Smart design of high-performance surface-enhanced Raman scattering substrates

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Abstract
Surface-enhanced Raman scattering (SERS) spectroscopy has renowned its fame for the ultra-high sensitivity and single-molecule detection ability, and listed as a fingerprint spectrum representative in various trace detection fields. Considerable efforts have been made by researchers to design high-sensitive SERS-active substrates ranging from noble metals to semiconductors. This review summarizes the fundamental theories for SERS technique, that is, the electromagnetic enhancement mechanism and chemical enhancement mechanism and the state-of-the-art design strategies for noble metal and semiconductor substrates. It also sheds light on the effective approaches to improve the SERS activity for noble metal substrates, that is, tuning the localized surface plasmon resonance position, the assembling of hot spots, and precise controlling of nanogaps. Although charge transfer is considered as the main reason for the enhancement mechanism for semiconductors at the present stage, the underlying theoretical basis remains mysterious. This review summarized the critical points for SERS-active substrates design and prospected the future development direction of SERS technology.

Keywords
applications, enhancement mechanisms, SERS-active nanomaterials, smart substrate design

1 | INTRODUCTION

1.1 | History and developments of SERS

Raman effect is a kind of scattering spectrum originating from the interaction between the incident laser and the recipient molecules, which is discovered by an Indian physicist named C. V. Raman in 1928.¹ In the Raman spectrum, molecular structure information about molecular vibrational energy level and rotational energy level can be easily obtained.²–⁵ The position, intensity, shape, and the half-height width of the Raman peak are all important

Abbreviations: AAN, AuNC-AuNP nanostructure; BBD, boron-doped diamond; DFT, density functional theory; EBL, electron-beam lithography; EF, Fermi energy; EF, enhancement factor; EM, electromagnetic; FDTD, finite-difference time-domain; HAuNF, hollow gold nanoflower; HOMO, highest occupied molecular orbital; HPWN, hexagon plum-blossom-like WO³⁻ₓ nanoarrays; h-BN, hexagonal boron nitride; LOD, limit of detection; LSPR, localized surface plasma resonance; LUMO, lowest unoccupied molecular orbital; PICT, photo-induced charge transfer; SERS, surface-enhanced Raman scattering; ZIF-8, zeolitic imidazolate-based metal–organic frameworks.

Xiangyu Meng and Lin Qiu are co-first authors and contributed equally to this study.

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information for identifying chemical bonds, functional groups, crystallinity, and strain. However, the intensity of Raman scattering is only $10^{-10}$ of the incident light intensity, which leads to the sluggish development in a few decades after its discovery. Regarding this, scientists have been exploring effective strategies to amplify the Raman signal. A milestone occurs in 1974, when Fleischmann et al. obtained high-performance Raman spectra of a monolayer pyridine molecule adsorbed on a rough surface, which is amplified by $10^6$ compared with that of solution-phase pyridine. This is the first time that people validate the intensity of Raman scattering can be experimentally boosted to a range available for usage. Since then, a lot of work has been done in this study direction. This surface enhancement effect is related to the rough surface and is called the surface-enhanced Raman spectrum (SERS). As a fast detection technology, SERS presents many advantages, such as no photobleaching and self-quenching, avoiding mutual interference among multiple species in a complex system, realizing non-destructive detection. In addition, it is easy to prepare samples, solid samples can be tested directly, and liquid samples can be dropped on the surface of the silicon wafer for testing. SERS technology has been wildly used in many fields, such as trace detection, biological sensing, situ analytical chemistry, and electrochemical.

1.2 Enhancement mechanism

The enhancement mechanism of SERS is relatively complex and experiences a long-time development and upgrade. Researchers have found that the geometric features, the electron structures, the interaction between the light and rough surface, and the incident light features (the direction, intensity, frequency, and polarization) all have important influences on the resultant Raman signals. According to the classical electromagnetic field theory, the Raman intensity is proportional to the square of the induced dipole moment $P$:

$$P = \alpha \times E$$

where $E$ denotes the electric field intensity of incident light, $\alpha$ is molecular polarizability tensor. Hence, the mechanism of Raman enhancement is related to two factors, that is, $E$ related physical enhancements and $\alpha$ related chemical enhancement (CM).

1.2.1 Physical enhancement

When irradiated by light wave with a frequency of $\omega_0$, the surface plasma of the nanoscale substrate will couple with the light wave to form a near-field electromagnetic wave propagating along the metal surface. Plasma nanoparticles act as optical receivers to transform the far-field light energy into near-field electromagnetic energy, which can adjust the local electromagnetic field intensity. The electromagnetic (EM) field will be amplified when the frequency of the incident light coupling with the collective oscillation of electrons. Generally, the collective oscillation of noble metal is located at the visible region, which can couple well with the incident laser. As a result, the electromagnetic field at the surface of noble metal (Au, Ag, and Cu) can be amplified by $10^2$–$10^5$ folds due to the localized surface plasma resonance (LSPR). The enhancement factors (EFs) are proportional to the fourth power of EM field. The enhancement range of electromagnetic field can extend to hundreds of nanometers beyond the substrate surface, and thus the physical enhancement mechanism is a long-range effective enhancement effect.

1.2.2 Chemical enhancement mechanism

The CM mechanism is put forward to resolve difficult problems which cannot be well explained by physical enhancement mechanism in the early stage. CM focuses on the changes in electron density caused by the interaction between substrate and adsorbed molecules, which enlarges the molecular polarizability and scattering cross-section. Generally, the EFs of CM are around $10^{-3}$–$10^{-4}$ folds. There are three widely accepted models for the CM: (1) nonresonant enhancement, that is charge transfer through the chemical bonds between the substrate and absorbed molecule; (2) resonance enhancement, that is the new complex produced by the substrate can induce resonance with the absorbed molecule under excitations; (3) photo-induced charge transfer (PICT), that is charge transfer between the excited state or ground state of substrate and molecule. In the above-mentioned three models, the PICT mechanism is the most common and recognized and thus is regarded as the main reason for CM.

Recently, many reviews on SERS substrate materials have been published. Compared with the above reviews, this study pays more attention to the design of substrate materials, that is, tuning the localized surface plasmon resonance position, assembling of nanoparticles, precise controlling of nanogaps. And it introduces the development of SERS substrate materials from noble metals to semiconductors more comprehensively. Especially for the introduction of amorphous SERS substrates, it is proposed that the late-model of
amorphous-noble metal composite substrate has great development potential. This review presents a more comprehensive and systematic design strategy of SERS substrate materials.

2 | SMART DESIGN OF NOBLE METAL SUBSTRATES

LSPR is the main reason for electromagnetic field enhancement of noble metal substrates. The charge will be concentrated at the sharp tips, edges, or corners due to the lightning rod effect, leading to strong LSPR at local positions. Therefore, nanostructures with abundant sharp tips or corners are considered to be excellent SERS-active substrates. In addition, hot spots in the nanogaps between nanoparticles in nanometer or even sub-nanometer size can also magnify EM field excellently. However, the space occupancy per unit area for hot spots is often low due to the random distribution of hot spots on the SERS substrate. Hence, only part of the analytes can be truly accounted for. Therefore, adjusting the morphology of the substrate and constructing of uniform hot spots are two urgent issues to improve the SERS activity of noble metal substrates.

2.1 | Nanoparticles with sharp tips and corners

Simple spherical morphology is the most widely used nanoparticle which shows a moderate Raman signal enhancement due to its high symmetry. According to the simulated theoretically by finite-difference time-domain (FDTD), nanoparticles with sharp tips or corners are more conducive to amplifying EM field. Various methods have been applied to fabricate branched nanostructures, such as colloidal synthesis, electrochemical deposition method, reactive ion etching, and electron-beam lithography (EBL). In addition, the LSPR of different anisotropic Au nanoparticles can be tuned from visible light to the NIR region by adjusting the size, shape, and radius of curvature. In recent years, various morphologies with sharp tips are designed to achieve sensitive SERS-active substrates, such as nanoflowers, nanostar, bowtie, dendritic, nanotriangles, and hedgehog. Nanoflowers is a specialized nanostructure with abundant branches and sharp edges on the surface. These sharp tips servers as hot spots and generates strong LSPR, which provide excellent SERS activity. And the high surface-area-to-volume ratios of nanoflowers are beneficial for surface modification and drug loading. A novel drug nanosystem is prepared based on Au nanoflowers (AuNFs), which...
presents great potential for in-vivo treatment and imaging. Therefore, the preparation of nanoflowers with high SERS activity has aroused the interest of researchers. For example, Ye et al. synthesized the hollow gold nanoflowers (HAuNFs) using an auto-degradable nanofiber as a bifunctional template, which consists of an open hollow channel in the center and multiple branches/tips on the outer surface (Figure 1A). The nanofiber in the center is used as a threading template to promote the anisotropic growth of Au nanoparticles. In the conventional template synthesis, the products will inherit the shape of the template, but the nanoflowers structure present geometry and dimensionality which is distinct from the template. The single-particle SERS intensity of these HAuNFs is about 40 times higher than the similar-sized solid Au nanospheres, which is ascribed by the sharp edges, open cavity, and high-index facet of HAuNFs.

Nanostar is a kind of anisotropic nanoparticle with a central core and many protruding tips, which has attracted many interests from researchers. The LSPR of gold nanostar can be easily adjusted to the near-infrared region with good catalytic and photothermal performance. Nehra et al. prepared Au nanoparticles with different shapes (decahedral, hexagonal, triangular, and star) by a single-step method, in which only two chemicals (PVP and a gold pre-cursor) are used in different solvents. The tip sharpness of nanostar can be increased by changing the PH of the reaction medium, typically realized by adding NaOH solution. The influence of the tip number and the tip-to-core ratio on the SERS activity are discussed in detail, in which the number and sharpness of tips increased with increasing the concentration of NaOH, and the absorption peak shift from visible to the NIR region gradually. The EFs of nanostar is higher than decahedral, hexagonal, triangular due to its abundant sharp tips. Furthermore, the SERS activity is enhanced with the increasing number of tips. In addition, the EFs of BK8 are higher than others due to the higher number of tips (6) compared to BK4 (4) and BK7 (3). In 2017, Toma and his coworkers proposed the 3D Au-Ag bimetallic plasmonic nanostructures with multiple branches based on the EBL and RIE techniques (Figure 1B). The interparticle spacing is fixed at 200 nm to avoid strong near-field coupling between the individual nanostar. To investigate the effect of topology on the plasmon resonances, the number of nanostars is changed from 4 to 10. With increasing the number of nanostars tips, the SERS intensity increased monotonously due to the corresponding increase of hot spots density. Therefore, the number and sharpness of tips have a great influence on the SERS activity. In addition, Lee and Yoon proposed that the curvature radius of the sharp tips or corners also affects the position of the LSPR, which is proved by the FDTD simulations for Au nanocube-nanosphere dimers. Generally, the LSPR band

FIGURE 2 Different nanostructures with ship tips or corners. (A) Bowtie. Reproduced with permission: Copyright 2018, Wiley. (B) Dendritic. Reproduced with permission: Copyright 2019, Wiley. (C) Nanocaps and nanotriangles. Reproduced with permission: Copyright 2017, American Chemical Society. (D) Hedgehog. Reproduced with permission: Copyright 2018, American Chemical Society.
of nanocube redshifts as the corner sharpens due to that
the sharp corners of the nanocube facilitate the charge
separation and reduce the restoring force for the plasmon
oscillation, which decreases the resonance frequency.

Other nanostructures with sharp tips, edges, or cor-
ners are designed to improve the SERS activity, such as
bowtie, dendritic, nanocaps, nanotriangles, and
nanoprisms, and hedgehog (Figure 2A–D). Although
these nanoparticles with various morphologies effectively
enhance the local electromagnetic field, the nonuniform
distribution of nanoparticles will lead to uneven and
unstable SERS signals. In addition, the enhancement
from the sharp tips or corners is limited by the size of the
tips and the state of electron aggregation, therefore, it is
difficult for practical application.

2.2 Self-assemble of nanoparticles

The SERS activity can be effectively enhanced by con-
structing nanogaps on or inside the metal nanostructures.
The simplest nanogap is the interparticle nanogaps, pro-
duced from the coupled nanostructures, such as the nano-
particle dimers, oligomers, and nanoparticle arrays.
However, the distribution of nanogaps is usually random
due to the random aggregation of nanoparticles. Fabrication
of ordered structures is an effective way to form uniform
interparticle nanogaps. Another kind of nanogap is the
particle-substrate nanogap forming by the metal nano-
particles and the surface of the substrate which are usually
dielectric. It has been proved that the EM field in the
nanocube-surface nanogap is stronger than that in the
nanosphere-surface nanogap due to the sharp corner of na-
ocube. It is well known that the EM field enhancement
in nanogaps is more strong than that of a single particle,
and the size of nanogap has a great influence on the elec-
 tromagnetic field enhancement. The EM field will be ampli-
fied at the nanogap between nanoparticles, which are
usually called “hot spots.” The interstitial hot spots in the
dimer have been studied in detail, such as nanorod dimer,
nanosphere dimer, and nanocube dimer. Gold nanorods
are anisotropic nanoparticles that exhibit two different
plasma oscillations: one along the short axis (transverse os-
cillations) and the other along the long axis (longitudinal
oscillations). Each oscillation has its own specific LSPR band
and is related to the aspect ratio of the nanorods. The Raman
signal at the junction of gold nanorod dimer is stronger than
that at the edge due to the stronger EM field at the junc-
tion. The optical properties of side-by-side, end-to-end, and
end-to-side gold nanorod dimers have been investigated
(Figure 3A). First, in the side-to-side and end-to-side
assembly, the extinction of the initial transverse LSPR band
increases, and the band slightly red shifts to higher
wavelengths, while the extinction of the longitudinal band
decreases and blue shifts to lower wavelengths, thus result-
ing in the convergence of the two bands. However, in end-to-
end assembly, the bands behave quite differently, in which
neither the transverse nor the longitudinal band shifts. But
the extinction of the longitudinal band significantly de-
creases as the total average length of the GNR chain in-
creases. As a result, a third plasmon band appears at the
longer wavelengths and shift to longer wavelengths as the
GNR chain length increases. It has been shown that the end-
to-end assembly of GNRs produces a strong SERS template
and can be used in biosensing and contaminant detection.

The ordered 2D array consisting of plasma nano-
particles will introduce plasma coupling between adja-
cent nanoparticles, resulting in a strong and consistent
enhancement of the electromagnetic field over a func-
tional area of up to centimeters. The preparation of 2D
SERS substrates is usually by modifying noble metal
nanoparticles onto plane substrates. The wavelength of
LSPR can be adjusted according to the thickness and
surface morphology of the substrate. Self-assembly of
nanoparticles is a common method for preparing 2D
nanomaterials. The large-scale self-assembly of 6 nm-
diameter AgNPs can be applied to achieve highly en-
hanced and uniform Raman measurements over a large
area (>1 cm²; Figure 3B). The 2D hexagonal close-
packed superlattices of Ag nanoparticles formed in these
films allow for SERS detection over a large area with
excellent uniformity and high EFs. Ag array assembled
by Ag nanoparticles or nanowire also present excellent
SERS activity. Using graphene to isolate nanowire
arrays can not only effectively control the distance be-
tween nanowires, but also enhance the stability of the
materials. A better SERS enhancement can be obtained
between the graphene layer and the assembled Ag array
through electromagnetic coupling and chemical en-
hancement (Figure 3C). Bioinspired array consists of
regular Si micropyramids and regular Ag nanobowls is
designed to provide ordered light trapping SERS
substrate (Figure 3D).

The self-assembly 3D Au/Ag structure could improve
the SERS activity by increasing a large number of hot
spots. Tian et al. evaporated a droplet of citrate-Ag
sols on a fluorosilicate silicon wafer, and a large number
of hot spots in 3D space were produced during the eva-
poration process (Figure 3E). With the evaporation of
water, the space between particles in the droplet gradu-
ally shrinks until the particles are evenly deposited on
the surface, and finally it is easy to obtain the 3D hot
spots matrix. The interaction between particles generates
a “trap” through van der Waals gravity and electrostatic
repulsion, which can fix particles in 3D space and gen-
erate a large number of hot spots. Through theoretical
calculation, the adhesive force between Ag nanoparticles is greater than gravity, so the 3D structure can be maintained in the evaporation process. The limit of detection (LOD) for R6G is 0.05 amol which is more sensitive than the dried sample, indicating that the SERS activity of the 3D Ag sols on the fluorosilylated silicon wafer is better than the dried Ag nanoparticles. However, there are two disadvantages, one is that the SERS signals are not stable in the solution and rapidly decrease after the complete evaporation of water, the other is that the charge transfer between Ag nanoparticles weakens the electromagnetic field. To tackle these issues, Tian et al. improved the technology by adding aqueous glycerol to slow the evaporation process, and ultrathin SiO2 shells were used to prevent charge transfer (Figure 3F).53

As a result, the uniformity and stability of SERS activity are improved remarkably with increasing the evaporation time. The LOD for 4-MBA is up to $10^{-8}$ mol/L, suggesting that this 3D hotspots platform has great potential in plasmon-enhanced linear and nonlinear spectroscopy, as well as for practical sensor applications. Superlattice is highly ordered 3D assemblies of nanocrystals or nanoparticles, which may still maintain the inherent characteristics of their structural units, or may exhibit unique collective characteristics derived from the coupling effect between particles. Its optical properties are related to the arrangement, composition, and direction of nanoparticles. The basic principles and design rules of optimal spatial distribution are introduced in detail by García-Lojo.16,54
Hybrid nanostructures are considered as composed of at least two distinct materials, one of which must be a SERS active metal with a nanometer size, and the other to protect, support, or stabilize. The integration of inorganic nanoparticles within metal–organic frameworks (MOFs), paper, polymers, or SiO$_2$ offers the opportunity of creating multifunctional materials with novel or enhanced properties. To enhance the stability of the Au nanoparticles, some composite structures integrated by Au nanoparticles and various kinds of solid supports are designed (Figure 4A). As a typical example, Liz-Marzán’s group realized the detection and imaging of quorum sensing in Pseudomonas aeruginosa biofilm communities by three kinds of cell-compatible plasmonic platforms. One is the porous macroporous poly-N-isopropylacrylamide hydrogels loaded with Au nanorods (Au@pNIPAM), which can enhance diffusivity effectively and lead to a more homogeneous plasmonic detection of pyocyanin. Hydrogels play a supporting role and allow the proliferation of biofilms and homogeneous SERS sensing of the secreted phenazine across the substrate. The second is mesostructured Au@TiO$_2$ substrates obtained by covering the mesoporous TiO$_2$ thin film on the Au submonolayer, which can expand the detection range to millimeter-scale areas (20–50 μm). The third is mesoporous silica-coated micropatterned supercrystal arrays of Au nanorods made enabled plasmonic detection at early stages of biofilm formation and allowed imaging of the phenazine. These hybrid nanostructures not only provide advanced detection tools for probing important questions in quorum sensing, but can also serve for the investigation of other cellular communication processes based on SERS-active diffusible molecules. In addition, different methods have been proposed to encapsulate metal nanoparticles in MOFs, such as liquid/gas phase infiltration, in which MOF is exposed to a metal precursor and then diffused into the nanopores, and is subsequently reduced or decomposed into corresponding metal nanoparticles. However, this impregnation approach cannot precisely control the shape, size, and composition of the nanoparticles. Zheng et al. reported a convenient method to encapsulate metal nanoparticles within zeolitic imidazolate-based metal–organic frameworks (ZIF-8) without affecting its crystal structure by tuning the concentration of quaternary ammonium surfactant on the surface of metal nanoparticles. The hydrophobic hydrocarbon chains of quaternary ammonium surfactant molecules adsorbed on the metal surface can easily recombine with MOF crystals, thereby inducing the nucleation, adsorption, and further growth of zolate frameworks on the metal surface.

The recycling and reuse of SERS substrate have important economic benefits, which can be achieved through the composite of metal nanoparticles and magnetic materials. The incorporation of magnetic functionality into SERS-active nanomaterials has been demonstrated by synthesizing various core-shell nanostructures. For example, Fe$_3$O$_4$@Au nanostar has been applied to effectively magnetic separate histidine-tagged maltose-binding protein from a crude cell extract. Chang et al. reported the Fe$_3$O$_4$@SiO$_2$/Ag and Fe$_3$O$_4$/Ag@SiO$_2$ composite SERS nanoparticle substrates, which are }

**FIGURE 4** Schematic representation of hybrid nanostructures. (A) Metal nanoparticles embedded with different supports. (B) Magnetic Fe$_3$O$_4$@SiO$_2$/Ag nanoparticles. Reproduced with permission: Copyright 2018 American Chemical Society.
consisted of magnetic cores encapsulated with silica shell and satellite silver nanoparticles (Figure 4B). In the Fe₃O₄@SiO₂/Ag composite nanostructure, the magnetic force-induced aggregation can realize the SERS detection of low-concentration flow tracer analytes, thereby improving the possible application of this method for online continuous trace detection. In the Fe₃O₄/Ag@SiO₂ system, SERS active organic dyes are embedded into the nanoparticles during the synthesis process, each composite nanoparticle has SERS activity, and the detectability can be improved by magnetic control. In both cases, in-flow detection was realized by using a microfluidic approach combined with magnetic field concentration to improve detection sensitivity.

2.4 Precise controlling of nanogaps

Aggregation of metal nanoparticles is an effective method to improve SERS activity by generating more hot spots. However, the contributions of gap size and the molecule number are competitive when the gap width is comparable with the target molecule size, leading to oscillating behavior of SERS intensity with the gap size. Therefore, the size and position of the interparticle gap should be controlled carefully. Several strategies have been proposed to control the distance between particles, such as polymer/gel-induced aggregation, DNA/aptamer-directed dimer, applying strain to an elastic material, and loading nanoparticles on shape memory polymers. Metal nanoparticles can be loaded onto the substrate material with adjustable shapes, and the position of hot spots can be controlled by adjusting the shapes of the substrate. The gap size between Ag nanoparticles can be controlled with the shrinkage of PVC substrate (Figure 5A). Sun et al. proposed the plasmonic vesicles by grouping gold nanoparticles on a thermally responsive homopolymer vesicle membrane, in which the distance between individual gold nanoparticles changed with the temperature. The plasma vesicles were expanded with the increasing temperature, as a result, the distance between the gold nanoparticles on the vesicles was decreasing, which leads to the red shift of the LSPR peak. Therefore, the size and density of hot spots can be controlled by the temperature easily. Later, the visual control of hot spots is achieved under the optical tweezers-coupled Raman microscope by approaching two Ag-coated SiO₂ nanoparticles (Figure 5B), which can be used to characterize the protein structures and conformational fluctuations at physiological concentration. The relationship between the gap size and the SERS activity has also been studied extensively. With the distance between these two beads reduces from 30 nm to zero, the SERS activity is evidently enhanced, indicating that the interparticle gap can be precisely controlled. When the interparticle gap is zero, the maximal SERS activity is achieved, and the LOD for RhB is 10⁻¹¹ mol/L.

DNA origami nanostructures are formed from a long single-stranded scaffold strand and a suitable set of short artificial staple strands, by which the nanogap between nanoparticles can be regulated precisely. Recently, Wang et al. designed the stereo-controlled AuNC-AuNP
nanostructures (AANs) by transferring the essential DNA strands with predefined sequences and positions to the surface of AuNCs (Figure 6A). Different geometries are generated by controlling the predefined sequences on the surface of nanoparticles. The Raman signals of on-vertex and on-edge AANs are similar, which are stronger than the on-face AANs due to the stronger plasmon coupling between the sharp curvature of AuNCs at the vertices and edges and round AuNP surface. This DNA origami-based nanoprinting strategy can be extended to 3D structures, for manufacturing specific functionalized AuNCs. Simoncelli et al. proposed that the optothermal-induced shrinking of a DNA origami template can adjust the gap size between two AuNPs from 1 to 2 nm (Figure 6B). The gap size decreased from 3.3 to 1.3 nm after laser heating, leading to the 2 orders of magnitude enhancement in the Raman scattering signal due to the strong enhancement of EM in the nanoparticle hot spot. Moeinian et al. designed the single silicon nanowires decorated with DNA origami-based SERS probe by attaching four oligonucleotide-functionalized AuNPs to the complementary single-stranded extensions (binding sites) on six-helix bundle (6-HB) DNA origami nanotubes (Figure 6C). The AuNPs are accurately attached to the predefined binding sites on 6-HB DNA origami, from which the interparticle distance can be adjusted. Then, the negatively charged DNA origami is absorbed on the positively charged poly (L-lysine) functionalized SiNW surface. The interparticle gap between AuNPs is 2 nm, which contributes to a strong EM enhancement. In addition, the interparticle distance between nanoparticles can be adjusted continuously by the optothermal tuning of DNA origami. Quantitative analysis of molecules in a hot spot with fixed numbers and positions remains challenging. Fang et al. achieved the precisely localized of single dye molecules by DNA origami metatomolecules with Fano resonances. The number and position of adsorbed molecules can be controlled by hybridizing tagged DNA strands. The Raman intensity increased with increasing the number of ROX (carboxy-X-rhodamine) molecules first, and then tends to be plateau, however, the single ROX molecules lead to the maximal EFs. Sensing of single small molecules is achieved by the versatile DNA origami nanofork antenna structure, in which the gap size between Au/Ag nanoparticles can be controlled by DNA origami nanostructures. Small molecules can be accurately located in the hot spot zone, and even the gap size can be adjusted to accommodate differently sized molecules.

In this section, the design of noble metal SERS-active substrates based on EM is mainly summarized, including LSPR, hot spots engineering, and regulation of nanogaps.

Figure 6  Scheme of DNA origami nanostructures. (A) AANs at different gap morphology. Reproduced with permission: Copyright 2021, Wiley. (B) Laser-induced gap size shrinkage and gap size-dependent Raman enhancement. Reproduced with permission: Copyright 2016, American Chemical Society. (C) Representation of a DNA origami-based SERS probe decorated single SiNW. Reproduced with permission: Copyright 2019, American Chemical Society. AAN, AuNC-AuNP nanostructure; SERS, surface-enhanced Raman scattering.
On one hand, the sharp tips or corners can produce a stronger electric field than the nanosphere due to the lightning rod effect. Various morphology structures are designed to generate stronger LSPR. On the other hand, the hot spots between the nanoparticles will induce excellent EM enhancement. Dimer and self-assembly nanostructure with abundant and uniform hot spots have been proved to be beneficial for improving the SERS activity. In addition, the size and position of nanogaps also have an important effect on the electric field. Finally, the self-assembly of nanoparticles and regulation of hot spots are the research emphases for the development of new SERS substrate materials.

3 | SMART DESIGN OF SEMICONDUCTOR SUBSTRATES

Although noble metal substrates present excellent SERS activity, the EM enhancement has no selectivity because it is a long-range effective enhancement. Semiconductors present novel surface properties, diversity of active substrates, and controllable photo-electrical properties due to its adjustable bandgap. Therefore, it is of great significance to develop semiconductor substrates with high sensitivity and spectral stability. As mentioned above, charge transfer is considered as the main reason for the enhancement of semiconductors, which is first put forward by Gersten et al. Later, it is verified by Dumuth through the high-resolution electron energy loss spectrum of Pyridine molecules absorbed on the Ag nanoparticles. According to the resonance Raman theory, Albrecht proposes that the charge transfer process is caused by three terms, and the polarizability tensor can be described as \( \alpha = A + B + C \). In the metal-molecule system, \( A \) is the contribution of the totally symmetric modes conforming to the Franck–Condon selection rules, \( B/C \) represent the asymmetric vibration mode of the vibronic coupling between the excited/ground electron state of molecule and other excited electron state, which is attributed to the Herzberg–Teller rotational coupling (Figure 7A). The molecule will couple with the metal when the metal state is located around the Fermi energy \( (E_F) \), and the charge transfer is maximized by borrowing energy from two kinds of molecular transition \( (\mu_{K}) \): the molecule-to-metal transition \( (\mu_{EM}) \) through the Herzberg–Teller coupling term \( h_{MK} \) and the metal-to-molecule transition \( (\mu_{MK}) \) through the Herzberg–Teller coupling term \( h_{IM} \). For the molecule–semiconductor systems, Lombardi attributed \( B \) term to the charge transfer from molecule to semiconductor, and \( C \) term to the charge transfer from semiconductor to molecule. The Fermi energy is replaced by a band gap of conduction band edge and valence band edge (Figure 7B), thus the charge transfer can borrow intensity from four kinds of transitions: Molecular transitions \( (\mu_{KI}) \) through the Herzberg–Teller constant \( (h_{CK}) \) or \( (h_{VI}) \), exciton resonance \( (\mu_{VC}) \) through the Herzberg–Teller constant \( (h_{VI}) \) or \( (h_{CK}) \). The resonant of semiconductor–molecular system is complex, but the relative intensities of the Raman spectra are governed by strict selection rules.

3.1 | Quantitative description of CT

In many cases, such as transition metal oxide materials \( \text{Nb}_2\text{O}_5 \) and \( \text{W}_{18}\text{O}_{49} \), the EM and CM contributed to the enhancement of SERS simultaneously, in which the relationships between EM and CM should be investigated in detail. Lombardi and Birke proposed a quantitative measurement of the charge transfer degree by the following formula:

\[
\rho_{CT}(k) = \frac{I^k(CT) - I^k(SPR)}{I^k(CT) + I^k(SPR)}
\]

FIGURE 7 Schematic diagram of charge transfer. (A) Metal–molecule system. (B) Semiconductor–molecule system. Reproduced with permission: Copyright 2014, American Chemical Society
where \( k \) is an index used to identify individual molecular lines in the Raman spectrum. Two reference lines \( I_0^{\text{SPR}} \) and \( I_0^{\text{CT}} \) in a spectral region without charge-transfer contribution are needed, where \( I_0^{\text{SPR}} \) represents the intensity of the line \( k \) in question taken where only the SPR contributes to the SERS intensity, and \( I_0^{\text{CT}} \) represent a chosen totally symmetric line with only contributions from SPR. \( I_0^{\text{CT}} \) is the measured intensity of the line \( k \) in the region of the spectrum with the charge-transfer resonance contribution to the SERS intensity. There are three extreme cases: when \( a = 0 \), it can be regarded as no CT process; when \( a = 1 \), the contribution from CT progress is dominant; when \( a = 1/2 \), the contribution of CT and SPR is equal. This formula has been successfully applied to several systems with both CT and SPR effects. Han et al. analyzed the interface charge transfer of TiO\(_2\)/N\(_3\)/Ag according to this formula.\(^{76} \) In this experiment, the band at 1270 cm\(^{-1} \) originating from the \( \nu (C=\text{N}) \) and \( \nu (C-C) \) is sensitive to the CT progress, and the band at 1024 cm\(^{-1} \) originating from ring breathing is less sensitive to CT. Therefore, they defined that 

\[
I_0^{\text{CT}}(k) = I_{1270}, \quad I_0^{\text{SPR}} = I_{1024}.
\]

The formula can be simplified as follow:

\[
\rho_{\text{CT}}(k) = \frac{I_{1270}^{\text{mol}}}{I_{1024}^{\text{mol}}} \frac{1}{1 + \frac{I_{1270}^{\text{mol}}}{I_{1024}^{\text{mol}}}}
\]

(3)

By plotting the relationship between \( c \) and excitation energy, for the TiO\(_2\)/N\(_3\) sample, it can be obtained that when the excitation energy is below 2.071 eV, \( \rho_{\text{CT}} \) is basically unchanged; when the excitation energy is greater than 2.071 eV, \( \rho_{\text{CT}} \) increases with the increase of excitation energy, which indicates the selectivity enhancement in CT progress. For the TiO\(_2\)/N\(_3\)/Ag sample, the \( \rho_{\text{CT}} \) at other excitation wavelengths increased significantly except for the initial excitation wavelength of 785 nm. When the excitation energy is higher than 1.877 eV, the change of \( \rho_{\text{CT}} \) is slow due to the saturation effect of the CT progress. By comparing the CT progress among three samples calcinated at 400, 450, and 500°C, it is proved that 450°C is the optimal temperature for the CT progress because when calcinated at that temperature, the anatase-type TiO\(_2\) NPs has a relatively high degree of crystallization and a relatively rich surface defect. According to the XRD measurement, when the calcination temperature is 500°C, a small amount of rutile phase is generated, leading to the decrease of the surface defects and specific surface area. Hence, TiO\(_2\)/N\(_3\)/Ag assembly calcinated at 450°C shows the highest \( \rho_{\text{CT}} \) and lowest CT energy threshold.

LSPR and PICT are belonging to the EM mechanism and CM mechanism respectively, however, as mentioned above, these two kinds of mechanisms can coexist in many circumstances.\(^{77} \) Therefore, the coupling effect between LSPR and PICT progress needs to be investigated in detail. To solve this problem, Qiu et al. designed a double switch to control the LSPR and PICT progress respectively, in which highly ordered hexagon plum-blossom-like WO\(_{3-x}\) nanoarrays (HPWN) and WO\(_{3-x}\) film act as the switch for LSPR, and SiO\(_2\) film act as the switch for PICT.\(^{78} \) They found that the PICT on the HPWN (where LSPR exists) is greater than that on the WO\(_{3-x}\) film (where LSPR is hindered). In addition, the absorption of HPWNs shows a red shift compared with that of WO\(_{3-x}\) films and the corresponding change in energy is 0.197 eV, which indicates that the LSPR has a great influence on the PICT progress. The PICT contains two progresses: transfer from the highest occupied molecular orbital (HOMO) to CB (PICT\(_{h-c}\)) and from \( V_o \) to lowest unoccupied molecular orbital (LUMO) (PICT\(_{v-l}\)). There is a special rule between PICT\(_{h-c}\), PICT\(_{v-l}\), and \( \mu_{\text{mol}} \), in which PICT\(_{v-l}\) has a coupling enhancement with LSPR to improve the SERS activity, however, the PICT\(_{h-c}\) progress competes with \( \mu_{\text{mol}} \) and LSPR. Therefore, only when the excitation laser is close to the absorption wavelength of the absorbed molecules, coupling effect between LSPS and PICT\(_{v-l}\) can occur and SERS can be enhanced accordingly.

### 3.2 Defect engineering

It has been recognized that not only noble and transition metals exhibit the SERS effect, but also some semiconductor materials display a notable SERS activity.\(^{79} \) However, the application of semiconductor SERS-active substrates is limited by its lower EF than the noble metal substrates. Therefore, how to boost the EF of semiconductor substrates has been a research hotspot. Generally, the plasma collective oscillation of semiconductors is located at the near-infrared region,\(^{80} \) which indicates that the SERS enhancement of semiconductor substrate is originating from the CM mechanism. Thus, the SERS property can be adjusted by introducing new energy states. Defect engineering is an effective method for the SERS improvement of semiconductors by making new defects in the substrate materials. Several methods have been reported to fabricate defects in semiconductors, such as plasma treatment,\(^{81} \) ion doping,\(^{82} \) and gas annealing.\(^{83} \)

Oxygen vacancies and oxygen incorporation are two main ways for defect engineering which are applied to the semiconductors. In 2015, Cong et al.\(^{84} \) proposed that making oxygen vacancies is a powerful method for improving the SERS activity of semiconductor metal oxide based on the charge transfer between the substrate and...
the adsorbed molecules (Figure 8A). It can be clearly seen that a vibronic coupling exists among the defect state of oxygen vacancies, molecular ground state, and molecular excited states, which contributes to the molecular polarizability tensor and then leads to an effective charge transfer. The EFs for R6G molecule is up to $3.4 \times 10^5$, and the detection limit concentration is as low as $10^{-7}$ mol/L due to that the oxygen defect state induced new resonant. Two years later, they proposed that oxygen incorporation, the inverse process of making oxygen vacancies, is also an effective method to improve the SERS activity of semiconductors (Figure 8B). They concluded that oxygen incorporation concentration had a great influence on the SERS enhancement of R6G, and even minor changes in oxygen incorporation concentration could induce dramatic changes in EFs. Since then, defect engineering has been widely studied to improve the SERS performance of semiconductor substrates, such as WO$_{3-x}$, In$_2$O$_3$, MoO$_2-x$, ZnO, and Cu$_2$O semiconductors. For example, the SERS activity of α-MoO$_3$ is improved by introducing oxygen vacancy, and the relationship between the oxygen vacancy concentration and EFs has been investigated by Li et al. With the increasing of oxygen vacancy concentration, the Raman peak intensity increased first, and then decreased to a constant value due to the higher proportion of non-monolayer adsorption. Excited with the 532 nm laser, the detection limits of R6G and MB on α-MoO$_{3-x}$ nanobelts are as low as $10^{-8}$ and $10^{-7}$ mol/L, which is comparable with noble metal substrates.

Besides, optimization of chemical synthesis conditions can generate surface defects to achieve significant Raman signal improvement. Our group developed a recrystallization-induced self-assembly strategy for the construction of 3D cube-like Cu$_2$O superstructure (Figure 8C), during which a large number of defects are introduced due to the lattice fusion of neighboring Cu$_2$O mesoporous spheres. As a result, the SERS activity of Cu$_2$O is effectively improved with the introduction of defects. Zhao et al. proposed that the 2D ultrathin WO$_3$ synthesized by exfoliation and calcination strategy with abundant surface defects tend to exhibit sensitive SERS performances than its bulk counterparts (Figure 8D). At the ultrathin level, it is easy to produce abundant defective surface structures, which leads to the undersaturated central metal atom and promote the charge transfer between semiconductor and molecules.

Some physical methods can also construct defects in semiconductors, for instance, lithium metal grinding reduction will introduce surface defects in MoO$_2$ nanospheres (Figure 9A). The Raman intensity of R6G

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**Figure 8** Energy level diagram and charge-transfer pathway in the different molecule–semiconductor system. (A) R6G-W$_{18}$O$_{49}$ system. Reproduced with permission: Copyright 2015, Springer Nature. (B) R6G-MoS$_x$O$_y$ system. Reproduced with permission: Copyright 2017, Springer Nature. (C) R6G-Cu$_2$O superstructure system. Reproduced with permission: Copyright 2016, Wiley. (D) MB-WO$_3$ nanosheets system. Reproduced with permission: Copyright 2020, Wiley. 

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absorbed on the defective MO$_{2-x}$ substrate was greatly enhanced than that on the nonvacancy MoO$_2$. Femtosecond laser pulses also can fabricate defects on the surface of semiconductors. Zuo et al. introduced defect/active site on monolayer MoS$_2$ flakes by femtosecond laser pulses, and the EFs of R6G molecule on femtosecond laser-treated MoS$_2$ is 6.4 times higher than pure MoS$_2$ flakes. The physical-chemical adsorption and the charge transfer between absorbed molecules and monolayer MoS$_2$ flakes were enhanced under the excitation of femtosecond laser due to the introduced defects. In addition, Zhou et al. reported that the defect density in the WO$_{3-x}$ can be programmed by electrical tuning by controlling the oxide leakage current (Figure 9B). The SERS detection capability of the novel substrate can be invoked instantaneously, and the EFs can be further precisely modulated with the generating of defects.

3.3 Doping strategy

Doping strategy is an effective way to optimize the SERS activity of semiconductor substrates by tuning the energy band or increasing the concentration of free electrons. The energy band of semiconductor can be controlled by substituting the atoms into the lattice with other elements in similar radius or valence state. And the SERS performance of semiconductor enhanced by doping has been reported constantly, such as nitrogen-doped TiO$_2$, Ga-doped ZnO, S-doped SnSe$_2$, and Sm-doped CeO$_2$. As a wide-bandgap semiconductor, diamond presents unique properties such as high thermal conductivity and chemical inertness, but the SERS activity of diamond is not satisfactory. Gao et al. reported that the bandgap of diamond can be decreased in the boron-doped diamond (BBD) by hydrogenation or oxygenation on the surface. The band energy of BBD can match with energy levels of molecules, which promotes the PICT progress effectively. Recently, Lombardi et al. reported the Mo-doped Ta$_2$O$_5$ semiconductor SERS substrate with an ultrahigh EFs of $2.2 \times 10^7$ for methyl violet. They proposed a concept of “coupled resonance” (Figure 10A), that is, the molecular resonance, PICT resonance, and the electromagnetic enhancement contribute to the SERS enhancement synergistically. The bandgap became narrower with Mo substituting into the lattice of Ta, which leads to the quasi-match between the incident laser and the energy band of semiconductor. In addition, the EM enhancement around the “gap” and “tip” of anisotropic Ta$_2$O$_5$ NRs has a significant contribution to SERS enhancement. The concept of “coupled resonance” provides a new guidance for designing different semiconductor SERS substrates.

The plasmonic resonance of semiconductor is related to the doped elements. The smaller atom doped in the lattice gap can provide electrons, during which the lattice structure remains unchanged, and the SPR of semiconductor will shift to the visible light region with the increasing electrons density. Cheng et al. reported the hydrogen doped H$_x$MoO$_3$ and H$_x$WoO$_3$ semiconductor substrates, hydrogen bronzes, which render high SERS activity due to the LSPR in the visible light region (Figure 10B). The optical properties of hydrogen bronzes are related to the environment and delocalization extent of electrons. The H atom resides in the interlayer position and is bonded with terminal O atoms in H$_x$MoO$_3$, and the electronic charge introduced by H atom distribute uniformly on the Mo atom, which is expected
to support the LSPR when the electron density exceeds the critical concentration. In a marked contrast, the H atom resides in the tunnels in H$_x$WO$_3$, which is unstable to extract from the lattice and leads to the faster decay of plasmon resonance. However, the electrons in H$_x$V$_2$O$_5$ are confined, which cannot support the plasmon resonance. Therefore, it is very important to select the appropriate substrate material in the doping strategy.

3.4 Two-dimension semiconductor substrates

Graphene is a kind of new material composed of carbon atoms connected by sp$^2$ hybridization and tightly packed into a monolayer 2D honeycomb-like structure. It is considered as a revolutionary material in the future due to its excellent optical, electrical, and mechanical properties. Since the SERS activity of graphene was discovered by Liu et al.$^{104}$ the related theoretical and application exploration have attracted extensive attention.$^{105-107}$ The enhanced mechanism of conjugated and macrocyclic phthalocyanine and protoporphyrin IX molecules absorbed on graphene are studied. These two molecules lie parallel to the surface of graphene due to the π–π stacking, and the HOMO and LUMO of the molecules are all located on the two sides of the Fermi level of graphene, contributing to the charge transfer between graphene and the molecules. The first monolayer absorbed on the graphene presents a large contribution to the SERS enhancement, which is called “first-layer effect.”$^{108}$ In addition, both of the two surfaces of graphene can contribute to the charge interactions between monolayer and molecules (Figure 11A). The charge interactions on the two surfaces interfere with each other and result in different SERS enhancements. Tong et al. investigated the bifacial Raman enhancement on monolayer graphene and monolayer hexagonal boron nitride (h-BN),$^{109}$ however, different conclusions are obtained in these two materials. For the h-BN, the dipole–dipole interaction is the main reason for the SERS enhancement for h-BN, and the bifacial Raman enhancement of h-BN is about 1.5 times stronger than the single-layer enhancement due to that the z-dipoles are partially canceled out between the two interfaces (Figure 11B). For graphene, the bifacial Raman enhancement is twice stronger than the single-layer enhancement. The charge transfer at both interfaces of graphene is expected to be the same due to the high conductivity and free carrier density of graphene (Figure 11C). The layer number dependence of Raman intensities on graphene and h-BN is discussed in detail. The EFs in the h-BN system increase first and then decrease, which is ascribed to the competition mechanism between the optical effect and the additional Raman enhancement. However, the EFs of graphene decreased monotonously due to the increased absorption of the incident photons and scattering photons. Xi et al. proposed the flexible film
formed by the 2D δ-MoN nanosheets with an ultrahigh EFs of $8.16 \times 10^6$ for R6G due to strong LSPR effect (Figure 11D). The free electron density distribution obtained from the calculation of electron localization functions indicates that the electron gas density is high, and a large number of Mo–Mo metallic bonds are formed, which supports the LSPR process of δ-MoN nanosheets (Figure 11E). Besides, the large specific surface area and hot spots generated from the gaps and pores among the nanosheets all contribute to the high SERS performance of δ-MoN. The LOD for 2,5-dichlorophenol is as low as $10^{-10}$ mol/L (Figure 11F).

3.5 Amorphous semiconductor substrates

Amorphous phase refers to a substance with irregular shape, no fixed melting point, and no long-range order in its internal structure, but a structurally ordered arrangement within a small range of distances between several atoms. Surprisingly, amorphous phases exhibit excellent SERS activity owning to its abundant metastable electronic states. Our group designed the porous amorphous ZnO nanocages ($\alpha$-ZnO NCs) with excellent size uniformity and shape regularity in 2017. The SERS intensity of 4-MBA absorbed on $\alpha$-ZnO NCs

FIGURE 11 SERS spectra of 2D semiconductor substrates. (A) Schematics of molecules on one surface and both surfaces of a monolayer 2D material. (B,C) Bifacial Raman enhancement on monolayer h-BN and graphene, and EFs for Raman modes at 1453 and 1530 cm$^{-1}$ with the increase of thickness of h-BN and graphene. Reproduced with permission: Copyright 2019, American Chemical Society. (D) Flexible SERS substrate assembled by the 2D δ-MoN nanosheets. (E) Electron localization functions of δ-MoN nanosheets. (F) Raman spectra of 2,5-dichlorophenol absorbed on the flexible δ-MoN nanosheet substrate. Reproduced with permission: Copyright 2020, Springer Nature. SERS, surface-enhanced Raman scattering.
(6.62 × 10⁵) is higher than that on the crystalline ZnO nanocages (c-ZnO NCs; Figure 12A,B). On the one hand, the hollow structure can provide a huge surface area for the efficient adsorption of probe molecules. On the other hand, the long-range disordered structure of amorphous materials can facilitate the surface electron escape and transfer, which can promote the interfacial charge transfer process (ICTP) between the semiconductor and molecules. This is the first time to report the ultrasensitive SERS performance of amorphous materials.

Actually, the specific surface area is an important factor affecting charge transfer due to the fact that the coordination number of the surface atoms is seriously insufficient, which leads to the combination of the surface atoms with adsorbed molecules to form surface complexes and enhance the PICT resonance. However, there are some shortcomings of 2D materials, such as the wide bandgap and discontinuous band structure, which limit further development. Combined with the above analysis of amorphous ZnO, it can be seen that the metastable electronic states of amorphous semiconductor nanostructures can be regarded as intermediate energy levels in the bandgap, which can overcome the disadvantage of the wide bandgap. Therefore, we further designed the 2D amorphous TiO₂ nanosheets (α-TiO₂ NSs) to improve the interfacial PICT efficiency. As a result, the EFs of α-TiO₂ NSs are as high as 1.86 × 10⁶, which is much higher than that of 2D crystalline counterpart (c-TiO₂ NSs; Figure 12C,D). The reason for the stable surface charge-transfer (CT) is explained by calculating the density functional theory (DFT). First, the surface Ti atoms are disordered with a low coordination number, which leads to a high surface potential and thus allows static charger transfer from the adsorbed molecule to the 2D α-TiO₂. Secondly, due to the smaller bandgap and higher DOS of 2D α-TiO₂, the vibronic coupling in the substrate-molecule system is stronger, which can promote the PICT resonance and enhance the remarkable SERS activity effectively. Since then, more TiO₂ based amorphous substrates have been reported, such as amorphous TiO₂ nanotubes decorated with Ag/Au NPs, which indicates high SERS enhancement due to the effect of EM enhancement and CT enhancement simultaneously. Moreover, hydrogenation is an effective method to improve SERS activity of black TiO₂ nanowires, during which the amorphous shell is generated.

Quantum size effect and surface vacancies defects of quantum dots can improve the SERS activity effectively. Xu et al. reported a kind of uniform amorphous molybdenum oxide quantum dots with

**FIGURE 12** (A,B) SERS spectra of 4-MBA absorbed on amorphous ZnO nanocages. Reproduced with permission: Copyright 2017, Wiley. (C,D) SERS spectra of 4-MBA absorbed on amorphous TiO₂. Reproduced with permission: Copyright 2019, American Chemical Society. SERS, surface-enhanced Raman scattering
remarkable SERS activity with EFs as high as $9.5 \times 10^5$ (Figure 13A). The smallest size of approximately 4.0 nm can be obtained under 17 MPa SC CO$_2$, which endows the optimum plasmon resonance of H$_x$MoO$_3$ quantum dots. Simultaneously, the optimal absorption wavelength and a maximum intensity can be realized when the volume fraction of ethanol increases to 30%. When the above factors reach the best conditions, the enhancement of plasmonic resonance property for H$_x$MoO$_3$ can be achieved. Furthermore, the number of surface vacancy defects can be controlled by the fraction of H$_2$O$_2$. When the ratio of MoS$_2$:H$_2$O$_2$ increases to 17:3, much stronger absorption peaks can be observed (Figure 13B,C). Therefore, for the amorphous quantum dots, oxidation degree and quantum size play a significant role in SERS enhancement.

**SUMMARY AND PROSPECT**

SERS-active substrates are mainly divided into two categories: noble metal (Au, Ag, Cu) based on EM enhancement and semiconductor substrate based on CM enhancement. In this review, we elaborate the development of noble metal and semiconductor substrates. For the noble metal substrate, the EM field near the hot spots strongly depends on the shape, size, and arrangement of nanoparticles. Although various methods, such as colloidal synthesis, electrochemical deposition, reactive ion etching, and EBL, have been used to accurately control the morphology of nanoparticles, the preparation of nanoparticles with uniform morphology remains a challenge. Furthermore, the assembly of high-density 2D/3D structures with abundant and uniform hot spots is a key issue for uniform Raman enhancement. The large-scale
self-assembly structures have potential applications in new custom materials for plasma sensing, photocatalysis, and nanoscale light manipulation. In addition, tunable interparticle nanogaps can effectively locate hot spots and enrich molecules, which can promote quantitative analysis. For the semiconductor substrates, such as metal-oxide, sulfide, graphene, and amorphous are described, the enhancement is mainly achieved through the charge transfer between the semiconductor and absorbed molecules. For different semiconductor-molecular systems, the enhancement mechanisms are complicated and unclear. Defect engineering and doping strategy are two common methods to improve the SERS activity of semiconductors via promoting the charge transfer between the semiconductor and adsorbed molecules. In addition, the development of an amorphous semiconductor is introduced in detail, which is considered as a potential SERS substrate due to its abundant metastable electronic states. Certainly, semiconductors and noble metal substrates have their own shortcomings in practical applications. The noble metal material is expensive and unstable, so it is difficult to achieve quantitative detection. But the stability and selectivity of the semiconductor substrate are greater than noble metal, which is more suitable for quantitative detection and specific identification than precious metals. Another disadvantage of noble metal substrates is the photodegrade of dyes on the surface of metal NPs, which can be avoided by choosing a suitable excitation wavelength. For semiconductor substrates, there is a slight Raman shift of target molecules caused by the CM mechanism, which is unavoidable and even advantageous. Sometimes, it is a strong evidence of CM, such as the enhancement of B2 mode and pre-determination of the direction and degree of peak shift. Although SERS has the above shortcomings, it can be avoided by selecting the appropriate excitation wavelength and designing artful substrates for different systems. Therefore, SERS is still the most promising detection method.

Overall, semiconductor SERS-active substrates have been applied in many fields, especially in the in situ analytical chemistry and biometric identification due to the selective enhancement. However, its EFs are much lower than noble metal substrates, which restricts the further application of semiconductor substrates. Therefore, combining the both advantages of noble metals and semiconductors to develop the novel composite SERS substrates with large EFs and selective recognition is of great significance for the future development of SERS technology.

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CONFLICT OF INTERESTS
The authors declare no conflict of interest.

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