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Prosperity to challenges: recent approaches in SERS substrate fabrication

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Abstract: Surface-enhanced Raman spectroscopy (SERS) is a highly promising analytical technique that has been widely applied in health and environment monitoring. As a vibrational spectroscopic tool, its fingerprint spectrum contains abundant molecular information, and the greatly enhanced signal can be used to detect analytes at extremely low concentration, even down to the single molecule level. Because water molecules give very weak Raman response, Raman spectroscopy has also been applied for in situ monitoring of targets in solution. However, the Raman signal of an analyte could only be enhanced when it is in proximity to the SERS substrate, which enhances the signal depending on the shape, size, and orientation of the particles constituting the substrate. Further, when using the method for the detection of various analytes, it is necessary to functionalize the SERS substrates, with recognition ligands and encapsulation with a suitable shell among others. Hence, the fabrication of suitable substrates is a basic step in SERS-related research. Tremendous effort has been expended in the last decade in this area, resulting in the development of substrates with unique properties. In this review, we will introduce recent achievements in SERS substrate fabrication based on their structural features. Synthesized nanoparticles, two-dimensional planar substrates, and three-dimensional substrates with effective volume will be discussed in the context of their synthesis strategies along with their characteristic properties. In the future, with further improvement in SERS substrates, the applicability of SERS for detecting a range of analytes in complex environment will become possible.

Keywords: nanoparticles; planar substrate; surface-enhanced Raman spectroscopy; three-dimensional substrate.

Introduction

Raman spectroscopy was first observed by Sir. C. V. Raman in 1928 and was later named after him (Raman et al. 1928). In the initial several decades since its discovery, its application was greatly inhibited by the extremely low spectral intensity. In the 1970s, the discovery of surface-enhanced Raman spectroscopy (SERS) transitioned Raman spectroscopy to a practical realm impacting a range of fields (Fleischmann et al. 1974, Jeanmaire et al. 1977). This finding involved the greatly enhanced Raman signal of pyridine when it was absorbed onto the rough silver electrode. Although it was first attributed to the increased number of absorbed molecules, later research confirmed that this phenomenon was due to enhancement from the excited localized surface plasmon resonance (LSPR) on the surface of the substrate (Albrecht et al. 1977, Jeanmaire et al. 1977) Since then, numerous approaches emerged ranging from mechanistic evaluation, to substrate fabrication, to application in trace analyte detection with excellent sensitivity, even down to the single molecule level (Kneipp et al. 1997, Nie et al. 1997). All of these achievements contribute to the exploitation in demonstrating the vast potential of this unique technology in various fields of application.

SERS has affected many areas in analytical detection, surface property investigation, biological event and marker sensing and imaging, and environment monitoring. Several excellent reviews, themed journal issues, and books are available that expound on the basic concepts of SERS (Fan et al. 2011, Sharma et al. 2012, Schlücker et al. 2014), its application in analytical science (Kiefer et al. 2010, Fateixa et al. 2015), food science (McNay et al. 2011, Cho et al. 2014), environmental sciences (Alvarez-Puebla

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et al. 2010, Luo et al. 2014), and biomedical sciences (Lane et al. 2015).

Tremendous progress was made in the last decades on the fabrication of nanostructures based on SERS-active materials. These developments always come from the demands of specific application areas. The SERS effect was first observed on electrochemically roughed metal electrodes, which could define as the earliest substrates. With the demands of applying into extended areas such as aqueous and biological system in a convenient way, synthesized metallic nanoparticles (NPs) were developed yielding excellent enhancement effect and ease of use (Tong et al. 2011). To obtain better SERS enhancement, hybrid and assembled structures were proposed with more confined electromagnetic field distribution (Xie et al. 2011a). Considering the selective detection of specific targets, surface functionalization and modification was widely used with different capture scaffolds such as antibodies, aptamers, and host molecules (Alvarez-Puebla et al. 2012). Two-dimensional (2-D) planar structures such as paper-based structures were proposed for nondestructive detection while realizing substrate homogeneity (Polavarapu et al. 2013). By fabricating or assembly of nanostructures into three-dimensional (3-D) substrates, the contribution of 3-D effective volume was successfully applied for trace detection and imaging, and their self-standing property showed excellent prospect in real applications (Liu et al. 2015a). On the basis of their structural properties, they are divided into several groups, including NPs, planar substrates, and substrates with 3-D effective volumes. The focus of this review is to summarize their merits and potential weakness and to highlight the distinct advantages and limitations of the SERS substrate fabrication.

Basic concepts of SERS substrate fabrication

Different from normal Raman spectroscopy, SERS requires an essential component of enhancement substrate, on which the Raman signal of the reporter molecules can be greatly enhanced. When the LSPR is excited on such a nanoscale structure by irradiation, the strong electromagnetic field can produce a magnitude increase in the Raman signal of the reporter molecules because of the intense electromagnetic field (Wang et al. 2013). The Raman signal thus is greatly enhanced in magnitude from 10^3- to 10^9-fold. The exact mechanism of SERS enhancement is still in debate; however, the two commonly accepted modes of enhancement are the chemical enhancement and electromagnetic enhancement. The chemical enhancement comes from the chemical interaction between the reporter molecules and the substrate such as the charge-transfer interaction, which is believed to contribute to an enhancement factor in the range from 10^1 to 10^3. The Raman enhancement observed in the experiment predominantly comes from the electromagnetic mechanism. The electromagnetic mechanism has a uniform effect on the molecules close to the SERS substrate and is highly dependent on the component and morphological features of the substrate, which determines the state of the conduction electrons in a metallic nanostructure (Banholzer et al. 2008). Theoretical modeling is commonly applied to study the electromagnetic enhancement, which can, in turn, guide the design of the structures in the defined electromagnetic field (Cao et al. 2001, Thomas et al. 2012).

Although the application areas differ from one another, the fundamental aspects of substrate design and fabrication need to be emphasized (Stiles et al. 2008). The first key issue in substrate fabrication is undoubtedly the SERS-enhanced activity. To increase the SERS enhancement of a substrate, from the viewpoint of electromagnetic mechanism, the number of “hot spots” on the substrate should be increased (Fang et al. 2008). “Hot spots” are highly localized regions with intense local electromagnetic field, usually occurring within the interstitial crevices in metal structures, which have been claimed to lead to extraordinary enhancement (Shiohara et al. 2014). Hot spots can be obtained at the tip or pointed end of the metal structure and can also be found at the interparticle junctions between nanostructures in proximity (usually down to several nanometers) (Aravind et al. 1981). Several strategies were used to increase hot spots such as synthesis of anisotropic NPs with more tips and assembly of NPs into closely assembled structures (Wei and Xu 2013). Besides the manner of building hot spots for increasing the enhancement, other efficient methods include the synthesis of bimetal structure that can make use of the coupling effect of electromagnetic field between different materials (Yang et al. 2014a). For the chemical enhancement, surface modification and matching of the excitation laser source can introduce better SERS enhancement to specific molecules.

Homogeneity is another key point in the evaluation of the SERS substrate, especially when it is used for quantitative detection and imaging. The detection result is reliable only when the results from the substrate are reproducible because SERS is a localized phenomenon and it is highly sensitive to the local structure of the substrate and the surrounding environment. For the NP substrates, the homogeneity in size, shape, and aggregation state will increase the reproducibility. For the assembly- or array-based substrates, the controllable gap size and its distribution are very important. On the basis of the recently reported substrate, the homogeneity should better be ensured not only in 2-D but also at the 3-D scale (Liu et al. 2015a). Besides the higher enhancement or better homogeneity, the cost of substrate fabrication should also be considered in SERS applications.

Synthesized NPs directly used as substrate

To date, synthesized metal NPs are the most widely studied and used SERS substrates because of their facile synthesis procedure and good SERS performance. The key point in the preparation of NP substrates is to develop a better strategy to obtain NPs with controllable size, shape, and better SERS enhancement. Because of the ease of gold (Au) and silver (Ag) NP colloidal synthesis, these are the widely used substrates and also considered as the building blocks for further preparation of assembled substrates (Lee et al. 1982). Hybrid NPs that combine noble metal with other materials are also obtained for multifunctional structures, such as magnetic NPs, lab-on-bubble NPs, and so on (Yang et al. 2015).

Monometallic NPs with regular shapes

Monometallic NPs or the so-called nanocrystals attract extensive attention because of their unique and controllable optical properties. Their intrinsic properties highly depend on the component, size, and shape; thus, the controllable synthesis of NPs is important for achieving better SERS effect. Numerous strategies that make use of the shape-controlling agent or size controllable growth procedure were developed for such NPs (Bastús et al. 2011). For example, highly mono-disperse spherical Ag NPs with sizes ranging from 18 to 30 nm were synthesized by varying the concentrations of tannic acid, the reducing agent (Dadosh 2009). Au NPs with remarkably narrow size distribution were synthesized by seeding growth approach for efficient SERS application (Kwon et al. 2006). As mentioned previously, hot spots produced at tips of the nanostructures would induce significant enhancement of SERS; thus, nanostructures with corners or tips could produce better performance than spherical particles, such as nanoplate, nanocubes, nanorattles (as shown in Figure 1A), polyhedral nanocrystals, and so on (Zhang et al. 2013, Scarabelli et al. 2014, Liu et al. 2015b). In 2002, Xia et al. reported the first large-scale synthesis of monodisperse Ag and Au cubes (Sun et al. 2002). Since then, different cubes were synthesized for SERS application (Moran et al. 2013, Panikkanvalappil et al. 2014). Similarly, nanostructures with octahedral shape could be synthesized with suitable protective agents, which also showed good SERS performance (Xia et al. 2011).

Monometallic NPs with anisotropic shapes

Besides the above-mentioned regular shape NPs, the stronger electromagnetic field could be observed on the high curvature surface of anisotropic NPs with more tips and sharp edges such as dendrites and nanoflowers (Xie et al. 2008, Ren et al. 2011a). Nanoscale junctions and interstices could be realized on the single NP between the overlapped branches which would supply high SERS activity. Starting from polyhedral Ag nanocrystals, a chemical etch-based process was presented for anisotropic NPs with modified plasmonic characteristics in the near-infrared (Mulvihill et al. 2009). Sea urchin-like Au nanostructures with controllable surface morphology were synthesized via a secondary nucleation and growth process (as different surface shape showed in Figure 1B) (Fang et al. 2010). Au mesostructures and Ag nanoflowers with controllable surface topography have also been synthesized (Fang et al. 2010, Mettela et al. 2014). Later, a simple and low-cost method for the synthesis of Ag dendrites has been reported, and the relationship between the morphology and SERS activity has also been investigated (Ren et al. 2011b). Some more complex nanostructures comprising of hierarchical multipod microcrystals have been proposed with excellent performance as SERS substrates (Mao et al. 2016). Recently, by using a robust solution-phase method, Au nanostars with unprecedented degree of symmetry control with high yield and monodispersity yielding excellent SERS performance was proposed (Niu et al. 2015). Besides these solvent-based chemical reduction strategies, electrodeposition was also applied for anisotropic NPs. Special nanoscale structures such as the dendritic Au rods were obtained with a one-step electrodeposition, which was very convenient for the following SERS application combined with electrochemical observation (Choi et al. 2013).

These NPs with distinct optical property lead to good SERS performance; however, during their synthesis, shape-controlling or capping agents are usually required, which might also influence the SERS detection. When

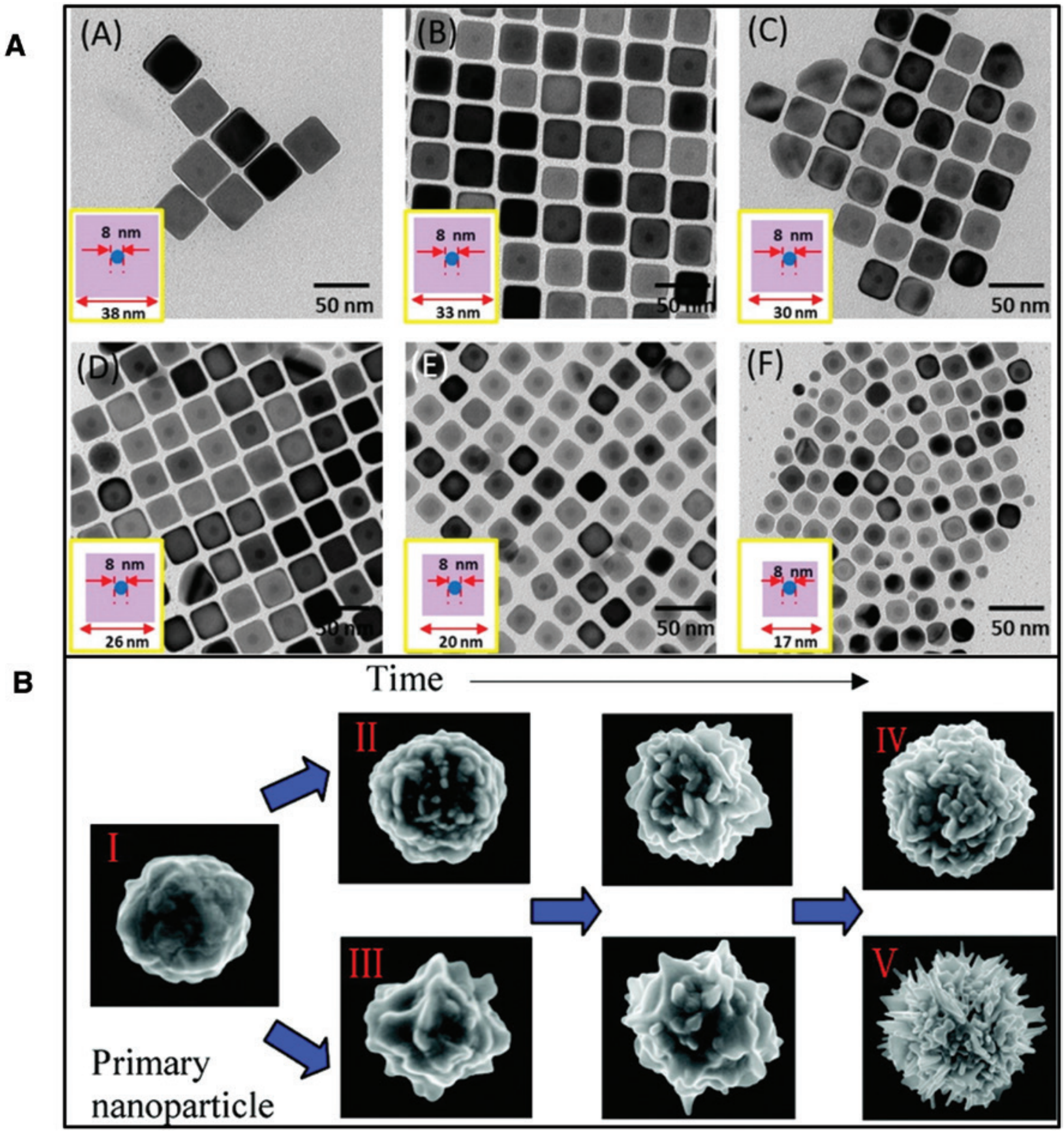

Figure 1: (A–F) TEM images of AuNS@Ag nanocubes obtained by adding (A) 0.15 ml, (B) 0.2 ml, (C) 0.5 ml, (D) 1.0 ml, (E) 2.0 ml, (F) 3.0 ml of AuNS into Ag shell growth solution. Inset of (A–F) shows schematic illustration of AuNS@Ag nanocube (not to scale). Adapted from Liu et al. *Chem. Mater.* **2015a**, *27*, 5261–5270. Copyright © 2015 American Chemical Society. (B) SEM images of Au mesostructures with a variety of surface topographies. Types I–V, synthesized at various conditions. Adapted from Fang et al. *Nano Lett.* **2010**, *10*, 5006–5013. Copyright © 2010 American Chemical Society.

synthesizing such NPs, besides the high SERS enhancement, the reproducibility is also very important, especially when they are used for quantitative detection.

Intracellular synthesized metal NPs

Because of the high sensitivity, low interference of the signal from water and abundant information encoded in the spectra, SERS is a powerful technique in biorelated observation and imaging. Here, the synthesized NPs are most commonly used, but compared with the process to have the cell uptake as-prepared NPs as substrates for SERS signal generation, it is an alternative way to directly reduce NPs in the cells. Meanwhile, the reduction process of NPs and the resulting SERS can uncover valuable intracellular fingerprints of molecules and metabolites. In our earlier work, when applying presynthesized NPs for intracellular SERS imaging, obstacles faced are aggregation and/or distribution of NPs inside the cell and poor translocation efficiency of NPs to the cytoplasm or nucleus (Shamsaie et al. 2007). Growing NPs inside cells is an effective approach to access the innermost confines of the cellular microcosm. By using intracellularly grown NPs as enhance substrate, we successfully performed SERS imaging for different organisms (one typical example for the intracellular Cr(VI) observation was showed in Figure 2) (Ravindranath et al. 2011, Ravindranath et al. 2012). Limitations are the uniformity of particle size, hotspots, and hence the enhancement.

Bimetallic NPs and nanocomposites

As the most commonly used NPs for SERS, Ag NPs exhibit good SERS enhancement with visible light excitation, but they have toxicity to organism and are easy to be oxidized. By contrast, Au NPs have relatively weaker enhancement, but they are biocompatible, easy to synthesize and amenable for further functionalization, and could be used with long wavelength laser excitation (Giljohann et al. 2010). The SERS-active NPs that combine these advantages together would be more favorable for certain applications. By using small Au NPs as seeds, a one-pot controllable synthesis of Au@Ag heterogeneous nanorods was proposed with a highly tunable plasmonic properties (Li et al. 2013a). Similarly, Au_xAg_y alloy and AuAg shell on Au core were used for SERS detection (Liu et al. 2011, Wang et al. 2014a).

The core-shell structure is also an effective SERS substrate. Samal et al. synthesized Au@Ag core-shell NPs, which exhibited higher SERS efficiency than Ag NPs of similar size under the near-infrared laser (Samal et al. 2013). Ag@Au core-shell nanostars showed much-decreased cytotoxicity with enhanced photostability and SERS performance and, interestingly, an excellent photothermal performance, which was also observed because of the Au shell (Zeng et al. 2015). Another famous core-shell structure for SERS is called "shell-isolated NPs," which was first reported by Tian's group (Li et al. 2010, 2013b). They used Au-core silica-shell NPs for SERS application with the shell surface in various composition and morphology, preventing direct interaction between Au core, and the analytes can reduce the alteration of the signal and the obtained enhancement effect can also be controlled by changing the shell thickness. Recently, multishell nano-matryoshka has been reported with built-in reporters as SERS tags, which was used with multiple markers by tuning the number of shells and tags in different gaps for biosensing and imaging (Figure 3A) (Lin et al. 2015). As a multifunctional layered material, graphene could be used as a protecting shell for noble metal NPs. Song et al. (2014a) proposed a graphene-coated AgCu, which exhibited excellent prospect for imaging (Figure 3B). Besides the above-mentioned inorganic material, polymer like dopamine was also proposed as a promising candidate to take advantage of the tailed flexibly (Song et al. 2014b, Huang et al. 2015a). For the core-shell structure, the first advantage is to combine the distinct properties of both core and shell; the other important advantage for SERS is to have tags built in the inner gap, which would be very useful for imaging, or as internal standard for quantitative detection. Besides, the biocompatibility and stability of SERS substrates will be improved with suitable shell protection. During the preparation of core-shell nanostructures as SERS substrates, it is a challenge to control the shell thickness and the coverage on the core while ensuring the effective electromagnetic enhancement. To date, most of the strategies are still complicated and the yield is low; simpler methods with high yield of homogenous core-shell structures will greatly benefit the corresponding SERS application.

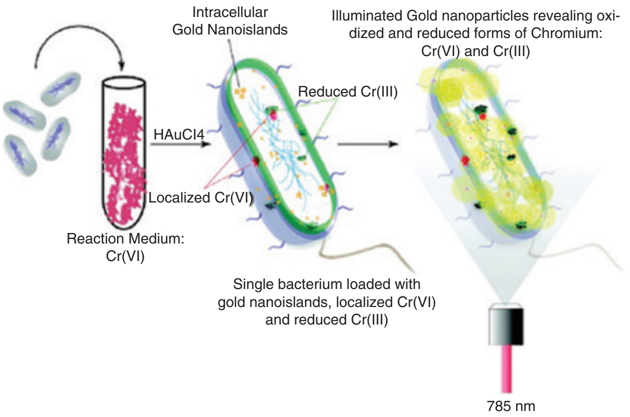

Figure 2: Single cell Raman chemical imaging driven by intracellularly grown gold nanoislands to obtain detailed chemical localization and oxidation state information for Cr(VI) and Cr(III) in living cells. Reproduced from Ravindranath et al. *ACS Nano* **2011**, *5*, 4729–4736. Copyright © 2011 American Chemical Society.

Nano- and multifunctional structures

Au- or Ag-based NPs have some weaknesses because they easily aggregate to result in poor homogeneity, and these nanoscale particles are not convenient to be recycled from the matrix for detection. An effective strategy to solve such problems is to form micro- and nanostructures by conjugating NPs onto other functional materials. In our former

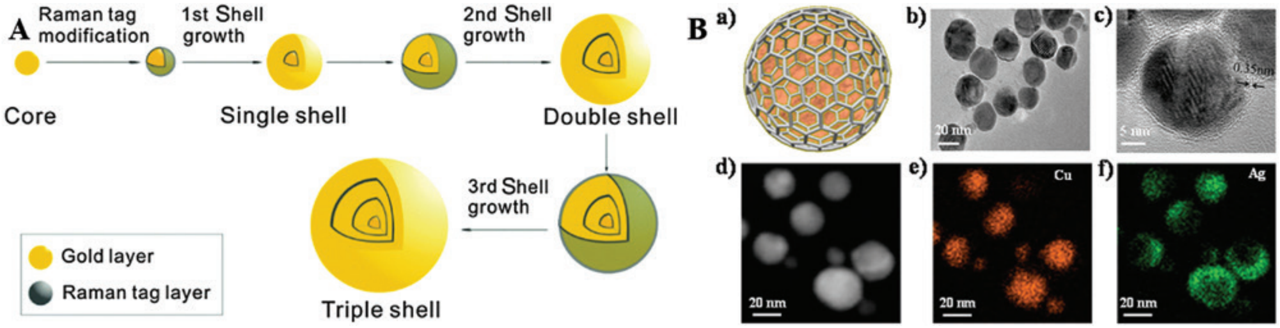

Figure 3: (A) Schematic illustration of the synthesis of nanomatryoshkas (NMs) with single, double and triple Au shell layers. Adapted from Lin et al. *Chem. Commun.* **2015**, *51*, 17740–17743, with permission from the Royal Society of Chemistry. (B) Advanced structural analysis of AgCu-graphene (ACGs) NPs. (a) Schematic diagram, (b) TEM image, (c) HR-TEM image, and (d–f) STEM images of ACGs. Adapted from Song et al. *J. Am. Chem. Soc.* **2014a**, *136*, 13558–13561. Copyright © 2014 American Chemical Society.

works, Ag NPs were successfully fixed onto different materials, including magnetic particles, SiO_2 bubbles, and C_3N_4 particles, to achieve better practicability such as magnetic recycle or self-floating on the liquid surface (Jiang et al. 2014, 2015, Ouyang et al. 2014). Graphite petals and graphene oxide decorated with Ag NPs were used for SERS detection with target capturing ability (Rout et al. 2010, Ren et al. 2011c). AgAuS microsheets decorated with Au NPs have been used for both SERS detection and photocatalytic degradation of plasticizers (Lin et al. 2012, Cao et al. 2014). Similarly, many other structures such as Ag-Cu_2O, Au-mesoporous polystyrene fiber, recyclable TiO_2-Ag nanowire, Ag-porous boron nitride fibers, and Au/FeS composite have also been reported (Schmit et al. 2011, Zhou et al. 2012, Ji et al. 2014, Dai et al. 2015, He et al. 2016, Ma et al. 2016). Copper (Cu) is SERS active with LSPR excited by the visible light (Stepanov et al. 2013). However, it has been less investigated because of its poor chemical stability. Such decorating strategy can be applied for promoting the stability of Cu NPs. For example, metallic Cu NPs was dispersed into a porous glass to form a micro- and nanostructure, and the obtained structures showed good SERS enhancement and stability (de Barros Santos et al. 2013). Cu/V_2O_5 hybrid structure was proposed with both enhanced SERS performance and catalytic activity and has been used for in situ monitoring of catalyst reaction (Cai et al. 2014). The Lewis acid-base properties of V_2O_5 helped improve the chemical enhancement via Lewis acid-base interaction. Such hybrid structure is also a convenient route to realizing multifunctional materials for more useful application. For example, multifunctional NPs have been successfully used for both SERS imaging and efficient cancer therapy at the same time (Huang et al. 2015b). Raman spectroscopy provides molecular vibrational spectrum and thus could be a very useful tool in the evaluation of catalytic reaction at the chemical bond level. In this area, substrates with multifunctional use as a SERS substrate with catalytic ability, such as Au@Pt NPs and Au-Pt-Au core-shell NPs have already shown good performance for in situ reaction monitoring and mechanistic studies (Xie et al. 2011b, Cui et al. 2014).

Micro- and nanodecorated substrates have the advantage of easy to obtain multifunctional NPs. As one of the most well-known example, magnetic NPs were commonly used in SERS because their ease of recycling and separation of analytes in samples (Saha and Jana 2013, Yang et al. 2015). Both SERS imaging and efficient cancer therapy were realized at the same time on multifunctional Fe_2O_3@Au nanoflowers (Huang et al. 2015b). The reusable substrates could be obtained by modification of Ag onto TiO_2, which could also be used for photoregeneration (Li et al. 2012, Ren et al. 2015). For the fabrication of micro- and nanodecorated substrates, the distribution and the assembly state of the plasmonic NPs are especially important because these determine the SERS performance of the hybrid structure.

Two-dimensional planar substrate

SERS is an advanced analytical technique; its priority application area is qualitative and quantitative detection. When using synthesized NPs as a substrate, although good SERS response could be realized, sometimes the random movement and the uncontrollable aggregation during the detection process induce serious signal alteration to result in poor reproducibility. It is a good option to fabricate substrate at the solid state or assembled state. Two-dimensional planar substrates have been widely studied because of their distinct optical and physical properties. In this section, we focus on special layered structures such as graphene and assembled 2-D substrates such as self-assembled NP array, and also paper and membrane-based planar substrates. Various methods exist for assembly or decoration of NPs onto planar structures, including self-assembly, support hybrid fabrication, and lithographic methods (Cecchini et al. 2013). Controlling the gap between particles or cavities to a suitable scale, simplifying the procedure for substrate preparation while maximizing SERS enhance uniformity, is crucial to optimize the SERS performance of the 2-D substrates.

Hybrid structures based on layered materials

Two-dimensional layered materials, exhibiting a flat surface without dangling bonds, were thought to be strong candidates for both Raman enhancement and target capture. Special 2-D materials such as graphene, hexagonal boron nitride, and molybdenum disulfide in previous research exhibited unique Raman enhancement effect with potential as Raman enhancement substrate (Ling et al. 2014).

Graphene was reported to display chemical effects that contribute to SERS enhancement with enhancement factor at approximately one or two orders of magnitude (Wang et al. 2014b). The unique carbon 2-D nanosheet is also favorable for aromatic molecule interaction via π-π stacking and hydrophobic interactions (Figure 4A) (Wang et al. 2014c). Tunable enhancement could be realized by controlling its surface structure and even its layer number (Huh et al. 2011). Despite directly applying graphene as a substrate, its hybrid structure with SERS-active metal NPs was also commonly used. The graphene-Au nanopyramid structure was used for single molecule detection with SERS enhancement factors more than 10 (Fateixa et al. 2015), and the substrates with graphene as inert surface were easily refreshed and resistant to the degradation (Wang and Irudayaraj 2013). Tuning plasmonic and chemical enhancement was realized with graphene-Au, graphene-Ag, and graphene-Cu hybrids (Ren et al. 2011c, Liang et al. 2015, Qiu et al. 2015). Graphene has also been used as a cover layer on the Cu NPs to promote the stability of Cu NPs, at the same time, the electromagnetic coupling between graphene and Cu NPs could also improve SERS enhancement (Xu et al. 2015a). Usually, the direct interaction between chemically inert graphene and NPs is not very strong, which would inhibit the effective electromagnetic coupling. To enhance the interaction between graphene and NPs, Xu et al. (2013) reported an annealing operation to form a graphene-veiled Au structure. In our former work, we performed a facile operation called laser shock lamination to fast and reproducible enhance the interaction between graphene and NPs (Figure 4B) (Hu et al. 2015). Besides graphene, other planar structures such as C_3N_4, MoS_2, and MoO_3 were also used to form such hybrids for SERS application (Sun et al. 2014, Tan et al. 2016).

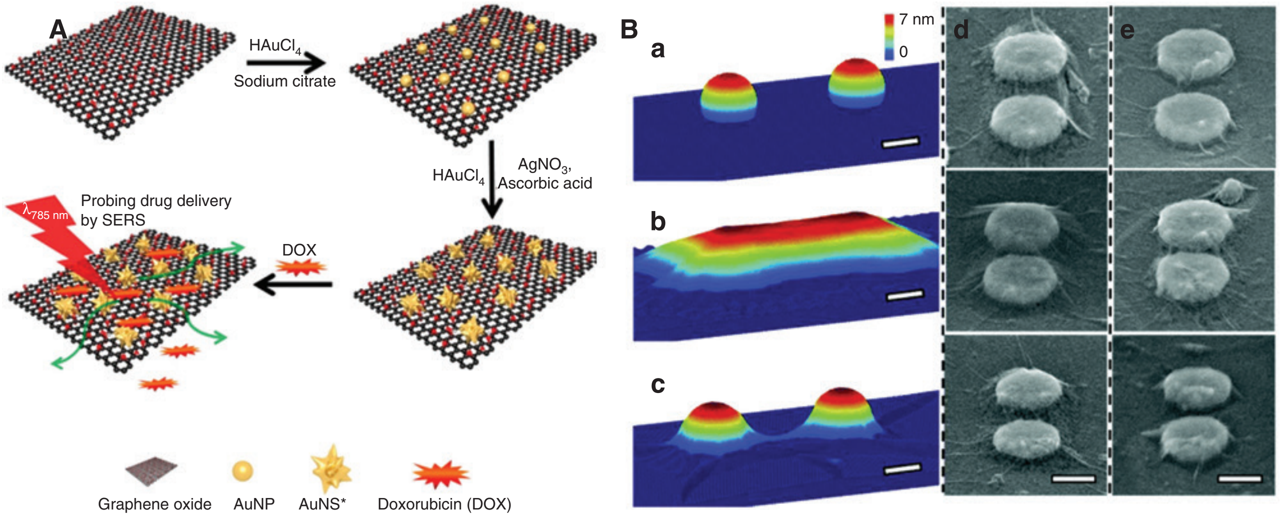

Figure 4: (A) Schematic illustration of the reduced graphene oxide-nanostar (rGO-NS) nanocomposite for drug delivery probed by SERS. Adapted from Wang et al. *ACS Appl. Mater. Interfaces* **2014c**, *6*, 21798–21805. Copyright © 2014 American Chemical Society. (B) (a–c) Molecular dynamics simulations of nanoparticles on the substrate, graphene wrinkles after wet transfer, and laser shock wrapped graphene, respectively. Adapted from Hu et al. *Nanoscale*, **2015**, *7*, 19885–19893, with permission from The Royal Society of Chemistry.

Because of the specific property of these 2-D materials, the complex transfer procedure and the relatively high cost are the primary limitations to the large-scale application, which requires the further development.

Planar structures by interfacial self-assembly

Self-assembly refers to those NPs or other discrete components that spontaneously organize into ordered and macroscopic structures (Grzelczak et al. 2010). It is a facile way to fabricate uniform structures with effective electromagnetic field coupling by making use of small particles as building blocks, at the same time, the obtained stable assembly structures are ready for using with good homogeneity. The self-assembly of NPs at the liquid-liquid interfaces has recently emerged as a promising strategy for 2-D structure fabrication for SERS application (Edel et al. 2013).

The dominating driving force for particle assembly at the interface is the reduction of interfacial energy, and the assembly is further controlled by lateral interface mediated capillary forces. By using self-assembly NPs at two immiscible phases, close-packed Au array was fabricated for multiphase trace analyte detection and reaction monitoring (typical assembly procedure is shown in Figure 5) (Zhang et al. 2014, 2015a). Such robust, self-healing, and reproducible structure could be controlled by modifying the NP functionality and changing pH or salt concentration, which makes this platform ideal for trace SERS detection (Cecchini et al. 2014). Au nanorods were commonly used as the building blocks for a 2-D array. The vertically aligned Au nanorods showed unique optical property and were successfully used for monitoring analytes at femtomolar concentration (Han et al. 2014). Wei and Ge 2013 showed that such array could even be constructed at air/water interface, which would be useful for gaseous state target observation. Similar strategy was applied to other types of NPs with suitable surface functionalization, such as Au-silica core-shell NPs, Au nanocrystals, Au@Ag nanorods, silver octahedral, and silver nanopetals among others (Ren et al. 2011d, Zhu et al. 2011, Su et al. 2012, Gómez-Graña et al. 2013, Lee et al. 2015). Obtained assembled structure showed excellent SERS enhancement compared with free NPs because of increased hot spots and stronger antenna effect (Zhu et al. 2011). Another advantage of the self-assembled structure at the interface is that it could be easily transferred or attached to other supported material, which would be used as functional, flexible substrate for facile sample gathering and detection (Lee et al. 2015). The weakness of poor stability of the obtained assembled structure even after it is transferred to another support is still a challenge for SERS application. At the same time, the development of an easy transfer procedure is necessary for the large-scale application.

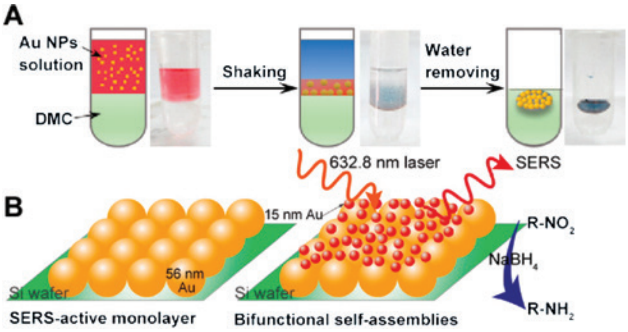

Figure 5: Schematic of the construction of hierarchically structured bifunctional Au nanoarrays via interfacial self-assembly for quantitative real-time SERS monitoring of the catalytic process. (A) The self-assembly process; (B) the SERS monitoring procedure for catalytic reaction. Reproduced from Zhang et al. *Anal. Chem.* **2015b**, *87*, 8702–8708. Copyright © 2014 American Chemical Society.

Planar structures by polymer-assisted assembly

Functional polymers could play a unique role in the assembly of NPs into planar structure because of, first, the various properties of candidate polymers such as molecular weight, chain length, hydrophilic, or hydrophobic property, resulting in designable assembled structure; second, the ease of functionalization of polymer onto the surface of NPs with special groups such as the –SH, $-NH_2$, or –COOH; and third, the controllable property of some stimuli-sensitive polymer used in the assembled structure in response to specific external stimulation (Mitomo et al. 2016). In the past decades, several polymer-assisted assemblies were proposed for SERS detection. A SERS sensor was constructed by drop-coating polystyrene-capped Au NPs on a glass surface, and the precise control of the packing density that directly relates to SERS performance could be realized with different polymer dosage (Yockell-Leliévre et al. 2015). Zhang et al. (2011) fabricated a wrinkled Au film by the thermal contraction of an underlying restrained polymer covered by Au NPs, and the wrinkled structure showed good performance for trace detection because of the abundant Raman-active nanogaps produced by deformation and fracture of Au ligaments. By using a photoresponsive polymer as the functional scaffold, a light-triggered reversible self-assembly Au oligomer was proposed with switchable plasmonic coupling for tunable SERS (Zhang et al. 2015b). These assembled structures could not only show SERS enhancement but also exhibit good homogeneity at the same time. However, with respect to specific targets, the effective capture is very important to realize trace detection; thus, a polymer with low interference to target absorption and with functional group that could act as scaffold for analytes is more suitable for the real application. For example, by the assembly of SERS-active nanocubes on a soft and optically semitransparent nanosheet, the polymer-based film could be conformably attached to different surfaces, which could serve as a versatile platform for real-world analytes identification (Lee et al. 2014a, Si et al. 2015).

Metal film over nanosphere (MFON)-based structures

The fabrication of complex structure on the patterned 2-D material is another effective way to obtain 2-D solid substrate. In 2002, Dick et al. (2002) developed the first strategy to form such ordered 2-D substrates, which was called MFON. By using monolayer nanosphere as a template, 2-D substrate with ordered nanoscale roughness could be obtained with good stability and reproducibility, at the same time, the morphology of the nanoscale structure could be easily controlled by the template structure. A hybrid plasmonic structure called particle-film plasmon on periodic Ag film (AgFON) was proposed with controllable particle-film gap distance; after decorating with Au NPs, further enhancement of 233 times was observed (Figure 6) (Lee et al. 2016). By using a flexible polymer as a support substrate, durable Au cap arrays have been synthesized with real-time tenability (Kang et al. 2013). MFON technology-based planar structures usually have the advantage of good SERS enhancement, good homogeneity, but it also suffers from the complex synthesis procedure and expensive equipment to form the metal film.

Planar substrates based on lithography or screen printing

The last decade observed the development of patterned 2-D materials, which could act as supports for obtaining planar SERS substrate. Evaporation or sputtering of metal is a straightforward technique to deposit SERS-active metals on to the designed structure. For example, oblique angle deposition could produce arrays of aligned silver nanorods with excellent SERS substrates (Chaney et al. 2005, Ingram et al. 2015). These techniques are good at forming SERS substrates with defined characteristics but have the disadvantages of the complex synthesis process, high cost, and requirement of specific instruments for the fabrication.

For a large-scale planar structure with controllable shape, size, and spacing, etching and lithography showed

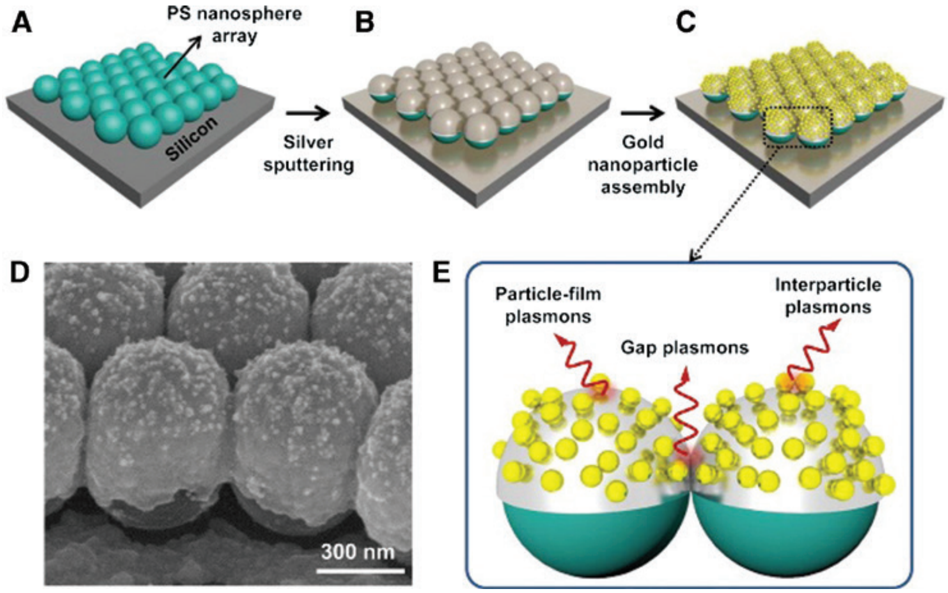

Figure 6: Fabrication procedures of AuNP-AgFON plasmonic systems. Reproduced from Lee et al. *ACS Appl. Mater. Interfaces* **2016,** *8*, 634–642. (A) Self-assembled 2D hexagonal arrays of polystyrene nanospheres on Si substrate, (B) deposition of Ag film by sputtering, and (C) electrostatic assembly of negatively charged Au nanoparticles on positively charged PDDA/AgFON surface. (D) SEM cross-sectional image of AuNP-AgFON-505. (E) Multiple field enhancements are generated from particle–film, interparticle, and crevice gap plasmon couplings. Copyright © 2015 American Chemical Society.

distinct advantages (Betz et al. 2014). Methods such as electron beam lithography, inkjet print, and screen printing have been successfully used in the fabrication of such structures (Qu et al. 2012, Wei and White 2013, Li et al. 2015). Among these techniques, the print-based methods showed unique benefits. For example, only common materials are needed, such as NPs (act as ink), inkjet printers, or screen printers. Moreover, the print pattern could be designed by a computer; by selecting a proper support (such as common papers), the obtained substrate could even replace upstream purification and concentration (Betz et al. 2014). The simplicity, low cost, and high homogeneity ensure its good prospect in large-scale use, but for the ongoing study, better enhancement and more precise control of nanoscale structure still require further efforts.

Paper and membrane-based planar substrates

Although most of SERS substrate-related study focused on fabricating a substrate with high enhancement, an important practical consideration in the fabrication of SERS substrates is the convenience of usage and efficiency of the sample collection and concentration. For example, in the case of explosive detection, which is inherently at a low vapor pressure, it is extremely difficult to collect particulates (few micrograms) with traditional NP-based substrate (Lee et al. 2010). In these cases, swabbing the suspected surface with the soft and flexible substrate is highly practical and efficient to collect the target for SERS observation. Paper or membrane-based planar substrate is appropriate and has already been successfully implemented (Yu et al. 2010, Lee et al. 2011).

Common filter paper could be used as a support for the fabrication of paper-metal NPs hybrid substrates. The obtained substrates were found to be highly sensitive, robust, and amiable for various analytes in different environments, and it was also cost-effective with high sample collection efficiency (Zhu et al. 2014). We performed membrane filter as a sample collector by hybrid magnetic NPs and Au NPs as a sensitive SERS method for the detection of bacterial (*Escherichia coli*) in ground beef (Cho et al. 2015a). Further improvement of paper-based SERS substrate is to integrate with advanced paper separation techniques, such as thin-layer chromatography (TLC) and lateral flow chromatography (LF). Such combination provides the ability of separation and concentration of analytes at the same time, which is very useful for multiplex detection. For example, the TLC-SERS method was performed for trace detection and on site reaction monitoring (Freye et al. 2013). Similarly, LF-SERS strip was used for separation, concentration, and detection of biomolecules (Cho et al. 2015b). Recently, a paper-based dipstick that enables the detection of food-borne pathogens was proposed by exploiting delayed fluid flow and channel partition formation on nitrocellulose membrane (Park et al. 2016). The weaknesses of poor control in NP distribution and the weak long-time stability still need consideration, and standard procedure is essential before large-scale application.

Two-dimensional superhydrophobic structures

SERS substrates capable of sensing highly diluted, small volume analytes is essential in trace toxins or biomolecules detection, but even with sensitive SERS method, such sample is still hard to detect because of the random spreading and dilution of analytes over the common hydrophilic substrate, especially for organic liquids with low surface tension. The 2-D superhydrophobic materials could overcome such limitation by concentrating analytes into a small volume. Inspired by this phenomenon, superhydrophobic substrates have been fabricated for both aqueous and organic trace target detection (Lee et al. 2013, Li et al. 2014). Recently, a universal platform that allows for the enrichment and delivery of targets into the SERS-sensitive sites was proposed for trace detection in both aqueous and nonaqueous fluids (Yang et al. 2016). The strategy to make use of superhydrophobic interaction can be extended to different structures and surfaces to further improve the applicability of SERS, from biomolecule detection to the monitoring of environmental pollutants.

Substrates with 3-D effective volume

Generally, the observed SERS signal is mainly attributed to the analytes within hot spots. The hot spots mentioned previously are obtained from gaps, sharp edges, or tips of NPs or in assembled planar substrates. In brief, these hot spots distributed in low-dimensional geometries are localized at a specific point or a single plane, whereas the laser confocal volume in SERS apparatus is a 3-D space, indicating that they have not fully realized the contribution from 3-D effective volume (Liu et al. 2015a). Fabrication strategies such as the assembly and template-based techniques can create substrates that confine the electric field within the entire region of the laser confocal volume, which is defined as the 3-D substrate, and the hot spots region that distributed in a 3-D manner was called 3-D effective volume (Stoerzinger et al. 2011). Within effective volume of the 3-D substrate, the greatest average field enhancement, maximizing the generation and collection of SERS signal, could provide stronger SERS response than the traditional low-dimensional substrates (Xu et al. 2000). On the other hand, for 3-D substrate, the incident laser need not be precisely focused on the confocal plane, which promotes the versatility of 3-D substrate for practical application combined with portable instruments. Hence, substrates with 3-D Raman effective volume provides a new mechanism to improve the SERS activity and to tailor the structures with large hot spot volumes (Stoerzinger et al. 2011).

Nanoscale 3-D structures

Advances in NPs fabrication and assembly technique have offered possibilities to tailor 3-D hot spots in a controllable manner. Nanofabricated pyramidal nanoshells were used to assemble into different particle configurations with 3-D effective volumes (Stoerzinger et al. 2010). The precise arrangement of Au nanopyramids into anisotropic shape allowed them to be organized into different particle configurations with 3-D Raman-active volumes, and the results also gave a direct proof of the contribution from 3-D space (Stoerzinger et al. 2011). By controlling the orientation of nanostructure, 3-D nanostar dimers with sub-10-nm gap were fabricated with the ability for single/few molecule detection (Chirumamilla et al. 2010). Effective volume with a depth of approximately 150 nm was observed within such 3-D nanostar dimer-based structures. Nanoscale 3-D substrate could be easily fabricated with bottom-up methods such as the template method and layer-by-layer assembly. For example, ordered sphere array was used as a template to construct 3-D nanoshell substrates yielding uniform SERS response (Rao et al. 2011). Chen et al. (2013) have aligned Ag nanowires into 3-D woodpile-like structures to achieve high-density hot spots in 3-D space. The layer-related SERS performance was observed because of an effective coupling of electromagnetic field between the different layer of Ag nanowires. Similarly, Au NPs were stacked up with the layer-by-layer technique to form a 3-D structure with suitable 2-D support provided by graphene oxide and MgAl layered double hydroxide (Figure 7) (Duan et al. 2015, Tian et al. 2015). Such strategy has also been applied in the fabrication of 3-D cross-point plasmonic nanoarchitectures containing dense hot spots with the help of solvent-assisted high-resolution nanotransfer printing (Jeong et al. 2016).

Low-dimensional structures could be applied as building blocks in the construction of 3-D structures. Both Ag and Au NPs have been assembled into 3-D superstructures

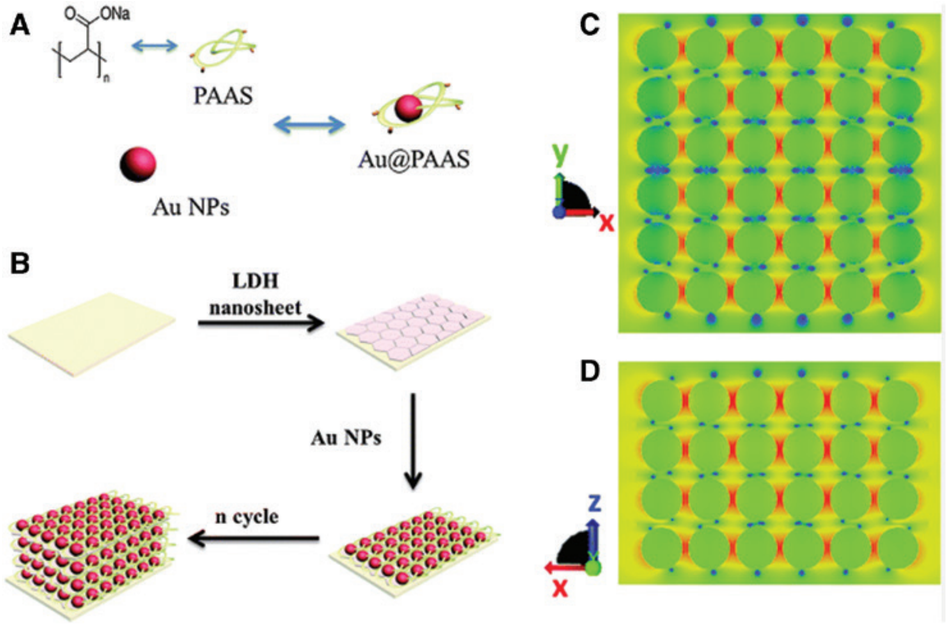

Figure 7: (A) Preparation of Au@PAAS precursor; (B) schematic representation of the assembly process; (C and D) finite-difference-time domain (FDTD) simulation in *x-y* and *x-z* planes. Reproduced from Tian et al. *J. Mater. Chem. C*, **2015**, *3*, 5167–5174, with permission from the Royal Society of Chemistry.

with excellent SERS performance (Urban et al. 2013, Yang et al. 2014b). Some functional molecules and materials such as DNA and viruslike particles were also induced for controllable assembly into 3-D substrates (Lee et al. 2009, Lebedev et al. 2016). For example, DNA-frame driven Ag 3-D pyramid networks were obtained based on a modification of designed DNA sequence for multiple disease biomarker detection (Xu et al. 2015b). In our former work, periodic and dynamic 3-D DNA-Au networks were fabricated to detect cancer stem cells based on cell surface marker monitoring (Lee et al. 2009). Three-dimensional and ordered hot spot matrix was obtained by an air-water interface assembly during the evaporation of a droplet of Ag sol on a fluorosilylated silicon wafer (Liu et al. 2014a). The trapping well for immobilizing particles in 3-D space can result in a large number of hot spots in a 3-D geometry, which could produce SERS enhancement at least two orders of magnitude larger than the random dried substrates. Such 3-D-assembled structure could also provide a structural basis for trapping molecules; thus, the detection capability could be further improved for various analytes.

Three-dimensional micro- and nanostructures

With specific 3-D materials as template or support, 3-D hybrid micro- and nanostructure could be easily fabricated. Compared with the low-dimensional substrate, the greatly increased surface area and the effective volume could contribute to better SERS activity. For example, cone-shaped ZnO nanorod array decorated with Ag NPs was used for trace detection (Xie et al. 2014). Similar strategies have been performed with different support structures such as TiO_2 nanorod array (Tan et al. 2012), aligned carbon nanotube (Lee et al. 2012), silicon nanowire array (Sun et al. 2015), metal-organic frameworks (Hu et al. 2014), and even bioscaffold array of cicada wings (Shao et al. 2014). Porous anodic aluminum oxide (AAO) could act as an excellent hard template for metal NPs for the fabrication of 3-D SERS substrates because of its controllable aperture morphology, and it is also easy to be removed, resulting in specific 3-D structure (Zhang et al. 2015c). Mesostructured polyoxometalate-silicatropic template has been obtained at the air-water interface and used as a template for in situ photoreduction to form Au NPs. The uniformly distributed Au NPs in 3-D silica channel showed good SERS performance (Lai et al. 2014). The construction of stable 3-D networks has also been realized directly on the inner walls of the microchannel. With the help of microfluidic enrichment and hot spots in the 3-D geometry, excellent SERS sensitivity has been observed for the trace detection of bovine serum albumin (Wang et al. 2014d). The 3-D support-based substrate showed good SERS performance because of dense hot spots in 3-D effective volume, and the structure is also suitable for analytes capture and concentration, whereas during the assembly of metal NPs, the uniform distribution of hot spots is very important to ensure the SERS homogeneity.

Polymer and hydrogel-based 3-D structures

Despite the above-mentioned hard support, soft support could also be applied to form 3-D substrates, such as polymer and flexible hydrogel. The advantage of flexible, compatible, and ease of use properties benefits their application in many specific areas. A facile way to use polymer as the support is the electrospinning technique. For example, Ag-nanosheet-grafted polyamide-nanofiber membrane have been synthesized as flexible 3-D SERS substrate with excellent signal reproducibility (Qian et al. 2014). Nanoporous polymer with bicontinuous nanochannels were used as a soft template for electroless plating of Au NPs. The resulting Au multibranches with tips and corners provided highly dense and uniformly distributed hot spots in a 3-D geometry (Figure 8A) Hsueh et al. 2014.

The free-standing hydrogel is also an excellent candidate as a 3-D support for metal NPs. In our former work, Ag NPs were fixed into the 3-D network of polyvinyl alcohol (PVA) hydrogel with in situ reduction procedure. Our observation confirmed a macroscale effective depth (up to ~100 μm) in such 3-D hydrogel (Figure 8B) (Ouyang et al. 2015a,b). Similarly, different hydrogels were used to form hydrogel-metal NPs hybrid structures for SERS detection, such as alginate gel (Bao et al. 2012), PVA dried gel (Yao et al. 2013), poly(dimethylsiloxane) (Wu et al. 2014), and bacterial cellulose hydrogel (Park et al. 2013). Functional metal NP hybrid with tunable plasmonic response could be obtained with stimuli-response hydrogel. For example, tunable plasmonic properties by both temperature and pH were obtained with Ag NP-decorated dual stimuli-reponse microgels (Liu et al. 2014b). The dependence of Raman signal enhancement on the gel strength has also been studied with a carrageenan-Ag gel (Fateixa et al. 2014). Similarly, in an Au/nanocellulose hydrogel, the pH-triggered molecular alignment was used for hot spots formation and SERS enhancement (Wei et al. 2015). For nondestructive measurement, the hydrogel-based substrate could act as a medium for the solvent mixture to confine its action in specific sampling area, and its

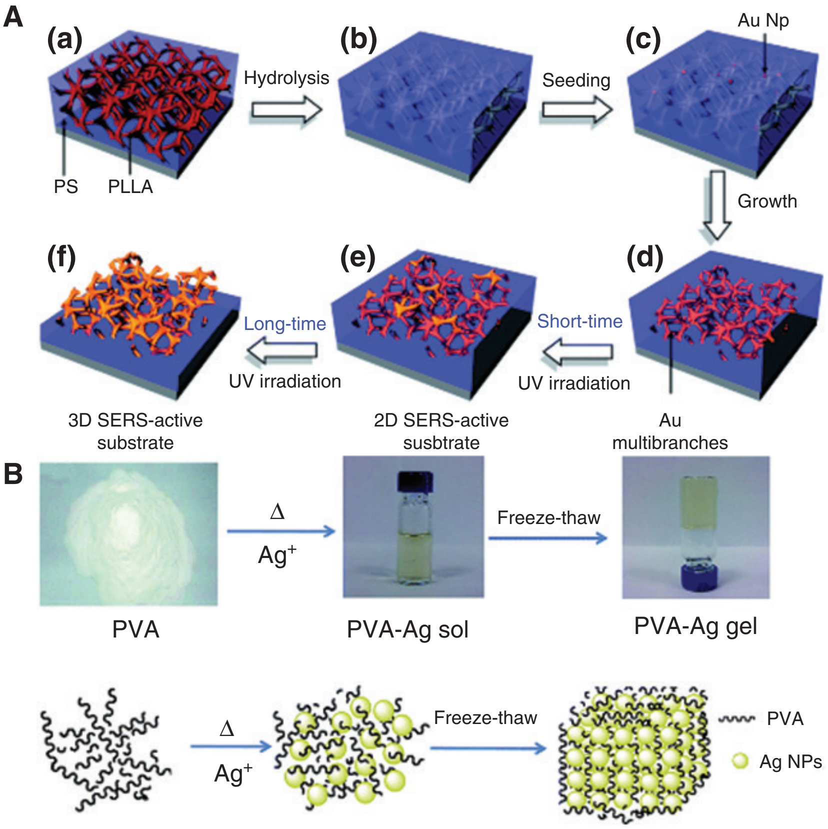

Figure 8: (A) Schematic illustration of the fabrication of a polymer-based substrate with protruded nanostructured Au from gyroid-structured air networks. Adapted from Hsueh et al. *J. Mater. Chem. C*, **2014**, *2*, 4667–4675, with permission from the Royal Society of Chemistry. (B) Preparation procedure of PVA-Ag hydrogel 3D substrate by an in situ reduction strategy. Adapted from Ouyang et al. *RSC Adv.*, **2015**, *5*, 2231–2238, with permission from the Royal Society of Chemistry.

free-standing structure is very convenient for SERS observation, especially with portable instruments for in situ or field detection (Leona et al. 2011). However, for such hybrid structure, the poor control in NP distribution and the poor selective capture ability still need more research.

Emulsion-based 3-D structures

Interface assembly is an effective strategy to form assembled structure, which could also find its own place in the fabrication of 3-D structures. For example, colloidosomes and Pickering emulsion are 3-D spherical microcapsules formed by the self-assembly of colloidal particles at an emulsion interface (Dinsmore et al. 2002). Such assembled structure has immense potential in SERS because of the following: (i) the close packing of the NPs enables intense electromagnetic fields facilitated by the incident LSPR of the plasmonic NPs, and (ii) it is stable in one phase while it holds another phase inside of it, which immensely benefits the quantification and identification of trace analytes in different phases common in industrial discharge and polluted water (Lee et al. 2014b).

In 2012, Au NPs coated with semifluorinated oligo(ethylene glycol) were developed to produce sub-100-nm NP vesicles without a template, and the resulting structures show good SERS performance (Niikura et al. 2012). The use of a SERS emulsion concept has also been attempted. For example, functionalized Ag cubes could be self-assembled into plasmonic liquid marbles and plasmonic colloidsomes and successfully used as 3-D platforms for multiphase sub-microliter toxin sensing (Figure 9A) (Lee et al. 2014b, Phan-Quang et al. 2015). A special Au-assembled colloidosome called black gold was fabricated with an emulsion-templating strategy. Such structure possesses hexagonal close-packed multilayer shells of Au NPs to promote stability and intense broadband absorption owing to the strong interparticle plasmonic coupling and exhibited excellent prospect in SERS application (Liu et al. 2015c). Surfactant and functional polymers could be used to control the hydrophilic property to assist in the assembly of metal NPs into emulsions

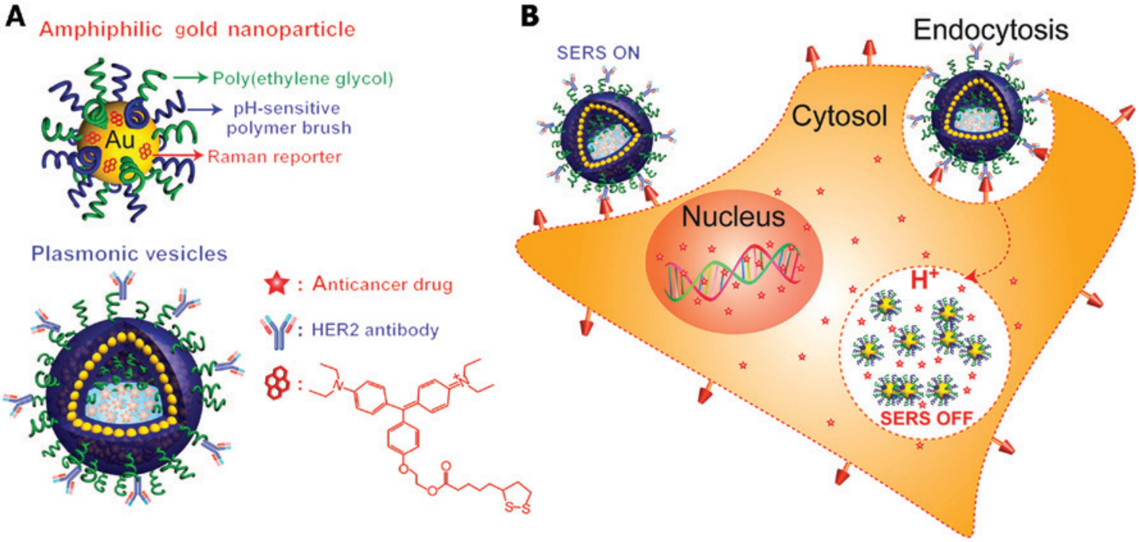

Figure 9: Schematic illustration of the amphiphilic gold nanoparticle assembled plasmonic vesicle for cancer cell targeting. Adapted from Song et al. *J. Am. Chem. Soc.* **2012**, *134*, 13458–13469. Copyright © 2014 American Chemical Society.

(Han et al. 2015, Ouyang et al. 2016). For example, Au NPs modified with mixed amphiphilic polymer brush were assembled into plasmonic vesicles for both SERS imaging and cancer-targeted drug delivery (Figure 9B) (Song et al. 2013). For the assembly of NPs into an emulsion, the basic driving force is the amphiphilicity driven interaction; thus, the design of suitable disperse phase and the building blocks with the suitable surface property are the key points. The emulsion-based 3-D substrates have wide applicability as miniaturized molecular sensing platforms because of their large surface area, excellent interfacial stability, and dense hot spot distribution. Although emulsion-based substrates show excellent prospect in SERS application, to date, the reported substrate is limited to certain solvents. These substrates have poor stability and their uncontrolled assembly state still needs to be researched.

Conclusion and future outlook

In this review, we focus on fabrication strategies of different SERS substrates with distinct structural properties. Their advantages, weaknesses, and comparisons are summarized as shown in Table 1. For the most widely used and studied NPs, which could be directly used as the substrate, their facile synthesis and ease of use make them good candidates for trace analyte detection and imaging. Because of limited reproducibility, the fabrication of solid state or assembled 2-D substrates was more favorable. Assembled 3-D substrates give rise to more confined hot spots as well as enhanced SERS performance. Of the reported substrates, each has its own characteristics, and more considerations should be given based on the real situation. For electromagnetic enhancement, NPs with sharp edges and corners were considered favorable. For hybrid or assembled structures, NPs fixed close to the supporting material were thought to increase the number of hot spots. Three-dimensional substrates with good SERS enhancement are excellent candidates for rapid detection combined with portable instruments, whereas emulsion-based 3-D substrates would be very useful in multiphase observation. Although significant improvements are possible in the synthesis of highly efficient plasmonic substrate. Challenges in the construction of stable, well-defined NPs and assembled structures require further research.

Although SERS activity is very important for trace analyte detection, the ability to obtain homogenous and reproducible results is also significant for quantitative detection. For accurate quantification by SERS, some internal standards could be used to reduce the signal variation because of the deviation of SERS activity during the detection process, thus yielding more reliable results. For practical application of SERS-based methods, especially in large-scale applications, more attention should be focused on the development of substrates that could be synthesized with a facile and low-cost method to provide good stability and to be convenient for frequent use. Furthermore, substrates that are compatible with hyperspectral and high-speed Raman imaging system are more favorable for the future applications.

Table 1: Summary of typical substrates mentioned in the text.

SERS substrate	Substrates classification-based structural properties	Superiority	Potential weaknesses and matters that need attention	Typical structures and references
Nanoparticles (NPs)	Metallic NPs (nanocrystals)	Easy synthesis and use; good enhancement activity	Low stability; low homogeneity; easy to aggregate; might have interference from shape-controlling or capping agent	Au NPs (Kwon et al. 2006), Ag NPs (Dadosh 2009), Au cubes (Sun et al. 2002), Ag plates (Zhang et al. 2013), polyhedral crystals (Liu et al. 2015b), nano-flowers (Xie et al. 2008), etc.
	Intracellular NPs	Convenient for *in situ* biological applications	Poor control particle shape, size; nonuniform distribution of particles and hotspots; limited enhancement activity	Intracellularly grown gold nanoislands (Ravindranath et al. 2011, 2012)
	Bimetallic or core-shell NPs	Combination of different materials to have better stability, biocompatibility, and enhancement effect; could have built-in tags as internal standards	Difficult to control the shell thickness and shell coverage on the core; low yield	Au@Ag core-shell NPs (Wang et al. 2014a), shell-isolated NPs (Li et al. 2010)
	Micro- and nanocomposites	Effective prevention of aggregation; easy to use or recycle; easy to obtain multifunctional structures	Difficulty in controlling the distribution and assembly state of the plasmonic NPs	Ag-graphene oxide (Ren et al. 2011c), TiO_2-Ag nanowires (Zhou et al. 2012), Fe_2O_3@Au nanoflowers (Huang et al. 2015b)
Planar substrates	Layered material-based substrates	Chemical enhancement; selective capture specific targets; large area homogeneity	Synthesis and transfer process is complex; high cost; poor control of NP distribution	Graphene-Au hybrid structure (Wang et al. 2013b), C_3N_4-Ag (Jiang et al. 2015), MoS_2-Au (Sun et al. 2014)
	Planar substrates by interfacial assembly	Uniform structures with effective electromagnetic field coupling; large area homogeneity; could be transferred or attached to other supported material	Poor stability; complex transfer process; poor control in the assembly state	Close-packed Au array (Edel et al. 2013), Au rod-based array (Cecchini et al. 2014)
	Polymer-assisted assembled structures	Controllable surface property leads to precise control of packing density; good homogeneity; specific stimuli response	Complex process for surface modification; interference from the target adsorption to the metal NPs	Polymer-Ag nanocomposite film (Zhang et al. 2011), light triggered reversible self-assembly Au oligomer array (Hariprasad et al. 2013)
	Planar substrates by MFONs	Large area ordered planar structure with good homogeneity and stability; morphology could be easily controlled	Complex synthesis procedure and needs expensive equipment to form the metal film	MFON (Dick et al. 2002), AgFON (Lee et al. 2016)
	Planar substrates based on lithography or screen printing	Easy to form SERS substrates with defined characteristics; convenient to realize large-scale production with good simplicity, low cost, and high homogeneity	Better enhancement and more precise control of nanoscale structure still difficult	Aligned Ag nanorods by oblique angle deposition (Chaney et al. 2005), Ag-coated polystyrene nanosphere (Ingram et al. 2015), and screen printed arrays (Qu et al. 2012)
	Paper/membrane-based substrates	Highly practical and efficient to collect analytes; cost-effective; ease of large area production; robust and amiable substrates	Poor controlling in NP distribution; weak long-time stability; standard fabrication and application procedure is needed	Membrane-assisted separation and detection (Cho et al. 2015a), TLC-SERS strip (Freye et al. 2013), LF-SERS strip (Cho et al. 2015b)
	Superhydrophobic substrates	Capable of sensing highly diluted, small volume analytes; have the ability to concentrate analytes into a small volume	Complex fabrication process; poor selective capture ability; limited detection targets	SLIPSERS (Yang et al. 2016)

Table 1 (continued)

SERS substrate	**Substrates classification-based structural properties**	**Superiority**	**Potential weaknesses and matters that need attention**	**Typical structures and references**
Three-dimensional substrate	Nanoscale 3-D substrates	Improved SERS enhancement; providing structural basis for trapping molecules	Limited 3-D volume; poor stability; poor homogeneity and large area reproducibility	Ag 3-D pyramid networks (Xu et al. 2015b), evaporation of a droplet of Ag sol (Liu et al. 2014a)
	3-D micro- and nanostructures	Greatly increased surface area; 3-D effective volume contributes to better SERS enhancement; suitable for analytes capture and concentration	Poor control in distribution of metal NPs; limited useful effective volume because of poor light transmittance	ZnO nanorod array decorated with Ag NPs (Park et al. 2015), aligned carbon nanotube (Lee et al. 2012), metal NPs decorated cicada wings (Shao et al. 2014)
	Polymer/hydrogel-based substrates	Flexible, compatible and ease of use; good platform for nondestructive measurement; convenient for observation combined with portable instruments	Poor control in NP distribution; poor selective capture ability	Au nanoparticles-modified alginate gel (Bao et al. 2012), PVA-Ag hydrogels (Ouyang et al. 2015a)
	Emulsion-based substrates	Close packing of the NPs enables intense electromagnetic fields coupling; suitable for trace analytes in different phases; convenient for interfacial observation	Poor stability under different conditions, poor control in assembly state, limited organic phases	Plasmonic liquid marbles (Lee et al. 2014b), black gold colloidsomes (Liu et al. 2015c), CD-Ag emulsions (Ouyang et al. 2016)

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