method [98–100].

When AuNP solution was deposited onto the sticky layer of the adhesive tape, the main chemical composition, acrylate adhesive, was swelled because of the presence of the water. Then the dry evaporation led to deswelling acrylate adhesive. This swelling and deswelling action would result in the half-embedded aggregation of AuNPs confirmed by scanning electron microscopy images. The surface of the adhesive tape, which was smooth and flat, after embedding AuNPs became a rough and ‘hilly terrain’ shaped structure. One advantage of
AuNPs in the formed SERS-active tape can remain its ‘sticky’ feature, which cannot be usually achieved by physical vapor deposition and a film transfer method.

In summary, the authors have demonstrated that the commercial tape decorated with AuNPs can be employed as a novel flexible and adhesive SERS-active tape. The SERS-active tape can retain its mechanical properties and remain ‘sticky’, providing the feasibility for easy sampling of complex surfaces. The presence of AuNPs endows the tape with SERS activity for the rapid and sensitive detection experiments demonstrated the high sensitivity, remarkable reproducibility, super stability and low cost of SERS tape. As a practical application, the authors demonstrated the qualitative detection of various pesticide residues such as para-thionmethyl, thiram and chlorpyrifos in green vegetables, cucumbers, oranges and apples. Compared to those commercially available methods based on the detection of the enzyme-inhibition rate, the proposed SERS tape method can surpass the commercial available methods based on the detection of the enzyme-inhibition rate, the proposed SERS tape method can be a practical alternative because it is quite stable when exposed in air under normal pressure and temperature.

### 6. Conclusion and discussion

We have presented a review on main SERS substrates which have been fabricated up to now. They can be classified according to their structures as follows: substrates using metallic nanoparticles with spherical shape, substrates using nanostructures with non-spherical shapes, substrates using multiparticle complex nanostructures and flexible substrates. There is a large number of substrates using metallic nanoparticles with spherical shape, whereas the number of substrates using various nanostructures with non-spherical shapes is smaller, and there are only few substrates using multiparticle complex nanostructures. Moreover, very recently some types of flexible SERS substrates were invented.

Thus until now there exists a rich variety of SERS substrates. The choice of a specified substrate to be used depends on the purpose of the application. Among above presented types of SERS substrates those with multiparticle complex structures promise to achieve very high sensitivity, where as the flexible ones certainly will have efficient and widespread practical applications.

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