



Hybrid SERS Platforms for Enhanced Biochemical Sensing

Jiazheng Bao¹, Bin Lian¹, Hyungmok Joh^{1,2}, Alan Xiaolong Wang^{3,*}, and Donglei Emma Fan^{1,2,4,5,*}

¹ Materials Science and Engineering Program, Texas Materials Institute, The University of Texas at Austin, Austin, TX 78712, USA

² Materials Nova Limited Liability Company, Austin, TX 78759, USA

³ Department of Electrical and Computer Engineering, Baylor University, Waco, TX 76798, USA

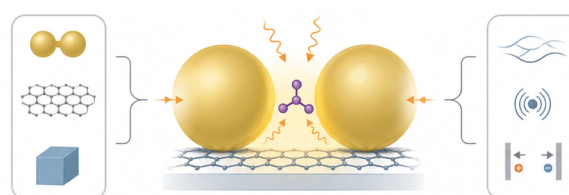
⁴ Department of Mechanical Engineering, The University of Texas at Austin, Austin, TX 78712, USA

⁵ Chandra Family Department of Electrical and Computer Engineering, The University of Texas at Austin, Austin, TX 78712, USA

* Correspondence: alan_wang@baylor.edu (A.X.W.); dfan@austin.utexas.edu (D.E.F.)

Received: 10 April 2026; Revised: 6 July 2026; Accepted: 30 July 2026; Published: 27 August 2026

Abstract: Surface-enhanced Raman scattering (SERS) is a powerful analytical technique for label-free, ultrasensitive biochemical detection, offering broad potential for biomedical, environmental monitoring, and defense applications. However, conventional noble-metal SERS substrates remain limited by chemical instability, insufficient enhancement reproducibility, and slow analyte detection in dilute aqueous solutions. Recently, hybrid SERS platforms that integrate plasmonic nanostructures with functional material systems—such as semiconductors, two-dimensional materials, photonic crystals, and active robotic modules—have emerged as promising strategies to overcome these limitations. In this review, we examine recent advances in hybrid SERS platforms from the perspective of material systems. Their working principles can be broadly categorized into two types: functional materials that regulate interfacial electromagnetic and chemical enhancement, and robotized systems that promote targeted analyte access or active enrichment at sensing hotspots. By linking material properties, working mechanisms, and sensing performance, this review provides a materials-based perspective to guide the rational design of high-performance, application-oriented SERS platforms.



Keywords: surface-enhanced Raman scattering; hybrid nanomaterials; charge transfer; photonic crystals; nanomotors; analyte enrichment

1. Introduction

Surface-enhanced Raman scattering (SERS) amplifies weak Raman fingerprints of molecules near nanostructured plasmonic surfaces [1–5]. In conventional SERS substrates, noble metals such as Au, Ag, and Cu dominate because their localized surface plasmon resonances in the visible and near-infrared regions produce intense near-field enhancement with relatively low optical losses [5–7]. This plasmonic amplification has enabled chemical, environmental, and catalytic analysis [8–15], biological and biomedical sensing [2,16–25], and emerging active or multifunctional SERS formats [26–30].

Despite their great potential, conventional noble-metal SERS substrates face several persistent limitations for practical applications [31]. Hotspot heterogeneity complicates quantitative comparison and substrate-to-substrate reproducibility. These challenges are further compounded by the limited stability of many noble-metal nanostructures, which can undergo oxidation, contamination, or nonspecific fouling in complex media [31–38]. In addition, the enhancement mechanism of metallic SERS substrates relies primarily on localized surface plasmon resonance, which is governed by the optoelectronic properties, geometry, and dimensions of the metal nanostructures [16,39]. This reliance on plasmonic enhancement alone motivates the exploration of complementary material strategies to further improve sensing performance. To address these practical sensing



challenges, recent literature has reported various strategies aimed at significantly improving the signal-to-noise ratio and overall reliability of SERS measurements through optical interface engineering, background noise modulation, and advanced hybrid plasmonic coupling [40–42]. Beyond sensitivity and stability, passive noble-metal nanostructures also suffer from low detection throughput in dilute aqueous samples, where analyte capture is often limited by slow diffusion to nanoscale hotspots [43].

Hybrid SERS platforms are SERS-active architectures that integrate plasmonic nanostructures with functional materials or active components that can modify the local optical field, interfacial electronic structure, analyte adsorption, or molecular transport. Material hybridization can address several limitations of conventional SERS: semiconductors and two-dimensional materials introduce tunable charge transfer (CT) channels, photonic crystals redistribute optical fields and local concentration, and active or robotic components enable targeted analyte detection or their enrichment at nanoscale hotspots. Therefore, hybrid SERS platforms can not only introduce new routes for signal amplification but also actively control analyte transport kinetics for improved throughput.

Although prior reviews have examined various aspects of SERS and its applications [18,33–36,44–51], this review provides a distinct view of SERS progress through the lens of mechanistically driven hybrid material platforms. The working mechanisms of these platforms are broadly categorized into two types: functional materials that regulate interfacial electromagnetic and chemical enhancement, and robotized systems that promote targeted analyte detection or active enrichment at sensing hotspots. Figure 1 summarizes the different hybrid platforms reported in the literature. Semiconductor-, two-dimensional-material-, and photonic-crystal-based hybrids fall into the first category. These interface-regulated platforms enhance SERS performance by tuning charge transfer, electromagnetic–chemical mechanism coupling, and optical-field localization. In contrast, micro/nanomotor and magnetic hybrid systems are discussed as robotic platforms that directly target analytes or accelerate their enrichment at sensing hotspots. Finally, because both interface-regulated enhancement and active enrichment can generate localized signal variations, this review briefly discusses how digital counting and data-driven spectral analysis may improve quantitative SERS measurements.

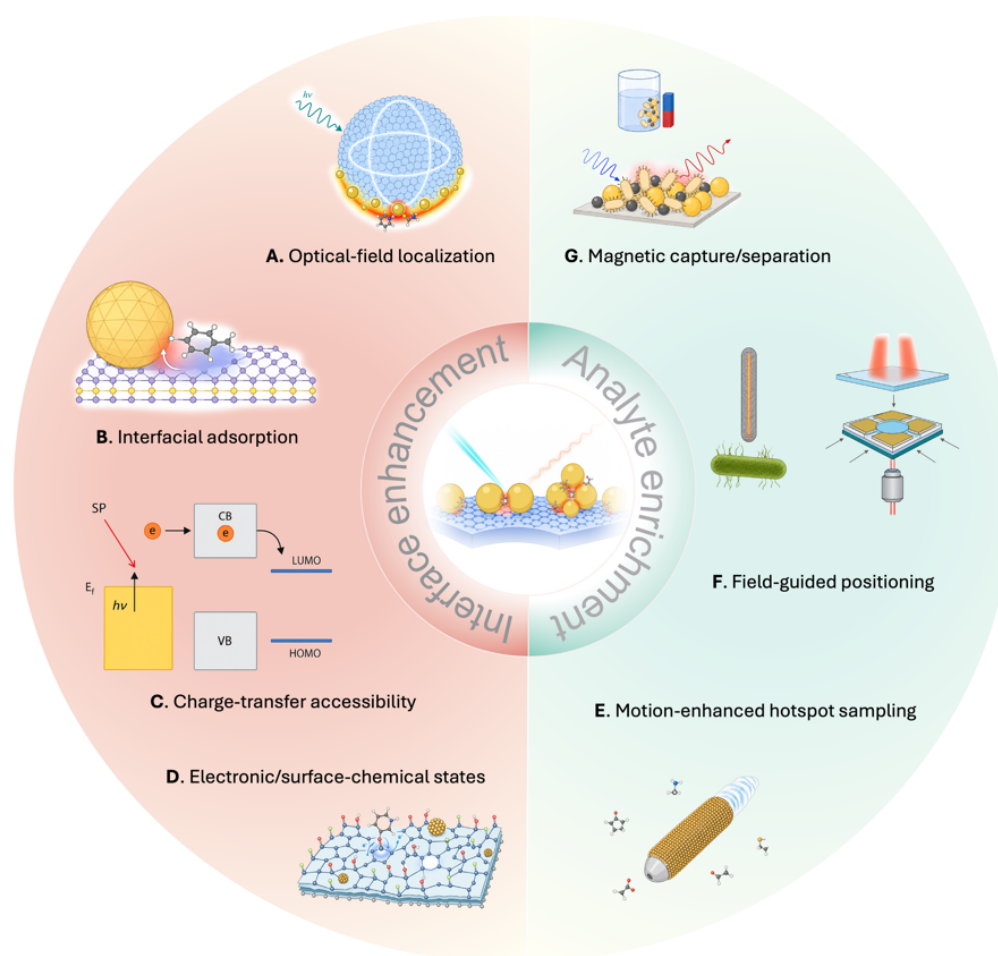


Figure 1. Mechanistic framework for hybrid SERS platforms. Hybrid SERS architectures improve sensing by regulating the SERS interface or by improving analyte access to SERS-active regions. (A) Optical-field localization, as in Mie-resonant ZnO superstructures [52], photonic-crystal-assisted plasmonic substrates [53,54],

and bio-photonic-crystal platforms [55,56]. **(B)** Interfacial adsorption and orientation, referring to analyte localization, binding geometry, and molecule-hotspot contact without necessarily requiring charge transfer; examples include graphene-spaced plasmonic junctions [11], RGO/Au breath-analyzer substrates [57], and carbonyl-functionalized organic-SERS interfaces [58]. **(C)** Charge-transfer accessibility, referring to whether band alignment, defect states, excitation energy, or adsorption geometry enables a charge-transfer pathway; examples include TiO_2 -Ag-MPY-FePc interfaces [59], oxygen-vacancy-mediated TiO_2 /PIERS systems [60], Ag/Ag-doped TiO_2 hybrids [61], and PIHET/PICTT metal-semiconductor systems such as Au-ZnO and Au-CdSe [62,63]. **(D)** Electronic/surface-chemical states, including surface terminations, vacancies, phase structures, oxidation states, conductivity, and active sites; examples include TiVC MXene [64,65], Ti_2N MXene [66], phase-engineered TMDs [67], and gas- or UV-modulated RGO/Ag hybrids [68]. **(E)** Motion-enhanced hotspot sampling, as in magnetic nanorobot SERS probes [69,70], light-powered nanomotor sensors [71], magnetic-film-actuated diatom frustules [26], and electric-field-driven rotary SERS nanomotors [72]. **(F)** Field-guided mobile hotspot positioning, in which optical or electric fields position, orient, or assemble SERS-active components at defined locations to form controllable nanogaps or localized sensing interfaces; examples include optical-tweezer-controlled Ag nanoparticle-coated silica beads [73,74], and 3D electrokinetic tweezer manipulation of SERS-active nanowire probes [75]. **(G)** Magnetic capture and separation, in which magnetic-plasmonic probes or magnetic enrichment substrates capture, isolate, and concentrate target species from complex matrices before Raman readout; examples include magnetic mesoporous nanosponges for pollutant enrichment [76], antibody-functionalized Mag-SERS strips for respiratory virus detection [77], and magnetic nanochain microfluidic biochips for rapid bioseparation and SERS detection [20].

2. Interface-Regulated Enhancement at Hybrid Interfaces

The electromagnetic and chemical contributions to SERS have been extensively reviewed [31,34,78] and are therefore discussed only briefly here to provide the necessary background. Building on this established understanding, this review focuses on what hybrid architectures contribute beyond conventional plasmonic enhancement. The approaches include regulation of optical fields, interfacial electronic structure, charge-transfer accessibility, surface chemistry, and analyte enrichment near SERS-active interfaces [3,6,39,43,79–81]. This emphasis provides the basis for comparing semiconductor, 2D material, photonic-crystal, and active-enrichment platforms without reducing their performance to EF or LOD alone. Therefore, EF and LOD are reported together with mechanistic studies, such as wavelength-dependent measurements, optical-field simulations, band alignment, defect-state control, adsorption tuning, and charge-transfer signatures.

2.1. Electromagnetic Enhancement Mechanism

Electromagnetic enhancement refers to the optical-field localization and antenna-mediated amplification of both Raman excitation and emission [82]. In noble-metal SERS, this contribution is commonly associated with localized surface plasmon resonance (LSPR), nanoscale junctions, sharp features, and spectral overlap between the excitation/Raman wavelengths and the plasmonic response. In hybrid platforms, however, optical-field localization can also be shaped by Mie-like resonances in semiconductor structures, guided-mode or slow-light effects in photonic crystals, and plasmonic gap engineering across atomically thin spacers such as graphene. This broader interpretation of EM enhancement facilitates a systematic comparison of plasmonic, dielectric, and photonic contributions within hybrid material architectures.

2.2. Chemical Enhancement Mechanism

Chemical enhancement is used here to describe interfacial electronic effects that alter molecular polarizability, directly modulating Raman emission, particularly through adsorption-mediated coupling and ground-state or photoinduced charge transfer (CT) [83–85]. In hybrid systems, this interfacial contribution often becomes a primary design target. Semiconductors, transition metal dichalcogenides (TMDs), MXenes, graphene, and molecular semiconductors can tune the energetic and chemical conditions for charge transfer through band alignment, density of states, defect levels, surface terminations, Fermi-level positions, and adsorption geometries. Together, these features can help hybrid interfaces support more selective electronic coupling between the substrate and the analyte, extending beyond simple molecular adsorption alone.

Photoinduced charge transfer, in addition, is particularly important in hybrid SERS because it connects optical excitation with interfacial electronic coupling. In metal-semiconductor hybrids, for example, this coupling can occur through several related but distinct pathways [79,85,86]. Plasmon-induced hot-electron transfer (PIHET) describes the injection of plasmon-generated hot carriers from a metal into an adjacent semiconductor before carrier relaxation. Direct interfacial charge-transfer transition (DICTT) refers to direct optical excitation across the

metal-semiconductor interface, whereas plasmon-induced interfacial charge-transfer transition (PICTT) describes plasmon-assisted interfacial transitions in strongly coupled heterostructures. These detailed pathways provide useful mechanistic distinctions for discussing hybrid interfaces, especially when correlated to wavelength-dependent measurements, band alignment, defect-state analysis, charge-transfer signatures, adsorption controls, and electromagnetic simulations.

While the transfer of plasmon-generated hot carriers facilitates chemical enhancement in SERS, these energetic carriers concurrently drive unintended plasmon-mediated photochemical reactions at the molecular interface [87,88]. Such processes have been reported to convert the molecules of interest into different chemical species during continuous laser excitation [89]. In these circumstances, the acquired Raman spectra reflect the newly formed photochemical products rather than the original analytes. This structural transformation can compromise the noninvasive nature of Raman spectroscopy, thereby limiting its reliability as an accurate molecular fingerprinting tool for quantitative sensing. Addressing this critical limitation is essential for the design of practical SERS sensors [90–93]. Within hybrid SERS platforms, structural and electronic engineering may offer viable strategies to preserve molecular integrity. For instance, it has been reported that introducing an ultrathin, inert dielectric spacer between the plasmonic surface and the target analyte can effectively block direct interfacial hot-carrier injection while maintaining the long-range electromagnetic field enhancement [91–94]. Furthermore, engineering the interfacial band alignment in metal-semiconductor heterostructures is reported to regulate hot carrier relaxation pathways, which may reduce the probability of analyte degradation [31,34,35,78,95]. These material-driven strategies illustrate how hybrid architectures can be designed to balance signal enhancement with molecular stability.

2.3. Coupled Contributions and Design Boundaries

The experimentally observed total enhancement (M_{total}) has often been discussed using the approximate relation ($M_{\text{total}} \approx M_{\text{EM}} \times M_{\text{CM}}$), where M_{EM} and M_{CM} denote the electromagnetic and chemical contributions, respectively; this relation is useful for conceptual comparison. In hybrid interfaces, however, optical-field localization and interfacial charge redistribution can mutually reinforce one another: local electromagnetic fields can increase the probability of charge-transfer transitions, while electronic redistribution can alter the dielectric environment experienced by the optical mode. The relative contribution of each process therefore depends on material architecture, excitation wavelength, interfacial electronic structure, and analyte adsorption geometry.

Analyte enrichment is another important factor influencing SERS sensing performance. Active motion, magnetic capture, optical trapping, field-guided assembly, and related enrichment strategies can increase molecular delivery to hotspots, improve encounter probability, and shorten detection time. These processes are essential for practical sensing performance in addition to interfacial enhancement. They are discussed separately.

Collectively, this review is framed into the following sections. Section 3 discusses semiconductor, two-dimensional-material, and photonic-crystal hybrids as platforms that regulate optical fields, interfacial electronic structure, or charge-transfer accessibility. Section 4 then considers active and field-guided architectures that improve molecular delivery, enrichment, separation, and hotspot encounter. Together, these two sections connect hybrid-material design with both intrinsic enhancement and practical sensing performance.

3. Hybrid SERS Platforms for Interface-Regulated Enhancement

Semiconductors, two-dimensional materials, and photonic crystals can modify SERS performance by tuning charge-transfer pathways, interfacial electronic structure, surface chemistry, and optical-field localization [34,58,96]. These effects do not replace electromagnetic enhancement from plasmonic nanostructures, but reshape how electromagnetic and chemical contributions are coupled at hybrid interfaces. The various platforms provide a useful basis for understanding how material composition, band structure, surface states, and photonic architecture influence SERS sensitivity, reproducibility, and selectivity.

The section is organized according to the main interfacial role enabled by each material class. Semiconductor hybrids are discussed first because they provide clear examples of band alignment, defect-state regulation, and plasmon-mediated charge-transfer processes, including PIHET and PICTT. Two-dimensional-material hybrids are then considered as atomically thin interfaces in which phase structure, conductivity, surface terminations, and spacer effects regulate adsorption, charge transfer, and plasmonic coupling. Finally, photonic-crystal hybrids are discussed as architectures that redistribute optical fields through guided-mode, slow-light, or Mie-like effects. Table 1 summarizes representative platforms, enhancement factors, detection limits, and operating features, while the discussion focuses on the mechanistic role played by each hybrid component in the SERS measurement.

Table 1. Comparative summary of interface-regulated hybrid SERS architectures.

System	Material	Hotspot	λ_{ex} (nm)	Probe Analyte	LOD	EF	Dominant Mechanism	Note	Ref.
Au triangular nanoarrays/n-layer graphene/Au NPs	Graphene-noble metal hybrid	Sandwich w/subnm hotspots gated by graphene spacer	532 nm (Renishaw inVia, 100×, 0.5 mW, 10 s)	Hg ²⁺ (TAMRA-DNA probe)	LOD 8.3×10^{-9} M	NR	EM (LSPR) + CM	Indirect detection via DNA probe; EF method NR	[11]
Ti ₂ N MXene	MXene (pristine)	2D paper-based substrate	532 nm (50× objective, NA = 0.55, 0.54 mW, 10 spectra × 5 s)	R6G (for the 10 ¹² EF measurement)	NR	≈10 ¹²	CM (ground-state CT)		[66]
1T'-WTe ₂ atomic layers	TMD (plasmon-free)	Monolayer/few-layer atomically thin	532 nm (~1 μm spot, 1 mW, 40 s)	R6G	LOD 40 fM	1.8×10^9	CM (CT, high DOS at EF)	Plasmon-free baseline	[97]
4H-Au@1T'-WS ₂ core-shell nanowires	TMD-noble metal hybrid	4H-Au NW core (~few-nm) + ~0.6 nm 1T'-WS ₂ monolayer shell	532 nm (R6G, 100× objective, NA = 0.85, 0.1 mW, 40 s); 633 nm (SARS-CoV-2 spike, 1 mW, 10 s)	R6G; SARS-CoV-2 spike protein	LOD 1×10^{-18} M (attomolar)	NR	EM (4H-Au LSPR) + CM (1T'-WS ₂ semi-metallic CT)	LOD reported for R6G dye and SARS-CoV-2 spike-protein	[98]
TiVC bimetallic solid-solution MXene	MXene (bimetallic)	2D MXene flakes	532 nm primary (100× objective, NA = 0.90, 0.2 mW, 20 spectra × 10 s); 785 nm tested	R6G (main); CV, MG, MB	fM detection	3.27×10^{12}	CM (PICT)		[64]
C ₈ -BTBT, D(C ₇ CO)-BTBT organic semiconductor films	Organic semiconductor	3D porous architecture (carbonyl-functionalized)	785 nm (Jasco NRS-4500, 20×, 30 mW, 10 s)	Methylene blue (selective)	NR	CT efficiency via anti-Stokes/Stokes ratio (D(C ₇ CO)-BTBT >> C ₈ -BTBT)	CM (analyte-specific resonance: HOMO/LUMO match only for MB)	Demonstrates molecular selectivity	[58]

Table 1. Cont.

System	Material	Hotspot	λ_{ex} (nm)	Probe Analyte	LOD	EF	Dominant Mechanism	Note	Ref.
CoFe ₂ O ₄ /Ag hybrid nanotubes	Magnetic spinel oxide/metal hybrid	Electrospun magnetic nanotubes decorated with Ag NPs	532 nm (Renishaw-1000)	PATP (sensitivity to 10 ^{−9} M); MB (catalytic monitoring)	PATP LOD = 10 ^{−9} M	≈10 ⁹ (vs. 10 ⁶ for Pd nanosphere, 10 ⁸ for nanoporous Ag)	EM + CT (CoFe ₂ O ₄ → Ag)	Dual SERS + catalytic platform	[15]
TiO ₂ -Ag-MPY-FePc	Semiconductor-metal hybrid	TiO ₂ NPs with Ag and molecular MPY-FePc bridge	633 nm primary (also 473, 514, 785 nm)	MPY (Raman reporter); FePc (CT-active layer)	NR	NR	EM (Ag SPR) + CM (interfacial CT, direction-controlled)		[59]
(Ag) _x (ZnS) _y co-sputtered films	Semiconductor-metal hybrid	Co-sputtered Ag-ZnS thin films	633 nm primary	4-MBA	NR	uses Lombardi b ₂ /a ₁ ratio (I ₁₀₁₂ /I ₁₅₈₆) vs. carrier density	EM (Ag LSPR) + CM (CT, carrier-density modulated; CTR + Herzberg-Teller)	Used to probe carrier-density/EF correlation, no absolute EF	[99]
Ag/Ag-doped TiO ₂ hybrid	Semiconductor-metal hybrid (Ag-doped)	Molecule-linked Ag NPs on Ag-doped TiO ₂	785 nm NIR (40 mW, 2 s)	4-MBA	NR	1.68×10 ⁶	EM (Ag LSPR) + CM (TiO ₂ → molecule CT, oxygen-vacancy-mediated)	Irreversibly accumulated SERS—EF measured under prolonged NIR Raman excitation	[61]
TiO ₂ + plasmonic NPs (PIERS)	Semiconductor-metal hybrid (PIERS)	Pre-irradiated TiO ₂ supporting plasmonic NPs	633 nm Raman; UVC pre-irradiation (Figure 2D)	Explosives (e.g., dinitrotoluene), pollutants, biomolecules	R6G LOD 10 ^{−7} M; DNT LOD 10 ^{−9} M; glucose 10 ^{−9} M; PETN/RDX 10 ^{−5} M; saturated TNT vapor calc 3.1 × 10 ^{−8} M	≈10× SERS → PIERS enhancement (1 order of magnitude); some bands up to 20×	Photo-induced enhancement (PIERS); UVC-generated O-vacancies → CT	EF decays over 30–60 min; regenerable by UVC	[60]

Table 1. Cont.

System	Material	Hotspot	λ_{ex} (nm)	Probe Analyte	LOD	EF	Dominant Mechanism	Note	Ref.
Cu ₂ O nanoarrays	Semiconductor (PIHET-driven)	Periodic Cu ₂ O nanoarrays	633 nm primary (also 532 nm)	PTCDA (primary); BCP, 4-MBA; SARS-CoV-2 RNA application	SARS-CoV-2 RNA LOD = 60 copies/mL in <5 min	3.19×10^{10}	PIHET: Cu ₂ O LSPR + LICT + hot-electron transfer	EF method NR	[100]
Amorphous MoO ₃ (a-MoO ₃) monolayers	Semiconductor or (amorphous oxide)	Amorphous oxide monolayers	633 nm main; 514 nm tested	MO (primary); R6G, MB, o-AAT (target carcinogen)	MO LOD 10 ⁻⁸ M; o-AAT LOD 10 ⁻⁹ M	2.5×10^6	EM-PIHET synergistic mechanism; amorphous defect DOS	Amorphous structure → defect-rich states	[101]
Au-ZnO heterogeneous nanorods	Semiconductor or-metal hybrid	Au-tipped ZnO nanorods	532 nm primary (Au plasmon match); 633, 785 nm tested	Dopamine	NR	$>1.2 \times 10^4$ (DA at 10 ⁻⁵ M)	PHET (Au → ZnO)	Recyclable via visible-light cleaning; quantitative EF NR	[62]
Cu-doped SnO ₂ -NiO p-n heterojunction	Semiconductor or heterojunction	p-n hetero NPs	785 nm primary (5 mW, 0.5 s, 50×); 532, 633 nm tested	CuPc (reporter); pyrene, 2-naphthalenethiol, EBZA (VOC targets)	CuPc 10 ⁻⁹ M; PYR ≈ 7.6 ppb; 2-NT ≈ 5.3 ppb; EBZA ≈ 4.1 ppb	1.46×10^{10} (CuPc on SnO ₂ -NiOx/Cu)	CM (~92%, p-n junction CT resonance) + EM (~8%, NIR LSPR)	Bandgap & p-n alignment driven; absolute EF NR	[102]
ZnO submicron-sized spheres (superstructure)	Semiconductor or (Mie-resonant)	Submicron spherical superstructures	532 nm (synergy demo); 633, 785 nm tested	4-MPy (non-resonant probe)	NR	$\approx 10^5$ (Mie + CT synergy at 532 nm; estimated as $\text{EF}_{\text{total}} \approx \text{EF}_{\text{Mie}} \times \text{EF}_{\text{CT}} \approx 10^2 \times 10^3 \approx 10^5$)	Mie resonance + ground-state CT (GSCT); synergistic	Mie size-dependent	[52]
DFP-4T organic semiconductor films	Organic semiconductor	π -conjugated DFP-4T thin films	785 nm (20× obj, 3 μm spot, 150 mW, 30 s)	MB (non-resonant at 785 nm by design)	LOD 10 ⁻⁹ M	2.7×10^5	Resonance CT (organic semi → analyte)	Metal-free organic semiconductor	[103]

Table 1. Cont.

System	Material	Hotspot	λ_{ex} (nm)	Probe Analyte	LOD	EF	Dominant Mechanism	Note	Ref.
DFH-4T films (alone) and DFH-4T + Au coating	Organic semiconductor/organic-metal hybrid	Nanostructured DFH-4T; Au-coated for high EF	785 nm (20× obj, 3 μm spot, 150 mW, 30 s)	MB (main); R6G	$<10^{-21}$ mol (subzeptomole, Au-coated)	3.4×10^3 (alone); $\approx 10^{10}$ (Au-coated)	CT + EM (with Au)	7-orders increase with Au coating	[104]
1T'@2H $\text{Mo}_{1-x}\text{Re}_x\text{S}_2$ lateral heterostructures	TMD alloy	Lateral 2H–1T' phase heterostructure (CVD)	532 nm (Bruker Senterra II, 2.5 mW, 15 s)	R6G (main); RhB, CV, MB	10^{-15} M for R6G	2.0×10^{11} (alloy substrate)	CT (1T' phase $\rightarrow$ high DOS at E_F)	Phase-tunable composition control	[67]
1T'- ReS_2 nanosheets	TMD (distorted 1T' phase)	Mono- and few-layer ReS_2 nanosheets	532 nm primary (R6G/RhB/CV); 633 nm (MB)	CuPc (~1 nm thermal deposition); R6G, RhB, CV, MB (solution adsorption)	R6G & MB LOD $\approx 10^{-9}$ M; RhB & CV $\approx 10^{-8}$ M (on monolayer ReS_2)	REF ≈ 2.94 (CuPc 1539 cm^{-1} on monolayer ReS_2 vs. SiO_2/Si)	PICT (layer-dependent; monolayer optimal)	Layer-dependent SERS	[105]
MXene/graphene oxide/Au nanoclusters fiber	MXene + GO + plasmonic	Flexible plasmonic fiber	532 nm (WiTec Alpha300R, 50× L, 0.1 mW, 5 s)	R6G (main); TNT, Tetryl (via L-cysteine)	R6G LOD 1×10^{-11} M; TNT 0.1 μM	2.01×10^9 (R6G)	EM (Au LSPR) + CM (PICT via MXene $\text{Ti}_3\text{C}_2\text{T}_x$); synergistic	75% Raman intensity retained after 90 d	[106]
TiVC MXene flexible membrane (alkaline-treated)	MXene (active-site-maximized)	Flexible wearable membrane	Not stated (handheld Raman)	R6G (and physiological biomarkers)	LOD 1×10^{-15} M	8.08×10^{10}	EM (Au LSPR) + CM (CT via TiVC DOS at Fermi)	Wearable form factor	[65]
$\text{Ti}_3\text{C}_2\text{T}_x$ MXene + Au NP dimers	MXene-noble metal aptasensor	MXene loaded with Au NP dimer (aptamer-functionalized)	785 nm (Horiba LabRAM HR; 100 mW, 10× obj, 20 s $\times$ 2 accumulations)	AFB1 via BPE Raman reporter (1,2-bis(4-pyridyl)ethylene at AuNP dimer hotspot)	LOD 0.6 pg/mL	NR	EM (Au dimer hotspot) + biorecognition (aptamer)	Bioaffinity-mediated	[107]

Table 1. Cont.

System	Material	Hotspot	λ_{ex} (nm)	Probe Analyte	LOD	EF	Dominant Mechanism	Note	Ref.
Self-assembled MXene-Au nanocomposites	MXene-noble metal	Au NPs on MXene flakes	633 nm (4-MBA, adenine); 785 nm (bacteria); HORIBA LabRAM HR Evolution, 100×, 10 s	4-MBA, adenine, <i>E. coli</i> , <i>B. subtilis</i>	4-MBA & adenine $\approx 10^{-9}$ M; <i>E. coli</i> LOD 10^6 CFU/mL; <i>B. subtilis</i> LOD 3×10^5 CFU/mL	NR	EM + CM; photothermal	Multifunctional (sense + $\approx 100\%$ germicidal in min); SERS EF/LOD not reported	[108]
Plasmonic MXene hydrogel microrobot	MXene hydrogel + plasmonic	Hydrogel-based microrobot	NR	R6G, MB (cationic); AR, AB (anionic)	R6G LOD 3.76 aM; MB 1.98 fM; AR 16.33 fM; AB 381.07 pM	5.5×10^6 (AEF, R6G)	EM (AuAgAu SPR) + MXene-driven analyte enrichment	Dual sense + remediation; EF NR	[109]
Graphene-Ag hybrids (theory + experiment)	Graphene-noble metal hybrid	Ag NPs (3–25 nm) on graphene layers	514.5 nm (Ar^+ ion laser, LabRam Jobin-Yvon T64000; 5 mW, $\sim 2 \mu\text{m}$ spot, 20 s)	graphene's own G-band (no external probe molecule)	NR	$\approx 10\times$ over pristine graphene (relative)	EM + CT ($\text{Ag} \rightarrow \text{graphene}$)	Ag-size-dependent; relative metric	[110]
rGO-PS@Ag substrate (UV-modulated)	Graphene-noble metal photoactive	RGO + Ag clusters; UV-modulated Fermi level under O_2/Ar atmosphere	532 nm Raman (7.8 W/cm^2 , 2 s) + 365 nm UV modulation (135 mW/cm^2 optimal)	R6G primary; CV, 4-MBA, 4-NTP; methyl-parathion (MP) pesticide on fruit peels	MP LOD $1.54 \times 10^{-6} \rightarrow 8.31 \times 10^{-7}$ mg/mL (with UV)	$1.77 \times 10^6 \rightarrow 6.75 \times 10^6$ in O_2 under UV ($\sim 4\times$ modulation); 4.07×10^6 in CO_2 ; $1.7\times$ in N_2	Tunable Fermi level via UV-driven O_2 adsorption/desorption on RGO	Photo-actively modulated	[68]
RGO-coated Au film + Au NPs	Graphene-noble metal hybrid	RGO/Au sandwich (no organic stabilizer on AuNPs)	785 nm (~ 2 mW; 0.1 s mapping/1 s spectra)	R6G + naphthalene (calibration); 14 VOC biomarkers (clinical breath analysis)	NR	6.34×10^8 (R6G); 1.02×10^6 (naphthalene)	EM + selective π - π adsorption on RGO	Diagnostic application (gastric cancer); EF/LOD NR	[57]

Table 1. Cont.

System	Material	Hotspot	λ_{ex} (nm)	Probe Analyte	LOD	EF	Dominant Mechanism	Note	Ref.
Au NPs/graphene heterojunction	Graphene-noble metal hybrid	Au NPs on graphene	532 nm (Horiba HR800, 10 mW, 50× obj, 1 μm spot)	Hg ²⁺	Hg ²⁺ LOD 0.1 nM (20 ppt); 0.1–6000 nM dynamic range	40× signal vs. blank substrate (before annealing)	EM + CT		[111]
Inkjet-printed diatom biosilica droplets + Ag NPs (Marangoni)	PC-plasmonic (bio-derived, evaporation-driven)	Diatomaceous biosilica with plasmonic NPs in evaporating droplet	532 nm (Horiba LabRam HR800; 100× obj; 1.5 μm spot; spectra range 800–1800 cm^{-1})	R6G (model dye, single-molecule regime via accumulation); TNT (label-free real target)	TNT 4.5×10^{-17} g (label-free); R6G $\approx$ 0.1 nM (single-molecule regime); 100 pL droplets, $\sim 17\times$ higher concentration on diatom vs. glass	10^6 – 10^7 optofluidic-SERS sensitivity improvement vs. conventional pipette SERS	PC field localization + Marangoni convective enrichment + LSPR		[112]
Diatom biosilica + self-assembled Ag NPs	PC-plasmonic (bio-derived)	Natural diatom frustule with Ag NPs	NR	NR (mapping demonstration)	NR	NR (intensity mapped on/off frustule)	PC slow-light/guided-mode resonance + LSPR	Demonstrates PC contribution by spatial SERS mapping; no absolute EF	[56]
PC-enhanced plasmonic mesocapsules + Ag NPs	PC-plasmonic (bio + meso)	Submicron porous mesocapsules with Ag NPs in microfluidic channel	532 nm (Horiba LabRam; 10× obj; 2.0 mW; 10 s integration)	R6G (model); benzene & chlorobenzene (real-water target)	R6G LOD $\sim 10^{-13}$ M (single-molecule, in microfluidic channel); benzene/chlorobenzene 1×10^{-9} M in tap water	100× over ordinary Ag NPs (relative)	EM (Ag) + PC field localization + microfluidic mixing	Approaches single-molecule optofluidic-SERS; relative metric only	[113]
Diatom biosilica + Ag NPs + anti-mouse IgG	PC-plasmonic immunoassay	Sandwiched immunoassay on functionalized diatom PC	NR	Mouse IgG (with Raman reporter)	LOD 10 pg/mL	NR	EM + biorecognition + PC enhancement	Bioaffinity-mediated; immunoassay LOD	[114]

Table 1. Cont.

System	Material	Hotspot	λ_{ex} (nm)	Probe Analyte	LOD	EF	Dominant Mechanism	Note	Ref.
Diatomaceous earth fluidic-channel TLC-SERS	PC-plasmonic TLC-SERS	TLC stationary phase patterned with fluidic channels (lateral-diffusion suppressed)	785 nm (BWS465-785S BW&TEK portable, 30 mW, 5 s $\times$ 3 averaged)	Histamine in tuna (artificial-spiked + real spoiled samples; 0–48 h spoilage)	10 ppm artificial-spiked; quantified via PCA-SVR ML (FDA limit 50 ppm; EU 100 ppm)	NR	PC enhancement of plasmonic NPs + chromatographic preconcentration	TLC-SERS application	[115]
Microfluidic diatomite analytical device	PC-plasmonic TLC-SERS (microfluidic)	Diatomaceous earth in patterned microfluidic channels (suppresses lateral diffusion)	785 nm (Horiba LabRam HR800, 50 $\times$ Olympus, 2 μ m spot, 200 μ m pinhole)	Pyrene + 4-MBA (model mixture); cocaine in human plasma	Pyrene LOD 1 ppb on μ DADs (vs. 2 ppm normal TLC, $\sim$ 1000 $\times$ improvement); cocaine 10 ppb in plasma	NR	PC field enhancement + microfluidic preconcentration		[116]

Abbreviations & notes: EF—enhancement factor. AEF/SSEF/SMEF—analytical EF/SERS substrate EF/single-molecule EF (Le Ru & Etchegoin convention). “NR” indicates not reported. CM/EM—chemical/electromagnetic mechanism. CT—charge transfer. PICT—photo-induced charge transfer. PIHET—plasmon-induced hot electron transfer. PICTT—plasmon-induced interfacial charge-transfer transition. PIERS—photo-induced enhanced Raman spectroscopy. LSPR—localized surface plasmon resonance. DOS—density of states; “DOS at EF” = density of states at the Fermi level. Resonant probe—analyte with electronic absorption near the laser excitation wavelength (e.g., R6G, crystal violet, rhodamine B, methylene blue at 532 nm). LOD—limit of detection. Relative EF—value reported as a ratio against an internal reference (e.g., “100 $\times$ over plain Ag NPs”). NR—not reported.

3.1. Semiconductor Hybrids for Charge-Transfer and Optical-Field Regulation

Semiconductor-mediated hybrid SERS platforms are not governed by a single enhancement mechanism; rather, they provide a versatile hybrid platform in which plasmonic field amplification can be coupled with tunable semiconductor electronic states. Semiconductors possess band gaps between those of conductors and insulators and offer adjustable electrical conductivity, Fermi-level position, intermediate electronic states, band-gap engineering, and high chemical stability [34,78,95]. At the same time, their lower free-carrier density relative to noble metals generally restricts visible-range localized surface plasmon resonance (LSPR), so standalone semiconductor-based SERS typically exhibits more modest enhancement, often on the order of $\approx 10^3$. The central value of semiconductor-mediated hybrid architectures therefore lies not simply in increasing the enhancement factor (EF), but in making several enhancement pathways experimentally tunable, including interfacial charge-transfer (CT) direction, carrier-density regulation, defect-assisted photoinduced charge transfer (PICT), plasmon-mediated hot-electron transfer, Mie-assisted field localization, and analyte-selective resonance CT.

One important route begins with interfacial CT and band-structure engineering. In these systems, the semiconductor component does not merely serve as a passive support for plasmonic nanoparticles, but actively modulates the direction, probability, or energetic feasibility of interfacial charge transfer. In a TiO_2 -Ag-MPY-FePc system (Figure 2A), TiO_2 nanoparticles were shown to alter the direction and pathway of interfacial CT, contributing to CT-enhanced SERS and illustrating the usefulness of SERS for probing interfacial CT processes relevant to photovoltaic systems [59]. A related example is the $(\text{Ag})_x(\text{ZnS})_y$ system, where controlled ZnS doping was used to regulate carrier density [99]. The observed linear correlation between the SERS intensity ratio of non-totally symmetric to totally symmetric vibrational modes and carrier density indicates that carrier-density modulation can influence the CT contribution to SERS enhancement. Heterojunction engineering further extends this principle by introducing built-in electric fields and band alignment as additional handles for charge separation and resonant CT. For example, Cu-doped SnO_2 -NiO p-n heterostructures have been used to illustrate how heterojunction design and band alignment can facilitate CT-related Raman enhancement [102]. These examples are mechanistically useful because they attempt to control interfacial electronic structure, rather than only reporting overall EF improvement.

Building on baseline CT control, defect and vacancy engineering provides a second route to semiconductor-mediated enhancement by introducing intermediate electronic states that improve energetic matching between the substrate and adsorbed molecules. Improving the efficiency of PICT generally requires favorable alignment between molecular orbitals, semiconductor band states, and the excitation photon energy [117,118]. Ag/Ag-doped TiO_2 hybrid systems, for instance, show an irreversible and accumulated SERS behavior under near-infrared (NIR) light irradiation, with the enhancement attributed to synergistic TiO_2 -to-molecule CT and electromagnetic (EM) amplification from Ag nanoparticles (Figure 2B) [61]. Similarly, PIERS-type systems based on pre-irradiated TiO_2 demonstrate that photo-generated oxygen vacancies can transiently enhance Raman signals at plasmonic nanoparticle sites (Figure 2D) [60]. More broadly, oxygen incorporation or extraction, ultrathin defective nanosheets, and other defect-state engineering strategies can tune band-edge density of states (DOS), carrier density, and bandgap structure, thereby facilitating PICT [96,117,119–121]. These observations support a defect-assisted PICT interpretation, although strict separation from adsorption changes, conductivity variation, local-field redistribution, and stability effects remain challenging. Therefore, defect-mediated enhancement is most convincing when performance data are paired with controls that distinguish electronic-state modulation from other defect-induced changes in surface chemistry and morphology.

Beyond defect mediation, plasmon-mediated charge-transfer mechanisms, particularly plasmon-induced hot-electron transfer (PIHET) and plasmon-induced interfacial charge-transfer transition (PICTT), provide a more direct link between noble-metal plasmon decay and semiconductor electronic states. In PIHET, hot electrons generated by non-radiative plasmon decay in the metal component are injected into the coupled semiconductor before relaxation losses dominate [100,101,122]. Nanoarrays of Cu_2O and amorphous MoO_3 (a- MoO_3) monolayers, for instance, reported EFs of 3.19×10^{10} and 2.5×10^6 , respectively; the enhancement was attributed in the original studies mainly to PIHET-related processes [100,101]. Au-ZnO heterogeneous nanorods provide another representative metal-semiconductor system, in which plasmon-generated hot electrons in Au are transferred into ZnO; the same architecture also shows reproducibility after visible-light-assisted cleaning, suggesting potential for recyclable SERS platforms [62]. In contrast, PICTT represents a more direct interfacial excitation pathway, in which plasmon decay promotes electron transfer from the metal into the semiconductor conduction band without relying solely on thermalized hot-carrier injection [63,123]. The Au-CdSe nanorods system is often used as a conceptual model for this distinction, because CdSe, with its narrow bandgap and Au-CdSe Schottky barrier, can facilitate electron-hole separation. However, direct assignment of PIHET or PICTT in

SERS systems generally requires careful control of excitation wavelength, band alignment, Schottky barrier energetics, hot-carrier dynamics, and competing EM contributions. The principal PIHET, PICTT, and DICTT pathways and their associated contact architectures are summarized in Table 2.

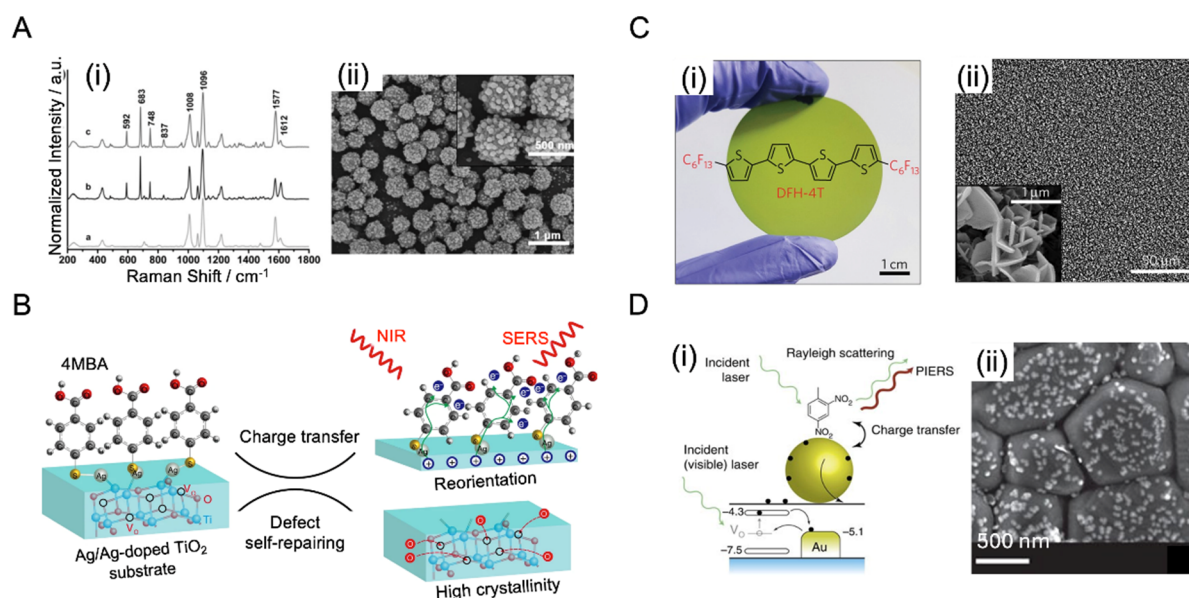
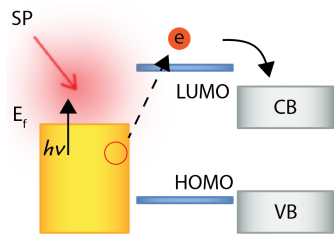
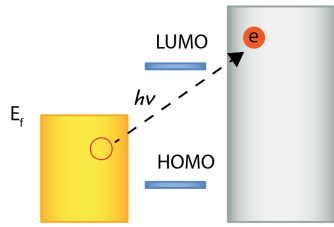


Figure 2. Semiconductor-Metal Hybrid SERS Substrates: Enhancement Mechanisms and Charge Transfer Dynamics. (A) Normalized SERS spectra of (i) Ag-MPY, Ag-MPY-FePc, and TiO₂-Ag-MPY-FePc systems in ethanol under 633 nm excitation. All spectra were normalized to the peak at 1008 cm⁻¹. (ii) SEM image of the TiO₂-Ag complex. Adapted with permission from Ref. [59]. Copyright 2019 Wiley-VCH Verlag GmbH & Co. KGaA. (B) NIR light-induced irreversible and accumulated SERS response of the 4MBA/Ag/Ag-doped TiO₂ hybrid system. The enhancement is attributed to a combination of synergistic effects, including NIR-induced thermal effects that increase crystallinity and modify polarizability, NIR-assisted charge transfer (CT) between the substrate and 4MBA via oxygen vacancies (*V*_o), and electrostatic attraction-driven molecular reorientation of 4MBA. Adapted from Ref. [61] under the terms of the Creative Commons Attribution 4.0 License; (C) (i) Optical image of a vapor-deposited DFH-4T film (5 cm diameter) with the chemical structure shown in the inset. (ii) Top-view SEM images of nanostructured DFH-4T films. Adapted with permission from Ref. [104]. Copyright 2017 Springer Nature. (D) Schematic of photo-induced enhanced Raman spectroscopy (PIERS). (i) Ultraviolet C light (UVC) pre-irradiation generates oxygen vacancies (*V*_o) in TiO₂ below the conduction band. Subsequent deposition of the analyte (e.g., dinitrotoluene) followed by 633 nm laser excitation promotes charge transfer from TiO₂ to the metal nanoparticles; the resulting increase in nanoparticle charge leads to PIERS enhancement. Furthermore, upon air exposure, oxygen fills the vacancies, reducing electron excitation and gradually diminishing the PIERS effect over 30 to 60 min, though the substrate can be subsequently regenerated by UVC exposure. (ii) SEM image of PIERS-active nanostructures. Adapted from Ref. [60] under the terms of the Creative Commons Attribution 4.0 License; changes were made.

Table 2. Representative Charge-Transfer Pathways in Molecule-Coupled Metal–Semiconductor Heterostructures.

CT Pathway	Schematic Diagram	Mechanistic Description	Contact Architecture
Plasmon-Induced Hot-Electron Transfer (PIHET)		Plasmon decay generates hot electrons in metal, which are transferred to semiconductor and then to molecule	Single and Multiple contact modes

Table 2. Cont.

CT Pathway	Schematic Diagram	Mechanistic Description	Contact Architecture
Plasmon-Induced Interfacial Charge Transfer Transition (PICTT)		Direct excitation of electrons from metal to molecule to semiconductor via plasmon decay	Sandwich contact mode
Direct Interfacial Charge Transfer Transition (DICTT)		Direct CT from metal to semiconductor mediated by a molecule, independent of plasmon effects	Sandwich contact mode

The schematic diagrams are adapted from Ref. [34] with permission from The Royal Society of Chemistry.

In parallel with electronic-state manipulation, semiconductor superstructures can also enhance SERS through optical-field localization. Besides LSPR, Mie scattering resonances in semiconductor structures, such as submicrometer-sized ZnO spheres, can generate strong local electromagnetic fields and thereby increase the probability of exciting charge-transfer states when spatial and energetic overlap is satisfied [52]. In this case, Mie resonance should be interpreted as an optical antenna effect rather than a direct CT mechanism: it enhances the local field and photon-matter coupling conditions, whereas CT and PICT modify molecular polarizability through electronic coupling. Mathematically, Mie scattering can be described by the scattering cross-section:

$$C_{\text{sca}} = \frac{2\pi}{k^2} \sum_{n=1}^{\infty} (2n+1)(|a_n|^2 + |b_n|^2) \quad (1)$$

Here, $k = 2\pi n_m / \lambda_0$ is the wavenumber in the surrounding medium, where n_m is the medium refractive index and λ_0 is the free-space wavelength; n is the multipole order, and a_n and b_n are the dimensionless electric and magnetic multipole scattering coefficients. Accordingly, C_{sca} has dimensions of area. Although the exact analytical framework is derived for highly symmetric geometries, Mie-like resonances can also arise in non-spherical semiconductor morphologies and are commonly evaluated using numerical methods such as discrete dipole approximation (DDA) or finite-difference time-domain (FDTD) simulations. In the context of hybrid SERS, this expression is most useful not as a direct quantitative predictor of EF, but as a conceptual boundary: Mie resonance describes optical field localization, whereas CT and PICT describe electronic coupling that modifies molecular polarizability. Distinguishing these contributions is important when interpreting semiconductor superstructures whose enhanced Raman response may arise from both optical antenna effects and interfacial charge transfer.

Organic semiconductors extend semiconductor-mediated SERS beyond inorganic heterostructures by demonstrating that charge-transfer enhancement can also be designed around molecular selectivity. Their advantages include structural versatility, solution-processable or vapor-deposited film fabrication, and tunable optoelectronic properties. For example, DFP-4T films with a fully π -conjugated structure exhibit an EF of 2.7×10^5 and a detection limit of 10^{-9} M, attributed to resonance CT between the organic semiconductor and the probe molecule, enabled by tuned molecular orbitals, electronic structure, and solid-state packing [103]. Nanostructured DFH-4T films similarly exhibit SERS activity even without a plasmonic layer, with an EF up to 3.4×10^3 ; after Au coating, the EF can increase to approximately 10^{10} , enabling sub-zeptomole-level detection (Figure 2C) [104]. More importantly, C₈-BTBT and D(C₇CO)-BTBT films demonstrate molecule-specific Raman enhancement only for methylene blue, the analyte with the lowest LUMO, suggesting an energy-feasible resonant transition from the organic semiconductor to the analyte frontier π orbitals [58]. These systems indicate that semiconductor-mediated SERS should not be evaluated solely by maximum EF, since orbital-level matching among the semiconductor, analyte, and excitation energy can introduce molecular selectivity into the enhancement pathway.

Overall, semiconductor-mediated hybrid SERS platforms should be evaluated by which enhancement pathway they render experimentally tunable, not only by their EF and limit of detection (LOD). These pathways include interfacial CT direction, carrier density, p-n band alignment, defect-assisted PICT, plasmon-mediated hot-electron transfer, Mie-assisted field localization, and analyte-selective resonance CT. EF and LOD remain key

performance metrics, but they do not by themselves identify the dominant enhancement pathway. Future studies would benefit from pairing performance evaluation with wavelength-dependent measurements, band-structure characterization, defect-state control, adsorption controls, and electromagnetic simulations, so that EM amplification, ground-state CT, PIHET/PICTT, Mie resonance, molecular adsorption, and analyte enrichment can be more clearly distinguished. Within the framework of this review, the systems discussed in this subsection correspond primarily to the synergistically coupled EM-CM, PIHET/PICTT-mediated, Mie-assisted, and analyte-selective CT entries summarized in Table 1.

3.2. Two-Dimensional Material Hybrids for Interface-Controlled Charge Transfer

Two-dimensional (2D) materials provide atomically thin platforms with rich physical and chemical properties for light–matter interactions, charge transfer, and molecular adsorption [124]. They are discussed here not as a simple list of SERS substrates, but as interfacial design platforms that control different variables in hybrid SERS enhancement. TMDs primarily tune phase-dependent density of states (DOS), band alignment, and layer-dependent charge-transfer (CT) efficiency; MXenes combine conductive carbide/nitride frameworks with termination-mediated adsorption and plasmonic assembly; and graphene regulates metal-molecule spacing, passivation, fluorescence quenching, adsorption, and externally induced CT modulation [125–129]. Table 1 provides coverage of representative 2D-material hybrid systems and analytical metrics, whereas the discussion below focuses on mechanistic design rules instead of ranking platforms by reported enhancement factor (EF) or limit of detection (LOD). The mechanism discussions are therefore based on the reported combination of energy-level alignment, phase/DOS analysis, wavelength dependence, molecular selectivity, CT or XPS evidence, electromagnetic/photonic simulations, and control experiments, rather than EF magnitude alone.

3.2.1. Phase and Layer Coupling in TMD Hybrid Interfaces

Two-dimensional TMDs have the general formula MX_2 , where M is a transition metal and X is a chalcogen. Their layer-dependent band gaps, tunable light absorption, and multiple crystalline phases, including 2H, 1T, and 1T', make them useful platforms for CT-mediated SERS [130,131]. In pristine semiconducting TMDs, the finite band gap and limited electronic coupling between substrate states and molecular frontier orbitals restrict the chemical mechanism (CM), even though the atomically flat surface can provide high spatial uniformity. Phase engineering therefore provides the first mechanistic handle: distorted 1T' or quasi-metallic phases increase the DOS near the Fermi level, lower the energetic barrier for interfacial CT, and strengthen interfacial dipole formation. Lateral 1T'@2H $\text{Mo}_{1-x}\text{Re}_x\text{S}_2$ is best viewed as a phase-engineered model substrate, in which rhenium (Re) incorporation controls the coexistence of semiconducting and quasi-metallic domains and thereby tunes CT-active DOS and adsorption sites within a continuous 2D lattice [29,67,132–136].

Layer number provides a second, material-dependent control variable. The comparison between PtSe_2 and ReS_2 indicates that layer-dependent SERS is not governed by thickness alone, but by whether interlayer coupling is strong enough to alter band alignment and charge distribution [137]. This distinction is important because weakly coupled layers may add surface area without substantially changing the CT pathway, whereas strong interlayer interactions can make stacking an electronic-structure tuning parameter. Distorted 1T'- ReS_2 nanosheets further support a photo-induced charge-transfer (PICT) contribution rather than energy transfer, with monolayer structures showing the strongest response [97]. Plasmon-free 1T'- WTe_2 and MoTe_2 atomic layers extend this point by showing that high-DOS telluride surfaces can support strong CT-driven SERS without noble-metal hotspots when analyte energy levels and substrate states are favorably matched [105,137].

Once a CT-active TMD interface is established, optical structures can amplify it through different routes. In 4H-Au@1T'- WS_2 nanowires, the 4H-Au core provides plasmonic field enhancement, while the ultrathin semi-metallic 1T'- WS_2 shell supplies an electronically active interface for CM/CT contribution; this coupled EM-CM architecture underlies the attomolar SERS detection reported for R6G and SARS-CoV-2 spike proteins (Figure 3B) [98]. In contrast, DBR-integrated 1T'- WTe_2 amplifies a plasmon-free CT platform through photonic field localization rather than through a noble-metal plasmonic junction [97]. These examples show why TMD hybrid SERS should be read through a sequence of linked variables: phase determines whether CT is electronically accessible, layer coupling determines whether it is tunable, and plasmonic or photonic architectures determine how effectively the CT-active interface is optically amplified.

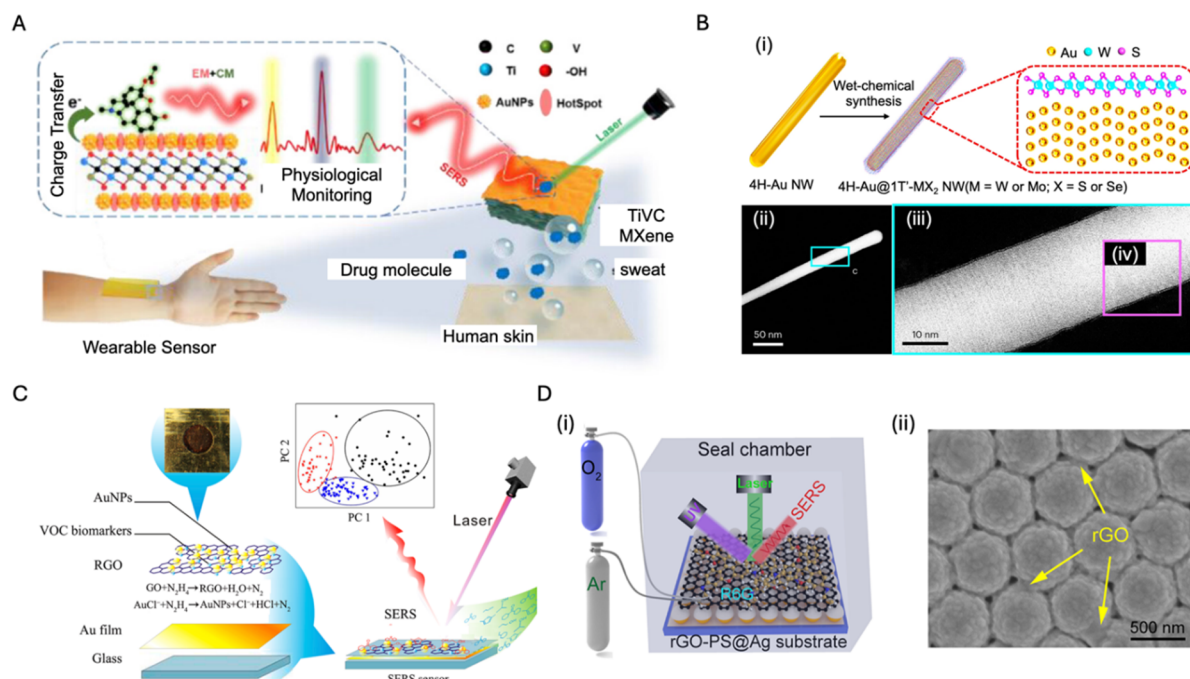


Figure 3. 2D Material–Hybrid Architectures for Advanced SERS Sensing. **(A)** Schematic illustration of a TiVC–OH–Au-based wearable SERS sensor for detecting drug molecules, such as nicotine, methotrexate, nikethamide and 6-acetylmorphine, from human sweat. Adapted with permission from Ref. [65]. Copyright 2024 American Chemical Society. **(B)** Synthesis and structural characterization of 4H-Au@1T'-WS₂ nanowires. **(i)** Schematic of the quasi-epitaxial growth of four types of 1T'-phase transition metal dichalcogenide (TMD) monolayers (WS₂, WSe₂, MoS₂, and MoSe₂) on 4H-phase gold nanowires (4H-Au NWs), forming 4H-Au@1T'-TMD core-shell nanowires. **(ii)** STEM image of a representative 4H-Au@1T'-WS₂ NW. **(iii)** HAADF-STEM image of the region marked in light blue in **(ii)**. **(iv)** Corresponding FFT pattern obtained from the pink region in **(iii)**. Adapted with permission from Ref. [98]. Copyright 2024 Springer Nature. **(C)** Schematic illustration of a SERS sensor integrated into a breath analysis platform, showing the overall sensing scheme. Adapted with permission from Ref. [57]. Copyright 2016 American Chemical Society. **(D)** Modulation of SERS signals in an O₂ atmosphere. **(i)** Schematic of in situ, real-time Raman measurements from a rGO–PS@Ag substrate under UV irradiation in O₂ (or Ar) atmosphere. The UV light is aligned with the Raman laser. **(ii)** SEM image of the rGO–PS@Ag substrate. Adapted with permission from Ref. [68]. Copyright 2022 American Chemical Society.

3.2.2. Surface Termination and Plasmonic Coupling in MXene Hybrid Interfaces

While TMDs primarily rely on phase and layer engineering to activate their semiconducting interfaces, MXenes introduce an alternative enhancement paradigm driven by their intrinsic metallic nature and rich surface chemistry. MXenes are transition-metal carbides and/or nitrides with the general formula $M_nX_nT_x$, derived from MAX phases by selective removal of the A element [66,138]. Their SERS behavior is distinguished from TMDs and graphene by the coexistence of metallic conductivity, high DOS, hydrophilicity, and chemically diverse surface terminations such as –O, –OH, and –F. These terminations are not merely structural labels: they determine adsorption geometry, localized dipole interactions, hydrophilicity, and the density of electronically active sites available for CT. Pristine or lightly modified MXenes therefore operate mainly through CM/CT pathways, while their limited intrinsic electromagnetic hotspots motivate integration with noble metals for coupled EM-CM enhancement [29,64,125,139].

Among intrinsic MXene examples, TiVC solid-solution MXene is a representative example because its high reported EF is linked to a bimetallic, high-DOS surface and a PICT-involved CM pathway [64]. Ti₂N paper substrates similarly show that conductive MXene surfaces can generate strong Raman enhancement without conventional noble-metal hotspots. Cross-study mechanistic comparisons require caution because EF definitions, resonant probe molecules, excitation wavelengths, adsorption protocols, and substrate uniformity vary substantially across reports [66]. The more defensible design rule is that MXene composition and surface chemistry should be selected to maximize electronically active adsorption sites and CT coupling for the target analyte [66]. Post-treatment can further turn this electronic potential into a more accessible sensing interface. For example,

alkaline-treated TiVC membranes increase the density of active sites and translate MXene-mediated CT into a flexible sensing format for molecular-level monitoring (Figure 3A) [65].

Noble-metal integration moves MXenes from predominantly CT-mediated substrates toward coupled EM-CM platforms. In MXene/graphene oxide/Au nanocluster fibers, Au nanoclusters provide plasmonic hotspots, while the MXene component contributes conductivity, CT participation, and mechanical flexibility; the reported retention of Raman intensity after long-term storage further highlights the translational value of stabilizing the MXene interface [106]. $\text{Ti}_3\text{C}_2\text{T}_x/\text{Au}$ nanoparticle dimer aptasensors illustrate a complementary design: the MXene sheet acts as a conductive and functional scaffold that brings plasmonic nanogaps and biorecognition elements into the same interfacial region for target-selective detection [107]. Other MXene-Au nanocomposites and plasmonic MXene hydrogels add antibacterial, photothermal, pollutant-enrichment, or remediation functions. Yu et al. synthesized MXene-Au nanocomposites capable of both rapid bacterial detection and efficient photothermal sterilization, achieving nearly 100% germicidal rates within minutes [108]. For environmental remediation and sensing, Yang et al. introduced plasmonic MXene hydrogels that not only achieve over 90% dye removal but also identify organic dyes at femtomolar-to-attomolar concentrations [109]. These deployment advantages should be distinguished from the primary enhancement pathway, which arises from the coupling of MXene-mediated adsorption/CT with plasmonic field localization.

3.2.3. Spacer Control and Charge Modulation in Graphene Hybrid Interfaces

Moving beyond the highly active charge-transfer interfaces provided by TMDs and MXenes, graphene highlights the critical role of structural and environmental regulation in hybrid systems. Graphene, a two-dimensional atomically thin crystal composed of densely packed sp^2 -hybridized carbon atoms in a honeycomb lattice, has attracted significant attention owing to its exceptional electrical, optical, mechanical, and thermal properties [140]. Graphene-based hybrids should be interpreted with a different emphasis. Pristine graphene can support molecule-graphene CT, while its visible-frequency plasmonic response and intrinsic Raman enhancement are weak relative to noble-metal substrates [110,140–142]. Its main contribution in hybrid SERS is therefore interfacial regulation. Graphene suppresses fluorescence, dissipates heat from plasmonic hotspots, protects analytes from photodamage, and provides π - π adsorption sites for aromatic molecules. These functions improve spectral cleanliness, reproducibility, and analyte localization, even when graphene is not the dominant source of Raman enhancement [68,124,143–147].

A clearly studied graphene-regulated architecture is the metal/graphene/metal junction. In Au triangular nanoarray/n-layer graphene/Au nanoparticle sandwich substrates, graphene acts as an atomically thin spacer that creates dense sub-nanometer plasmonic gaps while limiting uncontrolled metal-molecule contact; this enables sensitive and uniform Hg^{2+} detection through a TAMRA-tagged DNA probe [11]. This case is best described as EM-dominated hotspot engineering enabled by graphene-controlled spacing and passivation. Related Ag nanoparticle/graphene hybrids show that particle size and Ag-to-graphene CT can modulate the response, supporting a role for graphene-mediated interface control rather than a standalone high-EF graphene mechanism [110,111].

Graphene can also become an actively tunable CT medium when its Fermi level or surface electronic state is externally modulated. UV- and gas-atmosphere-controlled RGO/Ag hybrids demonstrate this behavior: exposure to O_2 , CO_2 , N_2 , or air under illumination changes the graphene-derived electronic environment and modulates CT at the plasmonic interface (Figure 3D) [68]. In real-sample sensing, RGO/Au breath-analyzer substrates highlight a more practical graphene function, namely selective adsorption and enrichment of volatile biomarkers at a plasmonic interface (Figure 3C) [57]. Together, these examples show that graphene hybrid SERS is strongest as a platform for controlling junction spacing, passivation, adsorption, and CT modulation, rather than as a direct analogue of high-DOS TMD or MXene substrates.

Taken together, 2D-material-supported hybrids are most useful when compared by the interfacial variable they control. TMDs emphasize phase- and layer-engineered CT, MXenes combine conductive and termination-rich surfaces with plasmonic assembly, and graphene regulates metal-molecule spacing, passivation, adsorption, and external CT modulation. This distinction allows Table 1 to serve for a mechanism-indexed comparison of representative architectures, with EF and LOD retained as context-dependent performance indicators rather than universal ranking metrics.

3.3. Photonic-Crystal Hybrid Interfaces for Field Localization and Analyte Enrichment

Photonic crystals (PCs) are a class of materials that provide novel capabilities in manipulating the flow of photons [148,149]. These materials consist of nanoscale periodic arrays of materials with different refractive indices, creating “photonic band gaps” in which photons cannot propagate through the material. PCs can be fabricated by

high-precision microfabrication, which offers substantial design control at higher cost. Naturally occurring structures offer low-cost alternatives but less design control. For the latter, materials such as diatoms [150] and opals [151] are two representative examples that display vivid colors due to their porous, periodic silica nanostructures.

Integrating PCs with traditional plasmonic nanostructures can create a new class of hybrid SERS substrates with multiple functionalities. Since PCs can intensify optical fields by slow-light effects [152] and guided-mode resonances (GMRs) [153,154], they can be used to further amplify metallic-nanoparticle plasmonic resonances, creating high-intensity hotspots for optimized SERS sensing [53,54]. Alongside simulation results showing meaningful SERS improvement for both individual plasmonic NPs [55] and a collection of randomly distributed NPs [112], the enhancement has also been experimentally verified by mapping SERS signals around a diatom frustule (Figure 4a) [56].

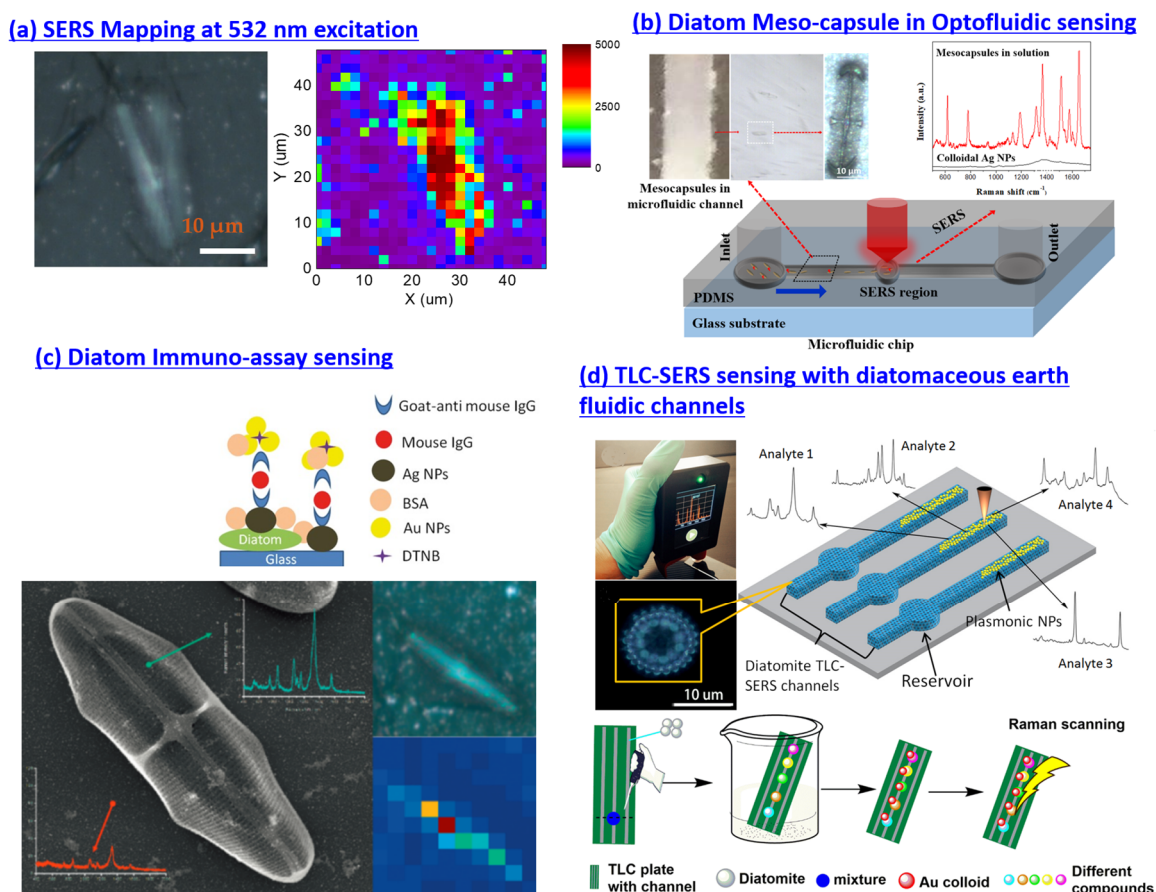


Figure 4. Diverse SERS sensing applications enabled by diatom photonic crystals. (a) Comparison of the optical image of a diatom frustule and its SERS mapping data (Reproduced with permission from Ref. [56]. Copyright 2014 IEEE.); (b) Schematic of diatom meso-capsule for optofluidic sensing with accelerated mass transport (Reproduced with permission from Ref. [113]. Copyright 2019 Wiley-VCH Verlag GmbH & Co. KGaA.); (c) Illustration of diatom SERS immunoassay and experimental results showing the enhanced sensitivity to detect mouse IgG (Adapted with permission from Ref. [114]. Copyright 2014 Wiley-VCH Verlag GmbH & Co. KGaA.); (d) Schematic of TLC-SERS sensing using diatomaceous earth fluidic channels (Adapted with permission from Ref. [116]. Copyright 2017 Elsevier B.V.).

Further improvements in SERS performance can be achieved by combining additional strategies such as (1) accelerating mass-transport to deliver trace analytes to the sensor surface in optofluidic sensing [112,155,156], or (2) subsequent functionalization of the PCs [157]. For the former, methods such as utilizing evaporation-based thermal Marangoni effects have shown that the resulting convection flow can combat the diffusive force, leading to label-free sensing of 4.5×10^{-17} g trinitrotoluene (TNT) at the diatom surface [112]. In another example, microfluidic channel-enabled mixing of PC-enhanced plasmonic meso-capsules and analytes, in conjunction with porous submicrometer mesocapsules decorated with Ag NPs, leads to an approximately 100-fold higher signal and a >1000-fold lower LOD, compared with ordinary Ag NPs (Figure 4b) [113]. For the latter, antibody functionalization of PCs has been explored for enhancing biosensing sensitivity and selectivity. One example

showcases a sandwiched SERS-active immunoassay substrate, functionalizing diatom PCs with anti-mouse IgG, showing the detection limit of mouse IgG down to 10 pg/mL (Figure 4c) [114]. Similar SERS immunoassays have also been applied to detect interleukins in blood plasma [158] and circulating cancer-specific protein biomarkers in serum [159].

PCs can also be used as the stationary phase of thin-layer chromatography (TLC). Compared with traditional analytical chemistry methods such as high-performance liquid chromatography (HPLC) and gas chromatography (GC), TLC is a rapid, cost-effective technique for separating and identifying mixed compounds [160]. The combination of TLC with SERS, or simply abbreviated as TLC-SERS, creates a lab-on-a-chip sensing platform that can simultaneously perform chemical separation and spectral sensing [161,162]. However, the biggest problem is that the TLC stationary phase is usually not a good SERS substrate, and the sensitivity of TLC-SERS is not sufficient for trace-level chemical sensing. Diatomaceous earth consisting of fossilized remains of ancient diatoms in geological deposits stands out as the TLC-SERS substrate because: (1) the porous hydrophilic feature makes it an excellent stationary phase for TLC separation, and (2) the photonic-crystal effect effectively enhances the plasmonic nanoparticles for SERS sensing. Diatomaceous TLC-SERS has been successfully applied to various real-world sensing applications, including identifying Sudan I in cooking oil [163], detecting histamine in seafood [115], and label-free sensing of phenethylamine and miR21cDNA in human plasma [164]. One noticeable improvement to TLC-SERS sensing is replacing traditional thin-layer plate with patterned fluidic channels formed by diatomaceous earth as shown in Figure 4d, which can prevent lateral diffusion of analytes as they move along the stationary phase [115,116]. As a result, the analyte concentration at the detecting spot is significantly improved, resulting in unprecedented sensitivity down to the parts-per-billion (ppb) level.

In summary, integrating PCs with SERS substrates can greatly improve SERS performance by utilizing their unique properties such as GMRs. Within the established mechanistic framework, bio-photonic-crystal-plasmonic platforms operate primarily in the electromagnetic (EM)-dominated regime, further augmented by photonic field localization. Notably, several of the systems surveyed in this subsection additionally result in localized mass-transport effects—such as Marangoni convection in evaporating diatomite droplets and chromatographic flow in TLC-SERS configurations. By dynamically concentrating analytes at the sensing interface, these transport phenomena effectively bridge passive architectures in Table 1 with the active platforms to be introduced in the following section and Table 3. Such mechanistically diverse PC-SERS platforms based on biological materials offer a framework for transitioning laboratory sensing into reliable, real-world biochemical applications.

Table 3. Comparative summary of active-enrichment and field-guided mobile SERS platforms.

System	Actuation Mode	Mechanism	Active Component	Target Analyte	LOD	Detection Time	Note	Operating Environment	Ref.
Ni/Au-decorated carbon helical nanorobots	Magnetic	Magnetic-field-driven helical propulsion	Carbon nanocoil with Ni/Au coating; helix length $8.6 \pm 0.8 \mu\text{m}$	Intracellular HeLa cytoplasm + nucleus (endogenous biomolecule fingerprints)	Subcellular fingerprints; LOD not reported	Real-time SERS at fixed cell location after entry	Magnetic corkscrew, $6.7 \mu\text{m/s}$ avg; $B = 5 \text{ mT}$, $f = 6\text{--}8 \text{ Hz}$; mechanical penetration of cell membrane + nuclear envelope	HeLa cells (intracellular); also DI water, FBS, PEG, intestinal fluid	[69]
MAuNS— Fe_3O_4 core + gold nanostar (AuNS) shell	Magnetic + Catalytic + Photothermal	Magnetic steering + glucose-oxidase-like nanozyme + photothermal	Core-island MAuNS = Fe_3O_4 core + Au-nanostar (AuNS) islands	CV + 4-MBA monolayer (model); intracellular HeLa contents	NR	Not stated; SERS integration 10 s	Glucose-fueled enhanced diffusion	Aqueous (glucose); intracellular HeLa	[165]
Ag-NP-coated diatom frustule + Ni magnetic film	Magnetic	Magnetic-field-driven rotational actuation (asymmetric Ni patch)	Bio-derived diatom photonic crystal frustule with self-assembled Ag NPs and asymmetric Ni magnetic coating	Salmon sperm DNA (large biomolecule, 724 & 1319 cm^{-1} peaks)	$\approx 80 \text{ nM}$ at $S/N = 5$; range $80 \text{ nM}\text{--}4 \mu\text{M}$	Characteristic capture time, τ_{cap} , scaled with rotation rate as $\tau_{\text{cap}} \propto \omega^{-0.41}$ over the reported operating range: $\approx 30 \text{ min}$ at 1200 rpm vs. 2 h passive ($\geq 4\times$ capture-rate speedup); $\sim 3\times$ detection-speed improvement at 80 nM at 630 rpm	Magnetic rotation up to 1200 rpm ; 532 nm Raman, $500 \mu\text{W}$, $25 \mu\text{m}$ spot	Aqueous solution	[26]

Table 3. Cont.

System	Actuation Mode	Mechanism	Active Component	Target Analyte	LOD	Detection Time	Note	Operating Environment	Ref.
Magnetic nanochain integrated microfluidic biochip	Magnetic	Magnetic mixing + bioseparation in microfluidic channel	Magnetic nanochains in microfluidic biochip	Cancer biomarkers (PSA, AFP, CEA—clinical serum, n = 20); bacteria (<i>E. coli</i> O157:H7, <i>S. aureus</i>); SERS reporters MATT/DCTP/DFT P/TFTP	LOD $\approx$ 10 pg/mL (proteins); 4/10/5 ng/mL (PSA/AFP/CEA); bacteria 10^0 – 10^4 CFU/ μ L range; EF > 10^5	$\approx$ 8 min from 1 μ L body fluid	Magnetic nanochains as nanoscale stir bars; 4 orthogonal electromagnetic coils; 100 $\times$ enrichment via volume difference (mixing vs. detection chamber); λ_{ex} 633 + 785 nm, 2–5 μ m spot	Body fluid (1 μ L)/clinical microfluidic chip	[20]
Photocatalytic matchstick-like nanomotor (Ag-NW/silica core-shell + AgCl tail)	Optical (photocatalytic)	Light-induced self-diffusiophoresis (phototaxis)	Silver nanowire/silica core-shell with AgCl photocatalytic tail	Crystal violet (CV, 10^{-4} M); MCF-7 breast cancer cells	10^{-4} M CV demonstrated; no LOD reported	$\approx$ 10 s of focused UV irradiation to form aggregates	Light-powered self-diffusiophoresis (AgNW@SiO ₂ /AgCl matchlike, $\sim$ 15 μ m long); positive phototaxis aggregation; SHIERS via 5–10 nm SiO ₂ shell	Aqueous (water); fixed MCF-7 cells (cellular)	[71]
Optoelectric Si-nanorod/Ag-NP Raman nanosensor	Electric + optical	Light-gated optoelectric enrichment at the laser spot	Si nanorod array with root electrodes and dense Ag NPs	Adenine; vertebrate DNA	0.6 fM adenine	$\approx$ 15 min to reach $\approx$ 150-fold enhancement at -0.8 V	LOD improved by five orders of magnitude at -0.8 V	Aqueous electrochemical cell	[166]
Magnetic micromotors with spiky gold nanoshells	Magnetic	Magnetic-field-driven micromotor propulsion	Spiky Au nanoshell on magnetic core $\rightarrow$ high-curvature plasmonic hotspots	4-ATP (calibration reporter); thiram (target); <i>E. coli</i> , <i>S. aureus</i> (label-free)	Thiram LOD 10^{-8} M (Ag@Au); 4-ATP linear 10^{-11} – 10^{-8} M	Bacterial capture from bulk: hours to overnight	3D rotating B-field ($B_{xy} = B_z = 4.5$ mT; $\omega_M = 40\pi$ rad s $^{-1}$); on hydrogel 2–3 $\times$ faster than glass; closed-loop trajectory; λ_{ex} 785 nm, 0.438 mW, 10 s	DI water, lake water, salty culture medium; blood plasma	[70]

Table 3. Cont.

System	Actuation Mode	Mechanism	Active Component	Target Analyte	LOD	Detection Time	Note	Operating Environment	Ref.
Optical-tweezers-controlled hotspot—Ag-NP-coated silica beads	Optical (trapping)	Optical trapping → controllable plasmonic junction	Two AgNP-coated silica beads optically focused into a tunable plasmonic gap	Native protein structures—hemoglobin, lysozyme, BSA	100 nM hemoglobin; 1 μ M lysozyme/BSA; 1 μ M α -synuclein; 10^{-9} M and 10^{-11} M RhB	1 s acquisition; flow-through microfluidic continuous detection	Dual-trap optical tweezers; sub-nm interbead distance control (10–900 nm gap); 1.26 μ m AgNP-coated silica beads; λ_{ex} 532 nm Raman + 1064 nm trap	Aqueous; native-conformation conditions (no surface tethering)	[73]
Optical plasmonic tweezer + microfluidic flow chamber	Optical (trapping) + microfluidic	Optical plasmonic tweezing in flow	Plasmonic tweezer-trapped hotspot in microfluidic channel	Amylin (hIAPP)—pH-dependent species; transient amyloid intermediates	500 nM NBA proof-of-concept; 10^{-7} M MB/ 10^{-8} M NBA (BiASERS); 10 μ M hIAPP at pH 5.5 & 7.4; 50 μ M Tyr	Continuous on/off switching in seconds; 24 h pH-incubation studies	Optical plasmonic trap of single AgNP into bead-dimer junction (~20 nm gap via oligonucleotide tether); λ_{ex} = 532 nm, P = 2.7 mW (Raman); λ_{trap} = 1064 nm, P_{trap} = 8.0 mW (trapping)	Aqueous; pH-controlled; microfluidic	[74]
3D electrokinetic tweezers—anisotropic nanowire bioprobe	Electric	Composite electrokinetic effects (electrophoresis, dielectrophoresis, electrorotation, electroalignment)	Anisotropic nanowire bioprobe in AC/DC electric field	General-purpose nanowire bioprobng platform	NR	NR	20 nm 2D position precision; 0.5° angular precision; rotation up to 18,000 rpm; 90 nm position accuracy at 2.7 μ m/s; PI feedback anti-Brownian; 4 in-plane + 2 out-of-plane electrodes; λ_{ex} 532 nm Raman, 360 μ W after 20× obj	Aqueous solution (low ionic strength implied)	[75]
Plasmonically active Au–Ni–Au rotary nanomotor	Electric (rotary)	Electric-field-driven rotation; rotation speed modulates molecular release	Au–Ni–Au three-layer nanowire core/silica shell/dense Ag-NP outer layer	Nile Blue and R6G (single and multiplex release)	NR	Quasi-real-time Raman monitoring (0.5 spectrum s^{-1}); release tracked for up to 30 min	Release rate increases with rotation speed through convection-induced diffusion-layer thinning	DI water; electrically actuated microelectrode platform	[27]

Table 3. Cont.

System	Actuation Mode	Mechanism	Active Component	Target Analyte	LOD	Detection Time	Note	Operating Environment	Ref.
Porous superstructure I Au-nanorod/Ag-NP Raman nanosensor	Electric (transport/rotation and release control)	Electric-field-guided manipulation and AC-field-tuned molecular release	Au nanorod (~5 $\mu\text{m} \times 280$ nm) with ~850 nm porous silica superstructure and dense Ag NPs in concentric nanocavities	R6G; BPE; Nile Blue; adenine	R6G LOD 10^{-15} M (1 fM); BPE 10^{-13} M	Quasi-real-time Raman monitoring	Dual-function ultrasensitive detection and tunable release; $\lambda_{\text{ex}} = 532$ nm	Aqueous suspension under external electric fields	[167]
Ring-like $\text{Fe}_3\text{O}_4/\text{Au}$ nanozyme	Magnetic + Catalytic	Magnetic separation + peroxidase-like catalysis	Reusable ring-like $\text{Fe}_3\text{O}_4/\text{Au}$ nanozyme	TMB (probe via peroxidase oxidation); GSH and cholesterol (target biomolecules)	GSH LOD 0.10 μM (linear 1–150 μM); cholesterol LOD 0.08 μM (linear 1–100 μM); UV-vis comparison LODs 0.88/0.48 μM	30 min incubation at 37 $^\circ\text{C}$ for catalysis; 11 min reaction equilibrium for R- $\text{Fe}_3\text{O}_4/\text{Au}$	Superparamagnetic ring- Fe_3O_4 (160/60/50 nm OD/ID/thickness); magnetic recovery, 5 reuse cycles; $\lambda_{\text{ex}} 785$ nm portable Raman	Human serum (clinical, Xuzhou First People's Hospital); HAc-NaAc buffer pH 4.0	[168]
$\text{Fe}_3\text{O}_4@\text{TiO}_2$ exosome accumulation + target-triggered SERS	Magnetic	Magnetic-induced exosome accumulation	$\text{Fe}_3\text{O}_4@\text{TiO}_2$ core-shell + target-triggered Raman reporter	Exosomal microRNA (in situ)	0.21 fM exosomal miRNA-10b LOD; linear 0.33 fM–1.65 pM; tested 10^7 – 5×10^{10} exosomes/mL; 4 μL serum	3–4 h SERS-tag/exosome incubation + 10 min $\text{Fe}_3\text{O}_4@\text{TiO}_2$ magnetic capture (no ultracentrifuge, no lysis, no PCR amplification)	$\text{Fe}_3\text{O}_4@\text{TiO}_2$ (~200 nm) magnetic exosome capture via TiO_2 -phosphate affinity (96.5% in 10 min); LNA-Au@DTNB hotspot trigger inside intact exosome; $\lambda_{\text{ex}} 785$ nm, 10 mW, 50 $\times$ objective, NA = 0.75, 1 s	Serum from PDAC patients (n = 15) and healthy controls (n = 15); clinical liquid-biopsy	[169]

Table 3. Cont.

System	Actuation Mode	Mechanism	Active Component	Target Analyte	LOD	Detection Time	Note	Operating Environment	Ref.
Magnetic-induced mixing SERS—ternary specific antigens	Magnetic	Magnetic-induced mixing during SERS readout	Magnetic SERS substrate with ternary antigen-recognition labels	Liver cancer—simultaneous detection of three specific antigens	AFP 0.15 pg/mL; CEA 20 pg/mL; FER 4 pg/mL (LOD); ranges 0.5–500/50–2000/10–200 pg/mL	≈1 h immunoreaction at 37 °C × 2 (sandwich); plus magnetic separation	Carboxyl-coated Dynabeads MyOne (1.05 μm) for magnetic 3D packing/aggregation under external magnet; alkyne/nitrile reporters in biosilent 2105/2159/2227 cm ^{−1} window; λ _{ex} 632.8 nm, 40× obj, 10 s	2% human serum; 39 clinical samples; 86.7% liver-cancer diagnostic accuracy	[170]
Label-free magnetic SERS for exosomes	Magnetic	Integrated magnetic separation + label-free SERS	Magnetic SERS platform with integrated separation chamber	Exosomes (label-free)	NR	5 h Fe ₃ O ₄ /Au internalization + 1 min magnetic separation	Magnetic separation in 1 min (external magnet); superparamagnetic Fe ₃ O ₄ (~12 nm core) + Au shell (~20 nm); aggregation in exosome enhances SERS; FDTD validates hotspots	Cell culture supernatant (MCF-7, MDA-MB-231, MCF-10A, HepG2, Hep1-6, L02); mouse serum (healthy vs. tumor-bearing); PCA → 100% sens/spec	[171]
CRISPR-Cas-mediated SERS assay	Biomolecular (CRISPR) + plasmonic	dCas9/gRNA sequence-specific binding to target genomic DNA, followed by MB intercalation and magnetic enrichment; no trans-cleavage or target amplification	Au MNP–dCas9/gRNA probes with MB as an intercalating Raman reporter	Species-specific virulence-gene targets: spa (<i>S. aureus</i>), pgi (<i>A. baumannii</i>), and uge (<i>K. pneumoniae</i>)	14.1 fM (<i>S. aureus</i>); 9.7 fM (<i>A. baumannii</i>); 8.1 fM (<i>K. pneumoniae</i>)—without amplification	≈60.5 min for the listed assay steps (50 min target-binding incubation + 10 min MB intercalation + 30 s magnetic concentration), excluding washing and SERS readout; ≥6 h for PCR.	Au MNPs (Fe ₃ O ₄ ~110 nm core + SiO ₂ ~95 nm shell + Au; total ~390 nm); superparamagnetic (<i>M_s</i> = 58.7 emu g ^{−1} (= 58.7 A m ² kg ^{−1}); λ _{ex} 632.8 nm He-Ne, 50× obj, ~2.5 μm spot	Mouse blood and tissue homogenates (in vivo-derived); 3D nanopillar swab samples (skin/tail/foot/glove)	[172]

Table 3. Cont.

System	Actuation Mode	Mechanism	Active Component	Target Analyte	LOD	Detection Time	Note	Operating Environment	Ref.
Magnetic mesoporous nanosponge (β -cyclodextrin polymer + magnetic NPs)	Magnetic	Magnetic-induced bulk enrichment + chromatographic-like adsorption	Mesoporous β -CD polymer nanosponge with embedded magnetic NPs	Organic micropollutants	Lowers LOD by 2–3 orders vs. static SERS	$\approx 90\%$ removal in <1 min	$\approx 1000\times$ concentration factor	Aqueous (environmental water)	[76]
Polydopamine-enabled plasmonic nanogapped nanoparticles	plasmonic	Polydopamine-mediated tailored nanogap engineering	Plasmonic nanogap NPs with polydopamine spacer	RhB and 4-NTP Raman reporters; <i>E. coli</i> O157:H7 (food-borne pathogen); also MOF and AuNR cores	Linear $10\text{--}10^8$ CFU/mL; sensitivity $\sim 10^2$ CFU/mL	10 min magnetic separation	Magnetic separation enrichment via Fe_3O_4 core; polydopamine-templated 2 nm nanogap; λ_{ex} 633 nm (RhB) + 785 nm (pathogen)	Aqueous (general)	[173]
$\text{Fe}_3\text{O}_4\text{@Ag}$ magnetic SERS nanotag + lateral-flow strip	Magnetic + immunoaffinity	Magnetic enrichment + dual-Raman-label sandwich on LFA strip	$\text{Fe}_3\text{O}_4\text{@Ag}$ NPs functionalized with dual Raman dyes + virus-specific capture antibodies	Influenza A H1N1 + human adenovirus (HAdV)—simultaneous	H1N1: 50 pfu/mL; HAdV: 10 pfu/mL	≈ 20 min total assay (incubation + lateral flow); λ_{ex} 785 nm Renishaw inVia, 3 mW, 5 s, 50 μm spot, 20 $\times$ obj	$\approx 2000\times$ sensitivity improvement vs. traditional colloidal-Au LFAs	Real biological samples (human throat/nasopharyngeal swabs); no pretreatment	[77]

Abbreviations & notes: LOD—limit of detection. **Relative metric**—performance reported as a fold-improvement against an internal reference (e.g., “2000 $\times$ over colloidal-Au LFAs”). **LFA**—lateral flow assay. **MAuNS**—magnetic gold-nanostar nanozyme. **β -CD**— β -cyclodextrin (used as polymer host in mesoporous nanosponge). **CRISPR**—Clustered Regularly Interspaced Short Palindromic Repeats (here: dCas9/gRNA target recognition coupled with MB-based SERS reporting and magnetic enrichment). **hIAPP**—human islet amyloid polypeptide (amylin); single-molecule pH-dependent species used to probe amyloid intermediates. **NR**—not reported.

4. Hybrid SERS Platforms for Active Molecular Enrichment

Ultrasensitive SERS sensors that rely solely on passive molecular diffusion face an intrinsic barrier: the ultrahigh sensitivity enabled by nanoscale hotspots for detecting ultra-low-concentration analytes inevitably results in slow detection kinetics. Conventional nanosensors can require hours to detect analytes in the 1 pM–1 fM range [166]. Such prolonged detection times increase susceptibility to noise and compromise sensing fidelity.

To address this limitation, active and responsive SERS platforms improve analyte enrichment in three recurring ways. First, motion-enhanced platforms use mobile SERS-active probes or hotspots to increase molecular capture speed by a sensor's surface, reducing diffusion-limited detection times. Second, field-guided platforms use optical or electric fields to position plasmonic components, assemble hotspots, or bring analytes into defined sensing regions. Third, capture- and separation-assisted magnetic platforms isolate and concentrate targets from complex matrices before Raman readout. Across these cases, the inherited SERS enhancement pathway is coupled to an analyte-enrichment strategy. The examples listed in Table 3 therefore emphasize detection time, operating environment, and enrichment or actuation mode rather than EF alone.

4.1. Motion-Enhanced Hybrid SERS Platforms

This subsection focuses on hybrid SERS systems in which SERS-active probes or hotspots are actively transported, rotated, or propelled through the sample. Their main contribution is to accelerate molecular capture by a sensor's surface, while preserving the EM, CM, or coupled EM-CM enhancement mechanisms enabled by the sensing material.

Micro/nanomotors are miniaturized machines capable of dynamic responses such as transport, rotation, and swarming under chemical, magnetic, optical, or electric stimuli [36,174]. When integrated with SERS-active plasmonic structures, these platforms create “motile hotspots” that actively sample analyte-rich regions or enhance analyte–substrate interaction in solution. This strategy directly addresses a major limitation of static SERS sensors: at ultralow analyte concentrations, passive diffusion alone can make molecular capture at nanoscale hotspots slow and inefficient [26,27,175,176]. However, translating this “motile hotspot” concept from idealized, low-viscosity laboratory solutions to complex biological fluids presents significant challenges. Viscous biological media inherently limit propulsion efficiency due to the dominant viscous drag forces operating at low Reynolds numbers. Concurrently, the abundance of biomacromolecules in these environments leads to nonspecific surface adsorption that can physically block SERS-active nanogaps, impede targeted molecular enrichment, and generate severe background spectral interference. The propulsion mechanisms, summarized in Table 4, have been detailed in several review articles [175,177,178].

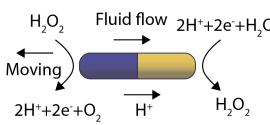
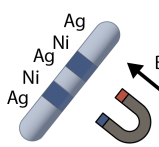
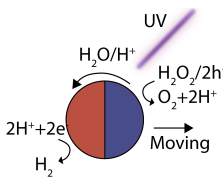
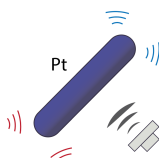
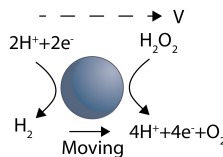
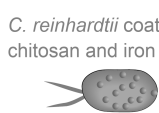
Magnetic Nanomotor Sensors: Magnetic-field-driven nanorobots represent a particularly attractive class of active SERS platforms due to their precise spatiotemporal control, fuel-free actuation, high reconfigurability, and generally benign operation in biological environments. Compared with chemically powered systems, magnetic actuation avoids the introduction of reactive fuels and offers superior controllability, which is advantageous for in vivo or intracellular applications. For instance, Ni/Au-decorated carbon helical nanorobots have demonstrated the capability to mechanically penetrate single-cell membranes and nuclear envelopes, enabling intracellular SERS interrogation of both cytoplasmic and nuclear compartments [69]. While such demonstrations highlight the potential for precise cancer theranostics with minimal cytotoxicity, challenges remain in achieving in vivo precision control and long-term stability.

Magnetic microrobots have also been explored for selective bacterial detection, including discrimination between *E. coli* and *S. aureus*, through active approach, contact formation, and localized SERS acquisition. Detection limits down to 10 nM for thiram have been reported, with operational stability maintained over weeks [70].

More recently, nanozymatic magnetic nanomotors (MAuNS), integrating a magnetic Fe₃O₄ core with gold nanostars, have combined magnetic propulsion with plasmonic and catalytic functionalities [165]. The Fe₃O₄ core enables remote magnetic steering, whereas the AuNS provide both strong SERS activity and glucose oxidase–like catalytic behavior, enhancing mass transport and cellular uptake for improved photothermal therapy. In addition, multimodal imaging, via magnetic resonance imaging of Fe₃O₄ and photoacoustic imaging of AuNS, facilitates real-time tracking. Despite these advances, integrating propulsion, hotspot uniformity, and quantitative SERS readout into a single robust platform remains an ongoing challenge.

Another notable strategy involves the active actuation of magnetic-film-coated bioparticles to accelerate biomolecule enrichment and detection [26]. In this study, Ag-nanoparticle-coated diatom frustules were asymmetrically functionalized with a magnetic Ni film, enabling rotational actuation under an external magnetic field while providing abundant plasmonic hotspots for SERS detection.

Table 4. Propulsion mechanisms of typical nanomotors.

Driven Type	Schematic	Components	Propulsion Mechanism	Advantage
Chemical		– Catalytic materials: Pt, Au, Ni, MnO₂ – Asymmetric structures: Janus microspheres, bimetallic nanowires	– Self-electrophoresis – Bubble recoil – Self-diffusiophoresis	– High-speed movement – Performance in high-ionic-strength media depends strongly on the propulsion mechanism and surface chemistry – Requires specific fuels
Magnetic Field		– Ferromagnetic materials: Fe, Ni – Ferrimagnetic material: γ-Fe₂O₃ – Helical or flexible structures	– Magnetic field gradients – Rotating magnetic fields induce helical motion – Oscillating magnetic fields drive flexible chains	– Fuel-free operation with remote controllability – Suitable for complex environments – Adjustable helix pitch for optimized propulsion efficiency
Light-Driven		– Photocatalysts: TiO₂, ZnO, Fe₂O₃, Au – Semiconductor materials	– Photochemical reactions – Photothermal interactions – Generation of electron-hole pairs leading to diffusiophoresis or bubble propulsion – Thermophoresis driven by local thermal gradients	– High temporal and spatial resolution control – Enables smart behaviors such as phototaxis and swarming – Can operate without externally added fuel in suitable photochemical systems – Precise trajectory control via light parameters
Ultrasound		– Asymmetric metallic nanowires – Bimetallic rods: Au or Pt with Rh, Ru, Pd, Ag)	– Acoustic radiation pressure generates net propulsion force – Structural density and shape influence propulsion	– High biocompatibility – Suitable for biomedical applications – Optimization of propulsion efficiency through acoustic field parameters
Electric Field		– Electrochemically active conductive micro-/nanoparticles – Asymmetric catalytic or bipolar-electrode interfaces	– Applied voltage drives electrochemical redox reactions – Ionic gradients and/or gas evolution generate self-electrophoretic or bubble-recoil propulsion	– Remote electrical control with adjustable propulsion speed – Performance depends on electrolyte composition and interfacial reactions – Requires suitable electrolytes and applied electric fields
Biohybrid		– Natural biological robots: sperm, bacteria, algae – Synthetic microstructures: microtubes	– Flagellar motion of biological robots combined with synthetic structures – Cell-driven self-powered propulsion	– Long-lasting and rapid movement – Enhanced biocompatibility – Supports chemotactic behavior and autofluorescence

In both cases, detection kinetics were rationally enhanced through active motion—specifically, increased rotational or translational speeds—which increased analyte flux toward the sensing surface. Numerical simulations and theoretical analyses revealed that such active propulsion effectively reduces the effective diffusion-boundary-layer thickness, thereby accelerating molecular flux to the sensor interface. As a result, detection speed is substantially improved while preserving high sensitivity [26].

Light-Powered Nanomotor Sensors: Light represents another widely adopted energy source for remotely actuating nanomotors, offering high spatial and temporal precision without direct physical contact [179]. Photocatalytically powered, matchstick-like nanomotors, which are composed of a silver nanowire/silica core–shell structure with a silver chloride tail, have been propelled via light-induced self-diffusiophoresis [71]. Their phototactic motion enhances local analyte concentration and signal intensity for biochemical sensing. Such systems have demonstrated light-controlled SERS detection of crystal violet as well as MCF-7 breast cancer cells, highlighting their potential for smart, on-demand sensing at the micro- and nanoscale. Nevertheless, challenges related to propulsion efficiency in complex media and long-term photostability remain to be addressed. In addition, optical scattering and inherent light absorption characteristics of complex biological tissues can significantly attenuate the penetration depth and intensity of driving optical fields, making *in vivo* applications challenging. Photocatalytic surfaces can be passivated by biological fluids, which directly suppresses light-induced diffusiophoresis, making it difficult to maintain sufficient propulsive force.

Electric Nanomotor Sensors: Electric fields are highly versatile for precise manipulation of various nanostructures, including metals, semiconductors, insulators, and their hybrids. Strategically applied electric fields can realize multimodal manipulation, including translocation, alignment, and rotation. The rich working mechanisms, depending on AC frequency, include electrophoresis, dielectrophoresis, electroosmosis, electrorotation, and electroalignment [75]. In motion-enhanced SERS, these mechanisms are most relevant when they translate, rotate, or reorient SERS-active probes to improve molecular transport and diffusion near plasmonic sensing interfaces. Kim et al. reported the rotary NEMS architecture and its operation at more than 18,000 rpm for 15 h [72]. In a related SERS-functionalized implementation, Ag-coated rotors were used to monitor rotation-dependent molecular release by Raman spectroscopy [27].

Taken together, motion-enhanced hybrid SERS platforms improve sensing primarily by increasing the mass transport of analyte molecules to (or away from) a sensor. Their value is therefore best assessed not only by EF or LOD, but also by detection time, dynamics, operational efficiency and durability in complex media, hotspot stability, and compatibility with quantitative readout.

4.2. Field-Guided Hotspot Positioning and Assembly

Field-guided platforms differ from motion-enhanced nanomotors because the external field is used primarily to position SERS-active components, assemble plasmonic junctions, or bring analytes into defined sensing regions, rather than to propel probes continuously through the sample. This strategy is particularly useful when SERS performance depends on forming reproducible nanogaps, interrogating a specific molecular interface, or maintaining spatial control over transient analyte–hotspot interactions.

Optical tweezers provide a representative field-guided strategy because highly focused laser beams can mechanically manipulate plasmonic components at defined locations [180]. When combined with plasmonic materials, such as Ag-nanoparticle-distributed silica beads, optical trapping enables the dynamic formation and control of plasmonic hotspots. By optically focusing and precisely positioning two AgNP-coated silica beads, a controllable plasmonic junction with single-molecule sensitivity has been achieved [73]. This dynamic detection configuration allows interrogation of protein structures, including hemoglobin, lysozyme, and bovine serum albumin, without perturbing their native conformations.

Furthermore, integration with microfluidic flow chambers enables real-time detection of globular proteins and facilitates studies of pH-dependent structural evolution of amylin (hIAPP), successfully capturing low-concentration, transient intermediates relevant to amyloid formation [74]. The capacity for continuous measurement at well-defined spatial locations makes optical tweezer-assisted SERS a powerful platform for probing molecular dynamics in complex biological environments.

Electric-field-guided manipulation provides another approach to hotspot positioning and probe orientation. Depending on AC frequency and field geometry, electrokinetic forces can translate, rotate, align, or orient anisotropic nanostructures in solution. Li et al. developed a versatile 3D electrokinetic tweezers technique that enables simultaneous 2D positional and 3D orientational control of anisotropic nanoparticles, with precision of 20 nm in position and 0.5° in angle (Figure 5B) [75]. Such control is valuable for SERS because the signal often depends strongly on probe orientation, molecule–surface contact geometry, and the precise placement of

plasmonic nanostructures near target interfaces. By growing dense Ag nanoparticles on the surface of Au nanowires, the electrically driven SERS-active motors enable probing of cellular surfaces at the subcellular level and direct detection of metabolite release [75]. When integrated into a magnetically anchored rotary micromotor, controlled probe rotation enhanced molecular release from the sensing surface while enabling simultaneous SERS monitoring [27]. Importantly, this strategy can be generalized to various electronic materials, whose electrical conductivity can be tuned by light or other stimuli, opening new opportunities for adaptive SERS sensing [181–183]. Meanwhile, extending electric-field-guided SERS manipulation to complex biological media will require careful control of ionic strength, medium composition, and electrode configuration.

Taken together, field-guided SERS platforms improve analytical performance by controlling where and when hotspots are positioned for deterministic sensing or targeted detection. The techniques are mostly suitable for on-chip *in vitro* applications.

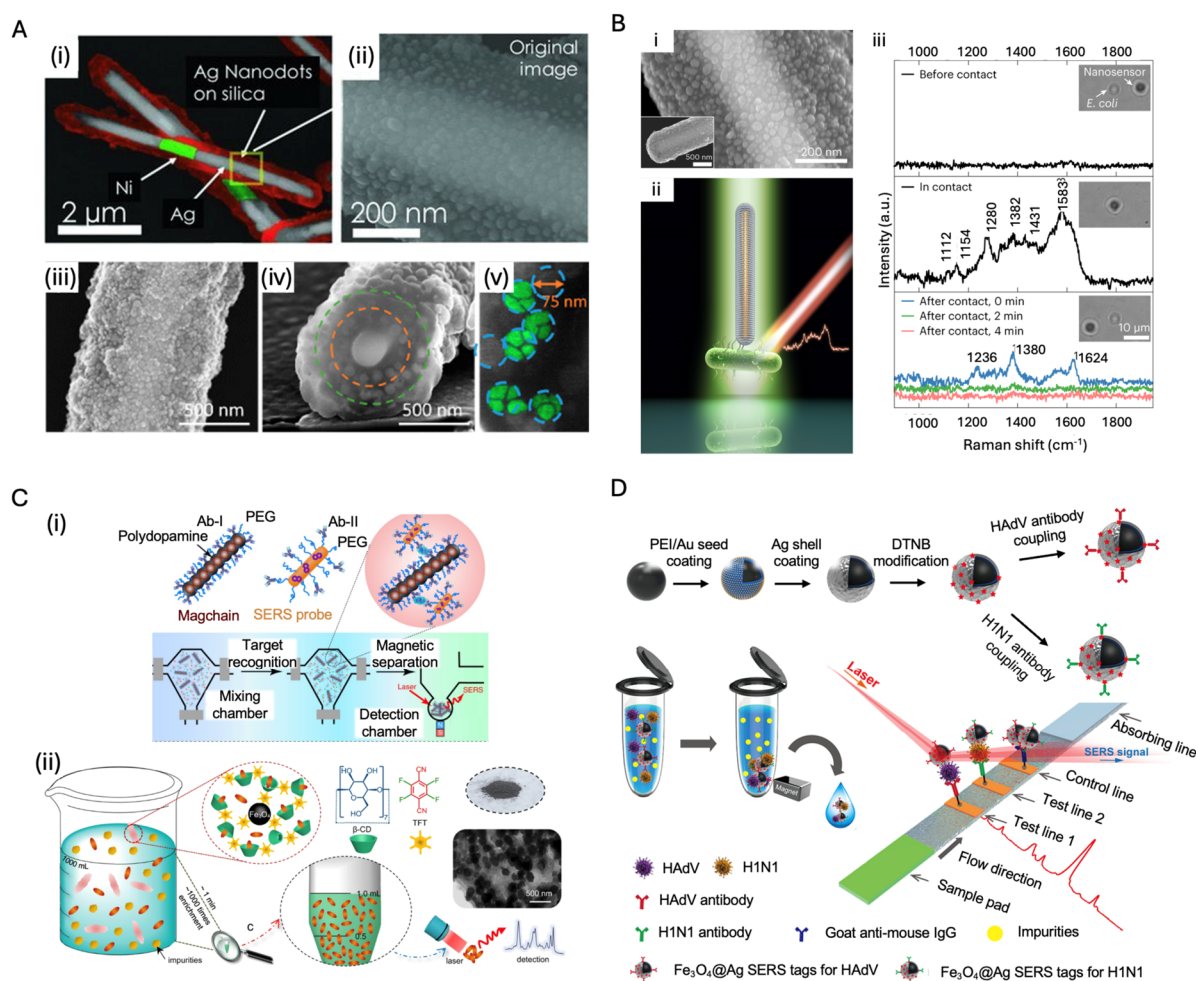


Figure 5. Stimuli-Responsive Nanostructures for SERS Bioanalysis and Molecular Sensing. (A) (i–ii) Low- and high-magnification SEM images of Ag/Ni/Ag-core, silica-shell nanocapsules decorated with Ag nanoparticles. Adapted with permission from Ref. [184]. Copyright 2012 Wiley-VCH Verlag GmbH & Co. KGaA. (iii–v) Surface, cross-sectional, and close-up SEM images of Ag nanoparticles and nanocavities in an Au-core nanoporous Raman nanosensor. Adapted with permission from Ref. [167]. Copyright 2018 American Chemical Society. (B) Localized detection of metabolites from a single *E. coli* cell using SERS-active nanocapsule sensors. (i) SEM image and (ii) schematic of a vertically aligned, silica-encapsulated nanowire coated with high-density Ag nanoparticles, enabling direct contact SERS measurement from a bacterial cell. (iii) Raman spectra collected at three positions (20 μm away, in contact, and 15 μm away after contact), with insets showing the corresponding optical images. Adapted with permission from Ref. [75]. Copyright 2023 Springer Nature. (C) (i) Schematic of the MiChip assay for biomarker detection. A sample is mixed with antibody-conjugated magnetic nanochains (Magchains) and SERS-encoded probes to form sandwich immunocomplexes, which are magnetically isolated and detected via Raman spectroscopy. Adapted from Ref. [20] under the terms of the Creative Commons Attribution 4.0 License; changes were made. (ii) Schematic of analyte enrichment and detection using magnetic nanoparticle-immobilized porous β -cyclodextrin polymer (MN-PCDP): (a) adsorption of organic pollutants from aqueous solution followed by

magnetic separation of MN-PCDP; (b) optical photograph and TEM image of MN-PCDP; and (c) desorption of the captured pollutants into ethanol for subsequent spectroscopic detection. The adsorption–desorption process enables up to approximately 1000-fold enrichment. Adapted from Ref. [76] under the terms of the Creative Commons Attribution 4.0 License; changes were made. **(D)** Synthetic route for antibody-modified $\text{Fe}_3\text{O}_4@\text{Ag}$ magnetic tags and schematic of a magnetic SERS strip for the simultaneous detection of two respiratory viruses. Adapted with permission from Ref. [77]. Copyright 2019 American Chemical Society.

4.3. Magnetic Capture and Separation for Enrichment-Assisted SERS

In contrast to motion-enhanced nanomotor platforms and field-guided hotspot positioning, magnetic enrichment-assisted SERS platforms mainly use magnetic components to capture, isolate, and concentrate target species from complex samples before Raman readout. Magnetic hybrid nanomaterials, often referred to as magnetic–plasmonic (MP) nanocomposites, represent a versatile class of substrates for SERS, particularly in bioanalysis [37,185]. These composites integrate the unique magnetic properties of materials such as iron oxides (Fe_3O_4 or Fe_2O_3) with the strong plasmonic capabilities of noble metals within a single particle system. In these systems, the magnetic component does not necessarily provide the primary electromagnetic or chemical Raman enhancement. Instead, it improves the probability that low-abundance analytes, target-bound probes, or pathogen-containing complexes are collected at SERS-active regions while reducing interference from the surrounding matrix [186].

First, the magnetic component enables efficient and rapid separation of target analytes from complex biological or environmental matrices, greatly simplifying sample pretreatment and improving analytical precision by reducing matrix interference [168]. This function is particularly important for detecting low-concentration biomarkers, pathogens, or contaminants that coexist with abundant interfering species.

Second, Mag-SERS platforms integrate enrichment functions, enabling ultrasensitive detection, even at the single-molecule level [169–172,187]. For example, Zhang et al. reported an enrichment-assisted sensing strategy based on a magnetic mesoporous nanosponge [76]. The nanosponges are made of porous β -cyclodextrin polymers combined with magnetic nanoparticles. When dispersed in solution, the nanosponges enabled rapid and efficient removal of organic micropollutants, achieving approximately 90% removal within 1 min and concentrating pollutants by up to ~1000-fold. This enrichment approach greatly enhances detection sensitivity for common organic pollutants, lowering detection limits by two to three orders of magnitude (Figure 5C(ii)). Here, the central contribution of the magnetic component is the physical concentration of target molecules before spectral acquisition.

The magnetic properties also allow for controllable aggregation and manipulation of these SERS substrates, which can dynamically create “hotspots” (regions of highly concentrated electromagnetic fields) at interparticle junctions, further boosting signal intensity and reproducibility [186]. However, in enrichment-assisted magnetic SERS, such hotspot formation should be interpreted together with target concentration and probe collection rather than treated as the sole origin of improved performance. When functionalized with biorecognition molecules such as antibodies or aptamers, magnetic–plasmonic probes can combine target isolation, enrichment, and SERS detection within the same assay format [173]. Additionally, the reusability of these magnetic substrates may further improve their cost-effectiveness and environmental friendliness [37].

Finally, the modular design and tunable surface chemistry of Mag-SERS platforms allow integration into diagnostic formats such as clinical assays and automated detection systems. For example, combining SERS-active particles with lateral flow assays (LFAs) or microfluidic systems can yield rapid, sensitive, and user-friendly diagnostic solutions [77,188]. In one study, a Mag-SERS-based LFA strip employing $\text{Fe}_3\text{O}_4@\text{Ag}$ nanoparticles was developed for simultaneous detection of influenza A H1N1 virus and human adenovirus (HAdV) (Figure 5D) [77]. The magnetic nanotags, functionalized with dual Raman dyes and virus-specific capture antibodies, enabled both magnetic enrichment and specific viral recognition. The detection limits for H1N1 and HAdV were 50 PFU mL^{-1} and 10 PFU mL^{-1} , respectively, representing a 2000-fold sensitivity improvement over traditional colloidal gold-based LFAs. Microfluidic integration further enhances the potential of Mag-SERS platforms for clinical diagnostics. As shown in Figure 5C(i), Xiong et al. reported a microfluidic biochip featuring magnetic nanochains that enable rapid mixing, bioseparation, and detection [20]. This system eliminates the need for external mixers or sensors and achieves highly sensitive detection of cancer biomarkers and bacterial species from just $1 \mu\text{L}$ of body fluid within 8 min. These integrated formats are useful when the analytical challenge involves not only Raman signal generation, but also sample preparation, target recovery, and reproducible probe placement in complex matrices.

Overall, active-enrichment hybrid SERS platforms improve sensing performance by addressing different stages of the detection process. Motion-enhanced platforms increase convective mass transport and analyte flux to (or away) from a sensing surface through probe propulsion or rotation. Field-guided platforms enable active

hotspot positioning and local interrogation. Magnetic capture-assisted systems improve target isolation, enrichment, and matrix removal. These strategies do not replace electromagnetic or chemical enhancement, but address a different aspect of nanosensing by improving analyte transport and capture, as well as targeted detection.

5. Summary and Perspective

First observed in 1974, SERS has transitioned from a fundamental spectroscopic phenomenon into a highly versatile analytical tool with single-molecule sensitivity over the last 50 years. As discussed throughout this review, hybrid SERS platforms can alleviate persistent limitations of conventional noble-metal substrates. By strategically integrating plasmonic nanostructures with semiconductors, two-dimensional materials, photonic crystals, and responsive nanomotor systems, these architectures combine localized electromagnetic field amplification and charge-transfer processes with dynamic hotspot manipulation and localized analyte enrichment for active sensing in complex biological media.

Despite the remarkable advancements, the translation of SERS into a practical quantitative tool for ultralow concentration analytes remains a major obstacle. Even in a simple dilute molecular solution, different molecular orientations and uneven electromagnetic field distributions within nanostructured hotspots frequently lead to notable single-molecule intensity fluctuations (SIFs) [189,190]. Standard quantification methods, which rely on the integrated intensity of all single-molecule signals, often struggle to maintain reproducibility and accuracy under these highly fluctuating conditions. To overcome this bottleneck, recent developments in digital (nano)colloid-enhanced Raman spectroscopy (d(n)CERS) present a promising solution [191,192]. By dispersing metallic colloidal nanoparticles in aqueous solutions to ensure uniform colloid-molecule interaction, this approach converts variable analog signals into discrete single-molecule counting events. Fundamentally, let $\lambda = N_{\text{events}}/N_{\text{voxels}}$ denote the mean number of analyte-hotspot events per voxel. Under a Poisson occupancy model, the ratio of positive voxels (RPV) is $\text{RPV} = 1 - e^{-\lambda}$, equivalently $\lambda = -\ln(1 - \text{RPV})$. Consequently, the detection probability is directly dictated by the number and density of available hotspots. While an increase in hotspot density enhances molecular occupancy probability, excessive colloidal concentrations may increase background scattering and reduce the number of effective hotspots. Furthermore, the accuracy of digital counting relies heavily on establishing a rigorous signal threshold to define an “on” event. A higher threshold can reduce false-positive detections, but it inevitably increases the false negative rate by filtering out authentic weak signals arising from hotspot heterogeneity. To mitigate these statistical fluctuations, practical substrate design must prioritize the spatial and temporal uniformity of the hotspots. Governed by Poisson statistics, this digitization effectively circumvents the limitations imposed by SIFs, facilitating reproducible quantification that is ultimately limited by the intrinsic Poisson noise of the measurement process.

Beyond solution-based colloidal dispersions, the spatial discretization of targets across solid-state arrays offers a complementary strategy for digital SERS by structurally enforcing the Poisson sampling requirements. For instance, the physical compartmentalization of molecular targets within uniform, plasmonically active microchamber arrays can facilitate the sensitive, molecular-selective, and multiplexed monitoring of single-enzyme reactions [193]. Similarly, digital nanopillar platforms leverage spatially isolated nanostructures to anchor and detect individual analytes at discrete plasmonic hotspots. Such architectures have demonstrated the capacity for attomolar-level quantification of cytokine biomarkers, enabling the longitudinal tracking of immune toxicities in cancer patients [194]. However, the translation of these digital SERS platforms into field-deployable sensors introduces a critical trade-off between the acquisition time needed for statistical confidence and the practical demand for rapid detection. Under ideal Poisson counting, the relative standard deviation of the accumulated “on” event count scales as $\text{RSD} \approx 1/\sqrt{N_{\text{on}}}$, where N_{on} denotes the accumulated number of “on” event. Achieving a statistically significant count at ultralow concentrations thus requires collecting a large number of discrete sampling events, which prolongs the data acquisition process and challenges the feasibility of rapid diagnostics. It has been reported that integrating wide-field illumination with wavelength-tunable narrow bandpass filters may offer a potential strategy to accelerate large-area imaging without compromising the extensive statistical sampling size [193]. Together, these array-based digitalization strategies illustrate the significant translational potential of converting highly variable spectroscopic phenomena into robust counting metrics for precision clinical diagnostics and dynamic disease monitoring [195,196].

However, as these solid-state digital platforms scale to accommodate multiplexed analysis across thousands of discrete spatial entities, they inherently generate massive, high-dimensional spectral datasets. The sheer volume and intricate complexity of these data—encompassing subtle spectral variations and spatially resolved molecular fingerprints—frequently surpass the processing efficiency and interpretive capacity of conventional analytical methods. Consequently, the successful translation and broad implementation of these high-throughput digital and

hybrid SERS methodologies will increasingly depend on the integration of artificial intelligence (AI) and machine learning (ML). Rather than operating as isolated analytical add-ons, AI frameworks can be intrinsically woven into both the design and data-processing phases of SERS development [197–199].

In the foundational design phase, deep learning algorithms, such as generative adversarial networks (GANs) and variational autoencoders (VAEs), may help map relationships among molecular structures, substrate properties, and topologies [200]. Such models could support data-driven optimization of hybrid substrates, although direct experimental validation of inverse-designed SERS substrates remains limited.

During data processing, AI-assisted methods can improve spectral quality, feature extraction, and interpretation [201,202]. The cited tools serve distinct purposes: RADAR removes spectral artifacts [203], SSNet performs spectral unmixing [204], PyFasma and RamanSPy provide preprocessing and multivariate-analysis pipelines [205,206], and peak-sensitive logistic regression (PSE-LR) supports spectral classification and interpretation [207]. SRS-Net, by contrast, is a physics-informed framework for modeling stimulated Raman scattering rather than a general SERS preprocessing tool [208]. Deep-learning classification has also been demonstrated for Raman-based liver-cancer diagnosis [209]. Recent studies have applied deep learning to distinct SERS tasks, including colloidal digital SERS analysis, therapeutic-drug monitoring on plasmonic metasurfaces, and leukemia classification [210–212]. More broadly, AI-assisted SERS workflows can support spectral classification and quality control across diverse sensing platforms [213–215]; these studies do not by themselves establish direct integration with digital single-molecule counting.

Looking ahead, a particularly promising direction is the development of broadly trained large Raman models built from expansive, multi-center spectral databases. However, the practical realization of these foundational models relies on overcoming significant data standardization challenges. SERS datasets frequently exhibit high variability across different instruments, substrate architectures, and analytical conditions. A major underlying issue, as previously noted, is the inherent non-reproducibility of SERS hotspots, which produces inconsistent absolute signal intensities and spectral profiles. To ensure that training datasets are sufficiently standardized and generalizable, researchers can adopt rigorous data curation protocols, including comprehensive metadata reporting and the utilization of universal calibration reference materials across different laboratories. Moreover, the integration of digital SERS methodologies can structurally mitigate this challenge; by converting highly variable analog signals into threshold-based binary molecular counts, the dependence of the final dataset on spatial heterogeneity among individual hotspots is partially reduced, thereby providing more reproducible inputs for model training. Although this field is still emerging, such models could provide a unifying foundation for the SERS workflow. When strengthened by transfer learning, these models could be efficiently adapted to new analytical tasks without requiring large task-specific datasets. At the same time, explainable AI could reveal which spectral features drive each prediction, improving transparency, scientific insight, and user confidence. Collectively, these advances could link rational nanomaterial design with automated, reliable practical diagnostics. More broadly, hybrid and digital SERS platforms with integrated AI could offer a potential route toward converting sensitive SERS analysis into standardized, rapid platforms for real-world applications.

Author Contributions: J.B. led the efforts, including literature search, analysis, and writing with important contributions from B.L., H.J. and A.X.W.; A.X.W. and D.E.F. initiated the scope and framework of this review; J.B. and D.E.F. substantially revised the manuscript to its final form; D.E.F. supervised the project. All authors have read and agreed to the published version of the manuscript.

Funding: This research was funded by the National Institutes of Health (grant number 1R43ES037145-01 and 1R41ES038039-01), National Science Foundation (grant number: 2506603, 2219221), National Science Foundation under Grant No.2610250 and Baylor University Mearse Chair Endowment fund in Biological and Biomedical Engineering.

Data Availability Statement: Not applicable.

Acknowledgments: We are thankful for the reviewers' helpful comments.

Conflicts of Interest: The authors declare no conflict of interest.

Use of AI and AI-Assisted Technologies: During the preparation of this work, the authors used AI-assisted tools for language refinement and the visual enhancement of selected figures. The authors reviewed the final content and took full responsibility for the published article.

References

1. Daniel, M.C.; Astruc, D. Gold nanoparticles: Assembly, supramolecular chemistry, quantum-size-related properties, and applications toward biology, catalysis, and nanotechnology. *Chem. Rev.* **2004**, *104*, 293–346. <https://doi.org/10.1021/cr030698>.
2. Cialla-May, D.; Zheng, X.S.; Weber, K.; Popp, J. Recent progress in surface-enhanced Raman spectroscopy for biological and biomedical applications: From cells to clinics. *Chem. Soc. Rev.* **2017**, *46*, 3945–3961. <https://doi.org/10.1039/c7cs00172j>.

3. Nam, J.M.; Oh, J.W.; Lee, H.; Suh, Y.D. Plasmonic Nanogap-Enhanced Raman Scattering with Nanoparticles. *Acc. Chem. Res.* **2016**, *49*, 2746–2755. <https://doi.org/10.1021/acs.accounts.6b00409>.
4. Kim, G.H.; Son, J.; Nam, J.M. Advances, Challenges, and Opportunities in Plasmonic Nanogap-Enhanced Raman Scattering with Nanoparticles. *ACS Nano* **2025**, *19*, 2992–3007. <https://doi.org/10.1021/acsnano.4c14557>.
5. Cardinal, M.F.; van der Ende, E.V.; Hackler, R.A.; McAnally, M.O.; Stair, P.C.; Schatz, G.C.; Van Duyne, R.P. Expanding applications of SERS through versatile nanomaterials engineering. *Chem. Soc. Rev.* **2017**, *46*, 3886–3903. <https://doi.org/10.1039/c7cs00207f>.
6. Pérez-Jiménez, A.I.; Lyu, D.; Lu, Z.; Liu, G.; Ren, B. Surface-enhanced Raman spectroscopy: Benefits, trade-offs and future developments. *Chem. Sci.* **2020**, *11*, 4563–4577. <https://doi.org/10.1039/d0sc00809e>.
7. Wang, X.; Huang, S.-C.; Hu, S.; Yan, S.; Ren, B. Fundamental understanding and applications of plasmon-enhanced Raman spectroscopy. *Nat. Rev. Phys.* **2020**, *2*, 253–271. <https://doi.org/10.1038/s42254-020-0171-y>.
8. Guerrini, L.; Rodriguez-Loureiro, I.; Correa-Duarte, M.A.; Lee, Y.H.; Ling, X.Y.; García de Abajo, F.J.; Alvarez-Puebla, R.A. Chemical speciation of heavy metals by surface-enhanced Raman scattering spectroscopy: Identification and quantification of inorganic- and methyl-mercury in water. *Nanoscale* **2014**, *6*, 8368–8375. <https://doi.org/10.1039/c4nr01464b>.
9. Wang, B.; Lv, X.; Feng, D.; Xie, L.; Zhang, J.; Li, M.; Xie, Y.; Li, J.; Zhou, H. Highly Stable Zr(IV)-Based Metal-Organic Frameworks for the Detection and Removal of Antibiotics and Organic Explosives in Water. *J. Am. Chem. Soc.* **2016**, *138*, 6204–6216. <https://doi.org/10.1021/jacs.6b01663>.
10. Hu, Y.; Liao, J.; Wang, D.; Li, G. Fabrication of Gold Nanoparticle-Embedded Metal-Organic Framework for Highly Sensitive Surface-Enhanced Raman Scattering Detection. *Anal. Chem.* **2014**, *86*, 3955–3963. <https://doi.org/10.1021/ac5002355>.
11. Zhang, X.; Dai, Z.; Si, S.; Zhang, X.; Wu, W.; Deng, H.; Wang, F.; Xiao, X.; Jiang, C. Ultrasensitive SERS Substrate Integrated with Uniform Subnanometer Scale “Hot Spots” Created by a Graphene Spacer for the Detection of Mercury Ions. *Small* **2017**, *13*, 1603347. <https://doi.org/10.1002/smll.201603347>.
12. Hu, R.; Tang, R.; Xu, J.; Lu, F. Chemical nanosensors based on molecularly-imprinted polymers doped with silver nanoparticles for the rapid detection of caffeine in wastewater. *Anal. Chim. Acta* **2018**, *1034*, 176–183. <https://doi.org/10.1016/j.aca.2018.06.012>.
13. Castro-Grijalba, A.; Montes-García, V.; Cordero-Ferradás, M.; Coronado, E.; Pérez-Juste, J.; Pastoriza-Santos, I. SERS-Based Molecularly Imprinted Plasmonic Sensor for Highly Sensitive PAH Detection. *ACS Sens.* **2020**, *5*, 693–702. <https://doi.org/10.1021/acssensors.9b01882>.
14. Li, S.; Shi, B.; He, D.; Zhou, H.; Gao, Z. DNA origami-mediated plasmonic dimer nanoantenna-based SERS biosensor for ultrasensitive determination of trace diethylstilbestrol. *J. Hazard. Mater.* **2023**, *458*, 131874. <https://doi.org/10.1016/j.jhazmat.2023.131874>.
15. Song, W.; Yang, Z.; Ma, F.; Chi, M.; Zhao, B.; Lu, X. Electrospun magnetic CoFe₂O₄/Ag hybrid nanotubes for sensitive SERS detection and monitoring of the catalytic degradation of organic pollutants. *RSC Adv.* **2017**, *7*, 40334–40341. <https://doi.org/10.1039/c7ra07786f>.
16. Plou, J.; Valera, P.S.; García, I.; de Albuquerque, C.D.L.; Carracedo, A.; Liz-Marzán, L.M. Prospects of Surface-Enhanced Raman Spectroscopy for Biomarker Monitoring toward Precision Medicine. *ACS Photonics* **2022**, *9*, 333–350. <https://doi.org/10.1021/acsp Photonics.1c01934>.
17. Zhang, K.; Wang, Y.; Wu, M.; Liu, Y.; Shi, D.; Liu, B. On-demand quantitative SERS bioassays facilitated by surface-tethered ratiometric probes. *Chem. Sci.* **2018**, *9*, 8089–8093. <https://doi.org/10.1039/c8sc03263g>.
18. Arabi, M.; Ostovan, A.; Zhang, Z.; Wang, Y.; Mei, R.; Fu, L.; Wang, X.; Ma, J.; Chen, L. Label-free SERS detection of Raman-Inactive protein biomarkers by Raman reporter indicator: Toward ultrasensitivity and universality. *Biosens. Bioelectron.* **2021**, *174*, 112825. <https://doi.org/10.1016/j.bios.2020.112825>.
19. Song, L.; Chen, J.; Xu, B.; Huang, Y. Flexible Plasmonic Biosensors for Healthcare Monitoring: Progress and Prospects. *ACS Nano* **2021**, *15*, 18822–18847. <https://doi.org/10.1021/acsnano.1c07176>.
20. Xiong, Q.; Lim, C.; Ren, J.; Zhou, J.; Pu, K.; Chan-Park, M.; Mao, H.; Lam, Y.; Duan, H. Magnetic nanochain integrated microfluidic biochips. *Nat. Commun.* **2018**, *9*, 1743. <https://doi.org/10.1038/s41467-018-04172-1>.
21. Zhang, D.; Huang, L.; Liu, B.; Ni, H.; Sun, L.; Su, E.; Chen, H.; Gu, Z.; Zhao, X. Quantitative and ultrasensitive detection of multiplex cardiac biomarkers in lateral flow assay with core-shell SERS nanotags. *Biosens. Bioelectron.* **2018**, *106*, 204–211. <https://doi.org/10.1016/j.bios.2018.01.062>.
22. Fu, X.; Cheng, Z.; Yu, J.; Choo, P.; Chen, L.; Choo, J. A SERS-based lateral flow assay biosensor for highly sensitive detection of HIV-1 DNA. *Biosens. Bioelectron.* **2016**, *78*, 530–537. <https://doi.org/10.1016/j.bios.2015.11.099>.
23. Tian, S.; Li, H.; Li, Z.; Tang, H.; Yin, M.; Chen, Y.; Wang, S.; Gao, Y.; Yang, X.; Meng, F.; et al. Polydiacetylene-based ultrastrong bioorthogonal Raman probes for targeted live-cell Raman imaging. *Nat. Commun.* **2020**, *11*, 81. <https://doi.org/10.1038/s41467-019-13784-0>.

24. Su, X.; Liu, X.; Xie, Y.; Chen, M.; Zheng, C.; Zhong, H.; Li, M. Integrated SERS-Vertical Flow Biosensor Enabling Multiplexed Quantitative Profiling of Serological Exosomal Proteins in Patients for Accurate Breast Cancer Subtyping. *ACS Nano* **2023**, *17*, 4077–4088. <https://doi.org/10.1021/acsnano.3c00449>.
25. Lin, X.; Wang, Y.; Wang, L.; Lu, Y.; Li, J.; Lu, D.; Zhou, T.; Huang, Z.; Huang, J.; Huang, H.; et al. Interference-free and high precision biosensor based on surface enhanced Raman spectroscopy integrated with surface molecularly imprinted polymer technology for tumor biomarker detection in human blood. *Biosens. Bioelectron.* **2019**, *143*, 111599. <https://doi.org/10.1016/j.bios.2019.111599>.
26. Guo, J.; Liang, Z.; Huang, Y.; Kim, K.; Vandeventer, P.; Fan, D. Acceleration of Biomolecule Enrichment and Detection with Rotationally Motorized Opto-Plasmonic Microsensors and the Working Mechanism. *ACS Nano* **2020**, *14*, 15204–15215. <https://doi.org/10.1021/acsnano.0c05429>.
27. Xu, X.; Kim, K.; Fan, D. Tunable Release of Multiplex Biochemicals by Plasmonically Active Rotary Nanomotors. *Angew. Chem. Int. Ed.* **2015**, *54*, 2525–2529. <https://doi.org/10.1002/anie.201410754>.
28. Zhang, C.; Huang, L.; Pu, H.; Sun, D. Magnetic surface-enhanced Raman scattering (MagSERS) biosensors for microbial food safety: Fundamentals and applications. *Trends Food Sci. Technol.* **2021**, *113*, 366–381. <https://doi.org/10.1016/j.tifs.2021.05.007>.
29. Zhu, X.; Zhang, Y.; Liu, M.; Liu, Y. 2D titanium carbide MXenes as emerging optical biosensing platforms. *Biosens. Bioelectron.* **2021**, *171*, 112730. <https://doi.org/10.1016/j.bios.2020.112730>.
30. Liang, X.; Li, N.; Zhang, R.; Yin, P.; Zhang, C.; Yang, N.; Liang, K.; Kong, B. Carbon-based SERS biosensor: From substrate design to sensing and bioapplication. *NPG Asia Mater.* **2021**, *13*, 8. <https://doi.org/10.1038/s41427-020-00278-5>.
31. Alessandri, I.; Lombardi, J. Enhanced Raman Scattering with Dielectrics. *Chem. Rev.* **2016**, *116*, 14921–14981. <https://doi.org/10.1021/acs.chemrev.6b00365>.
32. Li, J.; Zhang, Y.; Ding, S.; Panneerselvam, R.; Tian, Z. Core-Shell Nanoparticle-Enhanced Raman Spectroscopy. *Chem. Rev.* **2017**, *117*, 5002–5069. <https://doi.org/10.1021/acs.chemrev.6b00596>.
33. Li, J.; Anema, J.; Wandlowski, T.; Tian, Z. Dielectric shell isolated and graphene shell isolated nanoparticle enhanced Raman spectroscopies and their applications. *Chem. Soc. Rev.* **2015**, *44*, 8399–8409. <https://doi.org/10.1039/c5cs00501a>.
34. Liu, Y.; Ma, H.; Han, X.; Zhao, B. Metal-semiconductor heterostructures for surface-enhanced Raman scattering: Synergistic contribution of plasmons and charge transfer. *Mater. Horizons* **2021**, *8*, 370–382. <https://doi.org/10.1039/d0mh01356k>.
35. Han, X.; Ji, W.; Zhao, B.; Ozaki, Y. Semiconductor-enhanced Raman scattering: Active nanomaterials and applications. *Nanoscale* **2017**, *9*, 4847–4861. <https://doi.org/10.1039/c6nr08693d>.
36. Becerril-Castro, I.; Salgueiriño, V.; Correa-Duarte, M.; Alvarez-Puebla, R. Nano/Micromotor-Driven SERS for Highly Sensitive and Spatially Controlled Sensing. *Adv. Funct. Mater.* **2024**, *34*, 2314084. <https://doi.org/10.1002/adfm.202314084>.
37. Song, D.; Yang, R.; Long, F.; Zhu, A. Applications of magnetic nanoparticles in surface-enhanced Raman scattering (SERS) detection of environmental pollutants. *J. Environ. Sci.* **2019**, *80*, 14–34. <https://doi.org/10.1016/j.jes.2018.07.004>.
38. Xu, K.; Zhou, R.; Takei, K.; Hong, M. Toward Flexible Surface-Enhanced Raman Scattering (SERS) Sensors for Point-of-Care Diagnostics. *Adv. Sci.* **2019**, *6*, 1900925. <https://doi.org/10.1002/advs.201900925>.
39. Laing, S.; Jamieson, L.E.; Faulds, K.; Graham, D. Surface-enhanced Raman spectroscopy for in vivo biosensing. *Nat. Rev. Chem.* **2017**, *1*, 0060. <https://doi.org/10.1038/s41570-017-0060>.
40. Shin, M.; Kim, K.; Jeong, D.H. Enhancement of the signal-to-noise ratio in fiber-optics based SERS detection by rough-cutting the end surface. *Opt. Express* **2023**, *31*, 12645–12652. <https://doi.org/10.1364/OE.485021>.
41. Choi, M.; Kim, S.; Choi, S.H.; Park, H.-H.; Byun, K.M. Highly reliable SERS substrate based on plasmonic hybrid coupling between gold nanoislands and periodic nanopillar arrays. *Opt. Express* **2020**, *28*, 3598–3606. <https://doi.org/10.1364/OE.386726>.
42. Ranasinghe, J.C.; Sanders, S.K.; Wang, Z.; Mehrani, J.; Wu, W.; Dimitrov, E.; Wang, X.; Minns, A.M.; Rossi, R.M.; Lindner, S.E.; et al. Noise Management of Surface-Enhanced Raman Spectroscopy Using Two-Dimensional Materials. *ACS Sens.* **2026**, *11*, 1920–1932. <https://doi.org/10.1021/acssensors.5c03074>.
43. Zhou, L.; Huang, Q.; Xia, Y. Plasmon-Induced Hot Electrons in Nanostructured Materials: Generation, Collection, and Application to Photochemistry. *Chem. Rev.* **2024**, *124*, 8597–8619. <https://doi.org/10.1021/acs.chemrev.4c00165>.
44. Chang, K.; Zhao, Y.; Wang, M.; Xu, Z.; Zhu, L.; Xu, L.; Wang, Q. Advances in metal-organic framework-plasmonic metal composites based SERS platforms: Engineering strategies in chemical sensing, practical applications and future perspectives in food safety. *Chem. Eng. J.* **2023**, *459*, 141539. <https://doi.org/10.1016/j.cej.2023.141539>.
45. Ma, L.; Liu, M.; Zhou, X.; Li, C.; Wang, T. Metal-organic framework-based SERS sensing platforms for life and health detection. *Mater. Chem. Front.* **2023**, *7*, 4880–4899. <https://doi.org/10.1039/d3qm00471f>.
46. Allegretto, J.; Dostalek, J. Metal-Organic Frameworks in Surface Enhanced Raman Spectroscopy-Based Analysis of Volatile Organic Compounds. *Adv. Sci.* **2024**, *11*, 2401437. <https://doi.org/10.1002/advs.202401437>.
47. Zhang, Y.; Radjenovic, P.; Zhou, X.; Zhang, H.; Yao, J.; Li, J. Plasmonic Core-Shell Nanomaterials and their Applications in Spectroscopies. *Adv. Mater.* **2021**, *33*, 2005900. <https://doi.org/10.1002/adma.202005900>.

48. Ahmad, R.; Griffete, N.; Lamouri, A.; Felidj, N.; Chehimi, M.; Mangeney, C. Nanocomposites of Gold Nanoparticles@Molecularly Imprinted Polymers: Chemistry, Processing, and Applications in Sensors. *Chem. Mater.* **2015**, *27*, 5464–5478. <https://doi.org/10.1021/acs.chemmater.5b00138>.
49. Li, Y.; Yang, Y.; Han, S. Surface molecular imprinting technology integrated SERS sensing: Emerging trends and future perspectives toward on-site hazardous analysis. *TrAC Trends Anal. Chem.* **2024**, *179*, 117866. <https://doi.org/10.1016/j.trac.2024.117866>.
50. Guo, X.; Li, J.; Arabi, M.; Wang, X.; Wang, Y.; Chen, L. Molecular-Imprinting-Based Surface-Enhanced Raman Scattering Sensors. *ACS Sens.* **2020**, *5*, 601–619. <https://doi.org/10.1021/acssensors.9b02039>.
51. Bharati, M.; Soma, V. Flexible SERS substrates for hazardous materials detection: Recent advances. *Opto-Electron. Adv.* **2021**, *4*, 210048. <https://doi.org/10.29026/oea.2021.210048>.
52. Ji, W.; Li, L.; Song, W.; Wang, X.; Zhao, B.; Ozaki, Y. Enhanced Raman Scattering by ZnO Superstructures: Synergistic Effect of Charge Transfer and Mie Resonances. *Angew. Chem. Int. Ed.* **2019**, *58*, 14452–14456. <https://doi.org/10.1002/anie.201907283>.
53. Kim, S.M.; Zhang, W.; Cunningham, B.T. Coupling discrete metal nanoparticles to photonic crystal surface resonant modes and application to Raman spectroscopy. *Opt. Express* **2010**, *18*, 4300–4309. <https://doi.org/10.1364/Oe.18.004300>.
54. Xu, X.B.; Hasan, D.H.; Wang, L.; Chakravarty, S.; Chen, R.T.; Fan, D.L.; Wang, A.X. Guided-mode-resonance-coupled plasmonic-active SiO₂ nanotubes for surface enhanced Raman spectroscopy. *Appl. Phys. Lett.* **2012**, *100*, 191114. <https://doi.org/10.1063/1.4714710>.
55. Ren, F.H.; Campbell, J.; Wang, X.Y.; Rorrer, G.L.; Wang, A.X. Enhancing surface plasmon resonances of metallic nanoparticles by diatom biosilica. *Opt. Express* **2013**, *21*, 15308–15313. <https://doi.org/10.1364/Oe.21.015308>.
56. Ren, F.; Campbell, J.; Rorrer, G.L.; Wang, A.X. Surface-Enhanced Raman Spectroscopy Sensors From Nanobiosilica With Self-Assembled Plasmonic Nanoparticles. *IEEE J. Sel. Top. Quantum Electron.* **2014**, *20*, 127–132. <https://doi.org/10.1109/JSTQE.2014.2301016>.
57. Chen, Y.; Zhang, Y.; Pan, F.; Liu, J.; Wang, K.; Zhang, C.; Cheng, S.; Lu, L.; Zhang, W.; Zhang, Z.; et al. Breath Analysis Based on Surface-Enhanced Raman Scattering Sensors Distinguishes Early and Advanced Gastric Cancer Patients from Healthy Persons. *ACS Nano* **2016**, *10*, 8169–8179. <https://doi.org/10.1021/acsnano.6b01441>.
58. Deneme, I.; Liman, G.; Can, A.; Demirel, G.; Usta, H. Enabling three-dimensional porous architectures via carbonyl functionalization and molecular-specific organic-SERS platforms. *Nat. Commun.* **2021**, *12*, 6119. <https://doi.org/10.1038/s41467-021-26385-7>.
59. Wang, Y.; Liu, J.; Ozaki, Y.; Xu, Z.; Zhao, B. Effect of TiO₂ on Altering Direction of Interfacial Charge Transfer in a TiO₂-Ag-MPY-FePc System by SERS. *Angew. Chem. Int. Ed.* **2019**, *58*, 8172–8176. <https://doi.org/10.1002/anie.201900589>.
60. Ben-Jaber, S.; Peveler, W.; Quesada-Cabrera, R.; Cortés, E.; Sotelo-Vazquez, C.; Abdul-Karim, N.; Maier, S.; Parkin, I. Photo-induced enhanced Raman spectroscopy for universal ultra-trace detection of explosives, pollutants and biomolecules. *Nat. Commun.* **2016**, *7*, 12189. <https://doi.org/10.1038/ncomms12189>.
61. Zhou, L.; Zhou, J.; Lai, W.; Yang, X.; Meng, J.; Su, L.; Gu, C.; Jiang, T.; Pun, E.; Shao, L.; et al. Irreversible accumulated SERS behavior of the molecule-linked silver and silver-doped titanium dioxide hybrid system. *Nat. Commun.* **2020**, *11*, 1785. <https://doi.org/10.1038/s41467-020-15484-6>.
62. Zhou, J.; Zhang, J.; Yang, H.; Wang, Z.; Shi, J.; Zhou, W.; Jiang, N.; Xian, G.; Qi, Q.; Weng, Y.; et al. Plasmon-induced hot electron transfer in Au-ZnO heterogeneous nanorods for enhanced SERS. *Nanoscale* **2019**, *11*, 11782–11788. <https://doi.org/10.1039/c9nr02969a>.
63. Wu, K.; Chen, J.; McBride, J.R.; Lian, T. Efficient hot-electron transfer by a plasmon-induced interfacial charge-transfer transition. *Science* **2015**, *349*, 632–635. <https://doi.org/10.1126/science.aac5443>.
64. He, Z.; Rong, T.; Li, Y.; Ma, J.; Li, Q.; Wu, F.; Wang, Y.; Wang, F. Two-Dimensional TiVC Solid-Solution MXene as Surface-Enhanced Raman Scattering Substrate. *ACS Nano* **2022**, *16*, 4072–4083. <https://doi.org/10.1021/acsnano.1c09736>.
65. Liu, X.; Li, T.; Lee, T.; Sun, Y.; Liu, Y.; Shang, L.; Han, Y.; Deng, W.; Yuan, Z.; Dang, A. Wearable Plasmonic Sensors Engineered via Active-Site Maximization of TiVC MXene for Universal Physiological Monitoring at the Molecular Level. *ACS Sens.* **2024**, *9*, 483–493. <https://doi.org/10.1021/acssensors.3c02285>.
66. Soundiraraju, B.; George, B. Two-Dimensional Titanium Nitride (Ti₂N) MXene: Synthesis, Characterization, and Potential Application as Surface-Enhanced Raman Scattering Substrate. *ACS Nano* **2017**, *11*, 8892–8900. <https://doi.org/10.1021/acsnano.7b03129>.
67. Liu, Z.; Yang, J.; Liu, T.; Guan, G.; Han, M. Homogeneous Mo_{1-x}Re_xS₂ monolayer and lateral 1T'@2H heterostructures for significantly enhanced and highly reproducible SERS responses and mechanistic insights. *Appl. Surf. Sci.* **2025**, *682*, 161661. <https://doi.org/10.1016/j.apsusc.2024.161661>.
68. Zhou, L.; Pusey-Nazzaro, L.; Ren, G.; Chen, L.; Liu, L.; Zhang, W.; Yang, L.; Zhou, J.; Han, J. Photoactive Control of Surface-Enhanced Raman Scattering with Reduced Graphene Oxide in Gas Atmosphere. *ACS Nano* **2022**, *16*, 577–587. <https://doi.org/10.1021/acsnano.1c07695>.

69. Chen, Y.; Pan, R.; Wang, Y.; Guo, P.; Liu, X.; Ji, F.; Hu, J.; Yan, X.; Wang, G.; Zhang, L.; et al. Carbon Helical Nanorobots Capable of Cell Membrane Penetration for Single Cell Targeted SERS Bio-Sensing and Photothermal Cancer Therapy. *Adv. Funct. Mater.* **2022**, *32*, 2200600. <https://doi.org/10.1002/adfm.202200600>.
70. Yang, T.; Zhou, J.; Wang, Y.; Fan, B.; Qiao, J.; Chen, L.; Wang, X.; Guo, L.; Yang, H.; Li, Q. Magnetic Micromotors with Spiky Gold Nanoshells as SERS Sensors for Thiram and Bacteria Detection. *Small* **2024**, *20*, 2405193. <https://doi.org/10.1002/sml.202405193>.
71. Wang, Y.; Zhou, C.; Wang, W.; Xu, D.; Zeng, F.; Zhan, C.; Gu, J.; Li, M.; Zhao, W.; Zhang, J.; et al. Photocatalytically Powered Matchlike Nanomotor for Light-Guided Active SERS Sensing. *Angew. Chem. Int. Ed.* **2018**, *57*, 13110–13113. <https://doi.org/10.1002/anie.201807033>.
72. Kim, K.; Xu, X.; Guo, J.; Fan, D.L. Ultrahigh-speed rotating nanoelectromechanical system devices assembled from nanoscale building blocks. *Nat. Commun.* **2014**, *5*, 3632. <https://doi.org/10.1038/ncomms4632>.
73. Dai, X.; Fu, W.; Chi, H.; Mesias, V.; Zhu, H.; Leung, C.; Liu, W.; Huang, J. Optical tweezers-controlled hotspot for sensitive and reproducible surface-enhanced Raman spectroscopy characterization of native protein structures. *Nat. Commun.* **2021**, *12*, 1292. <https://doi.org/10.1038/s41467-021-21543-3>.
74. Fu, W.; Chi, H.; Dai, X.; Zhu, H.; Mesias, V.; Liu, W.; Huang, J. Efficient optical plasmonic tweezer-controlled single-molecule SERS characterization of pH-dependent amylin species in aqueous milieu. *Nat. Commun.* **2023**, *14*, 6996. <https://doi.org/10.1038/s41467-023-42812-3>.
75. Li, H.; Teal, D.; Liang, Z.; Kwon, H.; Huo, D.; Jin, A.; Fischer, P.; Fan, D. Precise electrokinetic position and three-dimensional orientation control of a nanowire bioprobe in solution. *Nat. Nanotechnol.* **2023**, *18*, 1213–1221. <https://doi.org/10.1038/s41565-023-01439-7>.
76. Zhang, L.; Guo, Y.; Hao, R.; Shi, Y.; You, H.; Nan, H.; Dai, Y.; Liu, D.; Lei, D.; Fang, J. Ultra-rapid and highly efficient enrichment of organic pollutants via magnetic mesoporous nanosponge for ultrasensitive nanosensors. *Nat. Commun.* **2021**, *12*, 6849. <https://doi.org/10.1038/s41467-021-27100-2>.
77. Wang, C.; Wang, C.; Wang, X.; Wang, K.; Zhu, Y.; Rong, Z.; Wang, W.; Xiao, R.; Wang, S. Magnetic SERS Strip for Sensitive and Simultaneous Detection of Respiratory Viruses. *ACS Appl. Mater. Interfaces* **2019**, *11*, 19495–19505. <https://doi.org/10.1021/acsami.9b03920>.
78. Itoh, T.; Prochazka, M.; Dong, Z.; Ji, W.; Yamamoto, Y.; Zhang, Y.; Ozaki, Y. Toward a New Era of SERS and TERS at the Nanometer Scale: From Fundamentals to Innovative Applications. *Chem. Rev.* **2023**, *123*, 1552–1634. <https://doi.org/10.1021/acs.chemrev.2c00316>.
79. Le Ru, E.C.; Etchegoin, P.G. Preface. In *Principles of Surface-Enhanced Raman Spectroscopy and Related Plasmonic Effects*; Elsevier: Amsterdam, The Netherlands, 2009; pp. xvii–xix. <https://doi.org/10.1016/B978-0-444-52779-0.00005-2>.
80. Cirera, B.; Litman, Y.; Lin, C.F.; Akkoush, A.; Hammud, A.; Wolf, M.; Rossi, M.; Kumagai, T. Charge Transfer-Mediated Dramatic Enhancement of Raman Scattering upon Molecular Point Contact Formation. *Nano Lett.* **2022**, *22*, 2170–2176. <https://doi.org/10.1021/acs.nanolett.1c02626>.
81. Otto, A.; Bruckbauer, A.; Chen, Y.X. On the chloride activation in SERS and single molecule SERS. *J. Mol. Struct.* **2003**, *661–662*, 501–514. <https://doi.org/10.1016/j.molstruc.2003.07.026>.
82. Stewart, M.E.; Anderton, C.R.; Thompson, L.B.; Maria, J.; Gray, S.K.; Rogers, J.A.; Nuzzo, R.G. Nanostructured plasmonic sensors. *Chem. Rev.* **2008**, *108*, 494–521. <https://doi.org/10.1021/cr068126n>.
83. Han, X.X.; Rodriguez, R.S.; Haynes, C.L.; Ozaki, Y.; Zhao, B. Surface-enhanced Raman spectroscopy. *Nat. Rev. Methods Primers* **2021**, *1*, 87. <https://doi.org/10.1038/s43586-021-00083-6>.
84. Wang, X.T.; Shi, W.S.; She, G.W.; Mu, L.X. Using Si and Ge Nanostructures as Substrates for Surface-Enhanced Raman Scattering Based on Photoinduced Charge Transfer Mechanism. *J. Am. Chem. Soc.* **2011**, *133*, 16518–16523. <https://doi.org/10.1021/ja2057874>.
85. Lee, J.; Crampton, K.T.; Tallarida, N.; Apkarian, V.A. Visualizing vibrational normal modes of a single molecule with atomically confined light. *Nature* **2019**, *568*, 78–82. <https://doi.org/10.1038/s41586-019-1059-9>.
86. Ye, J.; Arul, R.; Nieuwoudt, M.K.; Dong, J.; Zhang, T.; Dai, L.; Greenham, N.C.; Rao, A.; Hoye, R.L.Z.; Gao, W.; et al. Understanding the Chemical Mechanism behind Photoinduced Enhanced Raman Spectroscopy. *J. Phys. Chem. Lett.* **2023**, *14*, 4607–4616. <https://doi.org/10.1021/acs.jpcl.3c00478>.
87. Zhan, C.; Chen, X.-J.; Huang, Y.-F.; Wu, D.-Y.; Tian, Z.-Q. Plasmon-Mediated Chemical Reactions on Nanostructures Unveiled by Surface-Enhanced Raman Spectroscopy. *Acc. Chem. Res.* **2019**, *52*, 2784–2792. <https://doi.org/10.1021/acs.accounts.9b00280>.
88. Zhan, C.; Moskovits, M.; Tian, Z.-Q. Recent Progress and Prospects in Plasmon-Mediated Chemical Reaction. *Matter* **2020**, *3*, 42–56. <https://doi.org/10.1016/j.matt.2020.03.019>.
89. Xie, W.; Schlücker, S. Hot electron-induced reduction of small molecules on photorecycling metal surfaces. *Nat. Commun.* **2015**, *6*, 7570. <https://doi.org/10.1038/ncomms8570>.

90. Anema, J.R.; Li, J.-F.; Yang, Z.-L.; Ren, B.; Tian, Z.-Q. Shell-Isolated Nanoparticle-Enhanced Raman Spectroscopy: Expanding the Versatility of Surface-Enhanced Raman Scattering. *Annu. Rev. Anal. Chem.* **2011**, *4*, 129–150. <https://doi.org/10.1146/annurev.anchem.111808.073632>.
91. Li, J.; Tian, X.; Li, S.; Anema, J.; Yang, Z.; Ding, Y.; Wu, Y.; Zeng, Y.; Chen, Q.; Ren, B.; et al. Surface analysis using shell-isolated nanoparticle-enhanced Raman spectroscopy. *Nat. Protoc.* **2013**, *8*, 52–65. <https://doi.org/10.1038/nprot.2012.141>.
92. Li, C.; Le, J.; Wang, Y.; Chen, S.; Yang, Z.; Li, J.; Cheng, J.; Tian, Z. *In situ* probing electrified interfacial water structures at atomically flat surfaces. *Nat. Mater.* **2019**, *18*, 697–701. <https://doi.org/10.1038/s41563-019-0356-x>.
93. Wang, Y.; Zheng, S.; Yang, W.; Zhou, R.; He, Q.; Radjenovic, P.; Dong, J.; Li, S.; Zheng, J.; Yang, Z.; et al. In situ Raman spectroscopy reveals the structure and dissociation of interfacial water. *Nature* **2021**, *600*, 81–85. <https://doi.org/10.1038/s41586-021-04068-z>.
94. Li, J.; Huang, Y.; Ding, Y.; Yang, Z.; Li, S.; Zhou, X.; Fan, F.; Zhang, W.; Zhou, Z.; Wu, D.; et al. Shell-isolated nanoparticle-enhanced Raman spectroscopy. *Nature* **2010**, *464*, 392–395. <https://doi.org/10.1038/nature08907>.
95. Wang, X.; Guo, L. SERS Activity of Semiconductors: Crystalline and Amorphous Nanomaterials. *Angew. Chem. Int. Ed.* **2020**, *59*, 4231–4239. <https://doi.org/10.1002/anie.201913375>.
96. Song, G.; Gong, W.; Cong, S.; Zhao, Z. Ultrathin Two-Dimensional Nanostructures: Surface Defects for Morphology-Driven Enhanced Semiconductor SERS. *Angew. Chem. Int. Ed.* **2021**, *60*, 5505–5511. <https://doi.org/10.1002/anie.202015306>.
97. Tao, L.; Chen, K.; Chen, Z.; Cong, C.; Qiu, C.; Chen, J.; Wang, X.; Chen, H.; Yu, T.; Xie, W.; et al. 1T' Transition Metal Telluride Atomic Layers for Plasmon-Free SERS at Femtomolar Levels. *J. Am. Chem. Soc.* **2018**, *140*, 8696–8704. <https://doi.org/10.1021/jacs.8b02972>.
98. Li, Z.; Zhai, L.; Zhang, Q.; Zhai, W.; Li, P.; Chen, B.; Chen, C.; Yao, Y.; Ge, Y.; Yang, H.; et al. 1T'-transition metal dichalcogenide monolayers stabilized on 4H-Au nanowires for ultrasensitive SERS detection. *Nat. Mater.* **2024**, *23*, 1355–1362. <https://doi.org/10.1038/s41563-024-01860-w>.
99. Ma, N.; Chen, L.; Jing, T.; Zhang, X.; Han, B.; Xue, X.; Zhang, Y.; Zhao, B. New Insight into Charge-Transfer Enhancement for SERS in Cosputtering (Ag)_x(ZnS)_y System: The Carrier Density Effect. *J. Phys. Chem. C* **2019**, *123*, 28846–28851. <https://doi.org/10.1021/acs.jpcc.9b09922>.
100. Feng, E.; Zheng, T.; He, X.; Chen, J.; Gu, Q.; He, X.; Hu, F.; Li, J.; Tian, Y. Plasmon-Induced Charge Transfer-Enhanced Raman Scattering on a Semiconductor: Toward Amplification-Free Quantification of SARS-CoV-2. *Angew. Chem. Int. Ed.* **2023**, *62*, e202309249. <https://doi.org/10.1002/anie.202309249>.
101. Meng, X.; Yu, J.; Shi, W.; Qiu, L.; Qiu, K.; Li, A.; Liu, Z.; Wang, Y.; Wu, J.; Lin, J.; et al. SERS Detection of Trace Carcinogenic Aromatic Amines Based on Amorphous MoO₃ Monolayers. *Angew. Chem. Int. Ed.* **2024**, *63*, e202407597. <https://doi.org/10.1002/anie.202407597>.
102. Zhou, Y.; Gu, Q.; Qiu, T.; He, X.; Chen, J.; Qi, R.; Huang, R.; Zheng, T.; Tian, Y. Ultrasensitive Sensing of Volatile Organic Compounds Using a Cu-Doped SnO₂-NiO p-n Heterostructure That Shows Significant Raman Enhancement. *Angew. Chem. Int. Ed.* **2021**, *60*, 26260–26267. <https://doi.org/10.1002/anie.202112367>.
103. Demirel, G.; Giesecking, R.; Ozdemir, R.; Kahmann, S.; Loi, M.; Schatz, G.; Facchetti, A.; Usta, H. Molecular engineering of organic semiconductors enables noble metal-comparable SERS enhancement and sensitivity. *Nat. Commun.* **2019**, *10*, 5502. <https://doi.org/10.1038/s41467-019-13505-7>.
104. Yilmaz, M.; Babur, E.; Ozdemir, M.; Giesecking, R.; Dede, Y.; Tamer, U.; Schatz, G.; Facchetti, A.; Usta, H.; Demirel, G. Nanostructured organic semiconductor films for molecular detection with surface-enhanced Raman spectroscopy. *Nat. Mater.* **2017**, *16*, 918–924. <https://doi.org/10.1038/nmat4957>.
105. Miao, P.; Qin, J.; Shen, Y.; Su, H.; Dai, J.; Song, B.; Du, Y.; Sun, M.; Zhang, W.; Wang, H.; et al. Unraveling the Raman Enhancement Mechanism on 1T'-Phase ReS₂ Nanosheets. *Small* **2018**, *14*, 1704079. <https://doi.org/10.1002/smll.201704079>.
106. Liu, X.; Dang, A.; Li, T.; Sun, Y.; Lee, T.C.; Deng, W.; Wu, S.; Zada, A.; Zhao, T.; Li, H. Plasmonic Coupling of Au Nanoclusters on a Flexible MXene/Graphene Oxide Fiber for Ultrasensitive SERS Sensing. *ACS Sens.* **2023**, *8*, 1287–1298. <https://doi.org/10.1021/acssensors.2c02808>.
107. Wu, Z.; Sun, D.; Pu, H.; Wei, Q.; Lin, X. Ti₃C₂T_x MXenes loaded with Au nanoparticle dimers as a surface-enhanced Raman scattering aptasensor for AFB1 detection. *Food Chem.* **2022**, *372*, 131293. <https://doi.org/10.1016/j.foodchem.2021.131293>.
108. Yu, Z.; Jiang, L.; Liu, R.; Zhao, W.; Yang, Z.; Zhang, J.; Jin, S. Versatile self-assembled MXene-Au nanocomposites for SERS detection of bacteria, antibacterial and photothermal sterilization. *Chem. Eng. J.* **2021**, *426*, 131914. <https://doi.org/10.1016/j.cej.2021.131914>.
109. Yang, K.; Dong, Q.; Liu, H.; Wu, L.; Zong, S.; Wang, Z. A MXene Hydrogel-Based Versatile Microrobot for Controllable Water Pollution Management. *Adv. Sci.* **2024**, *11*, 2309257. <https://doi.org/10.1002/advs.202309257>.
110. Kaushik, V.; Kagdada, H.; Singh, D.; Pathak, S. Enhancement of SERS effect in Graphene-Silver hybrids. *Appl. Surf. Sci.* **2022**, *574*, 151724. <https://doi.org/10.1016/j.apsusc.2021.151724>.

111. Ding, X.; Kong, L.; Wang, J.; Fang, F.; Li, D.; Liu, J. Highly Sensitive SERS Detection of Hg²⁺ Ions in Aqueous Media Using Gold Nanoparticles/Graphene Heterojunctions. *ACS Appl. Mater. Interfaces* **2013**, *5*, 7072–7078. <https://doi.org/10.1021/am401373e>.
112. Kong, X.M.; Xi, Y.T.; LeDuff, P.; Li, E.W.; Liu, Y.; Cheng, L.J.; Rorrer, G.L.; Tan, H.; Wang, A.X. Optofluidic sensing from inkjet-printed droplets: The enormous enhancement by evaporation-induced spontaneous flow on photonic crystal biosilica. *Nanoscale* **2016**, *8*, 17285–17294. <https://doi.org/10.1039/c6nr05809d>.
113. Sivashanmugan, K.; Squire, K.; Kraai, J.A.; Tan, A.L.; Zhao, Y.; Rorrer, G.L.; Wang, A.X. Biological Photonic Crystal-Enhanced Plasmonic Mesocapsules: Approaching Single-Molecule Optofluidic-SERS Sensing. *Adv. Opt. Mater.* **2019**, *7*, 1900415. <https://doi.org/10.1002/adom.201900415>.
114. Yang, J.; Zhen, L.; Ren, F.; Campbell, J.; Rorrer, G.L.; Wang, A.X. Ultra-sensitive immunoassay biosensors using hybrid plasmonic-biosilica nanostructured materials. *J. Biophotonics* **2015**, *8*, 659–667. <https://doi.org/10.1002/jbio.201400070>.
115. Tan, A.L.; Zhao, Y.; Sivashanmugan, K.; Squire, K.; Wang, A.X. Quantitative TLC-SERS detection of histamine in seafood with support vector machine analysis. *Food Control* **2019**, *103*, 111–118. <https://doi.org/10.1016/j.foodcont.2019.03.032>.
116. Kong, X.M.; Chong, X.Y.; Squire, K.; Wang, A.X. Microfluidic diatomite analytical devices for illicit drug sensing with ppb-Level sensitivity. *Sens. Actuators B Chem.* **2018**, *259*, 587–595. <https://doi.org/10.1016/j.snb.2017.12.038>.
117. Wang, X.; Shi, W.; Wang, S.; Zhao, H.; Lin, J.; Yang, Z.; Chen, M.; Guo, L. Two-Dimensional Amorphous TiO₂ Nanosheets Enabling High-Efficiency Photoinduced Charge Transfer for Excellent SERS Activity. *J. Am. Chem. Soc.* **2019**, *141*, 5856–5862. <https://doi.org/10.1021/jacs.9b00029>.
118. Yang, L.; Peng, Y.; Yang, Y.; Liu, J.; Huang, H.; Yu, B.; Zhao, J.; Lu, Y.; Huang, Z.; Li, Z.; et al. A Novel Ultra-Sensitive Semiconductor SERS Substrate Boosted by the Coupled Resonance Effect. *Adv. Sci.* **2019**, *6*, 1900310. <https://doi.org/10.1002/advs.201900310>.
119. Cong, S.; Yuan, Y.; Chen, Z.; Hou, J.; Yang, M.; Su, Y.; Zhang, Y.; Li, L.; Li, Q.; Geng, F.; et al. Noble metal-comparable SERS enhancement from semiconducting metal oxides by making oxygen vacancies. *Nat. Commun.* **2015**, *6*, 7800. <https://doi.org/10.1038/ncomms8800>.
120. Zheng, Z.; Cong, S.; Gong, W.; Xuan, J.; Li, G.; Lu, W.; Geng, F.; Zhao, Z. Semiconductor SERS enhancement enabled by oxygen incorporation. *Nat. Commun.* **2017**, *8*, 1993. <https://doi.org/10.1038/s41467-017-02166-z>.
121. Wang, X.; Shi, W.; Jin, Z.; Huang, W.; Lin, J.; Ma, G.; Li, S.; Guo, L. Remarkable SERS Activity Observed from Amorphous ZnO Nanocages. *Angew. Chem. Int. Ed.* **2017**, *56*, 9851–9855. <https://doi.org/10.1002/anie.201705187>.
122. Boerigter, C.; Aslam, U.; Linic, S. Mechanism of Charge Transfer from Plasmonic Nanostructures to Chemically Attached Materials. *ACS Nano* **2016**, *10*, 6108–6115. <https://doi.org/10.1021/acsnano.6b01846>.
123. Rao, V.G.; Aslam, U.; Linic, S. Chemical Requirement for Extracting Energetic Charge Carriers from Plasmonic Metal Nanoparticles to Perform Electron-Transfer Reactions. *J. Am. Chem. Soc.* **2019**, *141*, 643–647. <https://doi.org/10.1021/jacs.8b11949>.
124. Zhang, L.; Yi, W.; Li, J.; Wei, G.; Xi, G.; Mao, L. Surfactant-free interfacial growth of graphdiyne hollow microspheres and the mechanistic origin of their SERS activity. *Nat. Commun.* **2023**, *14*, 6318. <https://doi.org/10.1038/s41467-023-42038-3>.
125. Huang, K.; Li, Z.; Lin, J.; Han, G.; Huang, P. Two-dimensional transition metal carbides and nitrides (MXenes) for biomedical applications. *Chem. Soc. Rev.* **2018**, *47*, 5109–5124. <https://doi.org/10.1039/c7cs00838d>.
126. Kannan, P.K.; Shankar, P.; Blackman, C.; Chung, C.-H. Recent Advances in 2D Inorganic Nanomaterials for SERS Sensing. *Adv. Mater.* **2019**, *31*, 1803432. <https://doi.org/10.1002/adma.201803432>.
127. Liu, Y.; Qin, Z.; Deng, J.; Zhou, J.; Jia, X.; Wang, G.; Luo, F. The Advanced Applications of 2D Materials in SERS. *Chemosensors* **2022**, *10*, 455. <https://doi.org/10.3390/chemosensors10110455>.
128. Luo, W.; Xiong, W.; Han, Y.; Yan, X.; Mai, L. Application of two-dimensional layered materials in surface-enhanced Raman spectroscopy (SERS). *Phys. Chem. Chem. Phys.* **2022**, *24*, 26398–26412. <https://doi.org/10.1039/d2cp03650a>.
129. Lin, J.; Liang, L.; Ling, X.; Zhang, S.; Mao, N.; Zhang, N.; Sumpter, B.; Meunier, V.; Tong, L.; Zhang, J. Enhanced Raman Scattering on In-Plane Anisotropic Layered Materials. *J. Am. Chem. Soc.* **2015**, *137*, 15511–15517. <https://doi.org/10.1021/jacs.5b10144>.
130. Huang, Y.; Yu, K.; Li, H.; Xu, K.; Liang, Z.; Walker, D.; Ferreira, P.; Fischer, P.; Fan, D. Scalable Fabrication of Molybdenum Disulfide Nanostructures and their Assembly. *Adv. Mater.* **2020**, *32*, 2003439. <https://doi.org/10.1002/adma.202003439>.
131. Huang, Y.; Guo, J.; Li, Y.; Li, H.; Fan, D.E. 2D-Material-Integrated Micromachines: Competing Propulsion Strategy and Enhanced Bacterial Disinfection. *Adv. Mater.* **2022**, *34*, 2203082. <https://doi.org/10.1002/adma.202203082>.
132. Dutta, R.; Bala, A.; Sen, A.; Spinazze, M.; Park, H.; Choi, W.; Yoon, Y.; Kim, S. Optical Enhancement of Indirect Bandgap 2D Transition Metal Dichalcogenides for Multi-Functional Optoelectronic Sensors. *Adv. Mater.* **2023**, *35*, 2303272. <https://doi.org/10.1002/adma.202303272>.

133. Guselnikova, O.; Lim, H.; Kim, H.; Kim, S.; Gorbunova, A.; Eguchi, M.; Postnikov, P.; Nakanishi, T.; Asahi, T.; Na, J.; et al. New Trends in Nanoarchitected SERS Substrates: Nanospaces, 2D Materials, and Organic Heterostructures. *Small* **2022**, *18*, 2107182. <https://doi.org/10.1002/sml.202107182>.
134. Yin, X.; Tang, C.; Zheng, Y.; Gao, J.; Wu, J.; Zhang, H.; Chhowalla, M.; Chen, W.; Wee, A. Recent developments in 2D transition metal dichalcogenides: Phase transition and applications of the (quasi-)metallic phases. *Chem. Soc. Rev.* **2021**, *50*, 10087–10115. <https://doi.org/10.1039/d1cs00236h>.
135. Thakur, A.; Singh, R.; Yadav, V.; Siddhanta, S.; Jayaramulu, K. Advancing SERS Applications of 2D Materials through the Interplay of Rational Design and Structure-Property Relationships. *Small Methods* **2025**, *9*, 2402056. <https://doi.org/10.1002/smt.202402056>.
136. Tang, X.; Hao, Q.; Hou, X.; Lan, L.; Li, M.; Yao, L.; Zhao, X.; Ni, Z.; Fan, X.; Qiu, T. Exploring and Engineering 2D Transition Metal Dichalcogenides toward Ultimate SERS Performance. *Adv. Mater.* **2024**, *36*, 2312348. <https://doi.org/10.1002/adma.202312348>.
137. Li, M.; Gao, Y.; Fan, X.; Wei, Y.; Hao, Q.; Qiu, T. Origin of layer-dependent SERS tunability in 2D transition metal dichalcogenides. *Nanoscale Horiz.* **2021**, *6*, 186–191. <https://doi.org/10.1039/d0nh00625d>.
138. Chen, J.; Huang, Y.; Kannan, P.; Zhang, L.; Lin, Z.; Zhang, J.; Chen, T.; Guo, L. Flexible and Adhesive Surface Enhance Raman Scattering Active Tape for Rapid Detection of Pesticide Residues in Fruits and Vegetables. *Anal. Chem.* **2016**, *88*, 2149–2155. <https://doi.org/10.1021/acs.analchem.5b03735>.
139. Anasori, B.; Lukatskaya, M.; Gogotsi, Y. 2D metal carbides and nitrides (MXenes) for energy storage. *Nat. Rev. Mater.* **2017**, *2*, 16098. <https://doi.org/10.1038/natrevmats.2016.98>.
140. Xu, W.; Xiao, J.; Chen, Y.; Chen, Y.; Ling, X.; Zhang, J. Graphene-Veiled Gold Substrate for Surface-Enhanced Raman Spectroscopy. *Adv. Mater.* **2013**, *25*, 928–933. <https://doi.org/10.1002/adma.201204355>.
141. Cao, Y.; Cheng, Y.; Sun, M. Graphene-based SERS for sensor and catalysis. *Appl. Spectrosc. Rev.* **2023**, *58*, 1–38. <https://doi.org/10.1080/05704928.2021.1910286>.
142. Wang, L.; Li, C.; Cao, C.; Lei, F.; Zhao, X.; Li, Z.; Zhang, C.; Jiao, Y.; Yu, J. Multifunctional Polymeric Nanoneedles with “Full-Spectrum Intrinsic Internal Standard” for Precise SERS Biosensing. *Adv. Funct. Mater.* **2025**, *35*, 2416789. <https://doi.org/10.1002/adfm.202416789>.
143. Wang, Z.; Ye, J.; Zhang, K.; Ding, L.; Granzier-Nakajima, T.; Ranasinghe, J.C.; Xue, Y.; Sharma, S.; Biase, I.; Terrones, M.; et al. Rapid Biomarker Screening of Alzheimer’s Disease by Interpretable Machine Learning and Graphene-Assisted Raman Spectroscopy. *ACS Nano* **2022**, *16*, 6426–6436. <https://doi.org/10.1021/acsnano.2c00538>.
144. Chen, S.; Wu, Q.; Mishra, C.; Kang, J.; Zhang, H.; Cho, K.; Cai, W.; Balandin, A.A.; Ruoff, R.S. Thermal conductivity of isotopically modified graphene. *Nat. Mater.* **2012**, *11*, 203–207. <https://doi.org/10.1038/nmat3207>.
145. Balandin, A.A. Thermal properties of graphene and nanostructured carbon materials. *Nat. Mater.* **2011**, *10*, 569–581. <https://doi.org/10.1038/nmat3064>.
146. Qu, L.; Wang, N.; Xu, H.; Wang, W.; Liu, Y.; Kuo, L.; Yadav, T.; Wu, J.; Joyner, J.; Song, Y.; et al. Gold Nanoparticles and g-C₃N₄-Intercalated Graphene Oxide Membrane for Recyclable Surface Enhanced Raman Scattering. *Adv. Funct. Mater.* **2017**, *27*, 1701714. <https://doi.org/10.1002/adfm.201701714>.
147. Xu, W.; Mao, N.; Zhang, J. Graphene: A Platform for Surface-Enhanced Raman Spectroscopy. *Small* **2013**, *9*, 1206–1224. <https://doi.org/10.1002/sml.201203097>.
148. John, S. Strong Localization of Photons in Certain Disordered Dielectric Superlattices. *Phys. Rev. Lett.* **1987**, *58*, 2486–2489. <https://doi.org/10.1103/PhysRevLett.58.2486>.
149. Yablonovitch, E. Inhibited Spontaneous Emission in Solid-State Physics and Electronics. *Phys. Rev. Lett.* **1987**, *58*, 2059–2062. <https://doi.org/10.1103/PhysRevLett.58.2059>.
150. Fuhrmann, T.; Landwehr, S.; El Rharbi-Kucki, M.; Sumper, M. Diatoms as living photonic crystals. *Appl. Phys. B* **2004**, *78*, 257–260. <https://doi.org/10.1007/s00340-004-1419-4>.
151. Aguirre, C.I.; Reguera, E.; Stein, A. Tunable Colors in Opals and Inverse Opal Photonic Crystals. *Adv. Funct. Mater.* **2010**, *20*, 2565–2578. <https://doi.org/10.1002/adfm.201000143>.
152. Notomi, M.; Yamada, K.; Shinya, A.; Takahashi, J.; Takahashi, C.; Yokohama, I. Extremely large group-velocity dispersion of line-defect waveguides in photonic crystal slabs. *Phys. Rev. Lett.* **2001**, *87*, 253902. <https://doi.org/10.1103/PhysRevLett.87.253902>.
153. Lin, C.Y.; Wang, X.L.; Chakravarty, S.; Lee, B.S.; Lai, W.C.; Luo, J.D.; Jen, A.K.Y.; Chen, R.T. Electro-optic polymer infiltrated silicon photonic crystal slot waveguide modulator with 23 dB slow light enhancement. *Appl. Phys. Lett.* **2010**, *97*, 093304. <https://doi.org/10.1063/1.3486225>.
154. Wang, S.S.; Magnusson, R. Theory and Applications of Guided-Mode Resonance Filters. *Appl. Opt.* **1993**, *32*, 2606–2613. <https://doi.org/10.1364/Ao.32.002606>.
155. Huang, M.; Yanik, A.A.; Chang, T.Y.; Altug, H. Sub-wavelength nanofluidics in photonic crystal sensors. *Opt. Express* **2009**, *17*, 24224–24233. <https://doi.org/10.1364/Oe.17.024224>.

156. Eftekhari, F.; Escobedo, C.; Ferreira, J.; Duan, X.B.; Girotto, E.M.; Brolo, A.G.; Gordon, R.; Sinton, D. Nanoholes As Nanochannels: Flow-through Plasmonic Sensing. *Anal. Chem.* **2009**, *81*, 4308–4311. <https://doi.org/10.1021/ac900221y>.
157. Gale, D.K.; Gutu, T.; Jiao, J.; Chang, C.H.; Rorrer, G.L. Photoluminescence Detection of Biomolecules by Antibody-Functionalized Diatom Biosilica. *Adv. Funct. Mater.* **2009**, *19*, 926–933. <https://doi.org/10.1002/adfm.200801137>.
158. Kaminska, A.; Sprynskyy, M.; Winkler, K.; Szymborski, T. Ultrasensitive SERS immunoassay based on diatom biosilica for detection of interleukins in blood plasma. *Anal. Bioanal. Chem.* **2017**, *409*, 6337–6347. <https://doi.org/10.1007/s00216-017-0566-5>.
159. Saridag, A.M.; Karagoz, I.D.; Wachsmann-Hogiu, S.; Kahraman, M. Diatomite-Based, Flexible SERS Immunosensor Platform for Rapid, Specific, and Sensitive Detection of Circulating Cancer-Specific Protein Biomarkers in Serum Using Raman Probes. *ACS Appl. Bio Mater.* **2024**, *7*, 1878–1887. <https://doi.org/10.1021/acsabm.3c01253>.
160. Sherma, J.; Rabel, F. Review of thin layer chromatography in pesticide analysis: 2016–2018. *J. Liq. Chromatogr. Relat. Technol.* **2018**, *41*, 1052–1065. <https://doi.org/10.1080/10826076.2018.1557055>.
161. Pozzi, F.; Shibayama, N.; Leona, M.; Lombardi, J.R. TLC-SERS study of Syrian rue (*Peganum harmala*) and its main alkaloid constituents. *J. Raman Spectrosc.* **2013**, *44*, 102–107. <https://doi.org/10.1002/jrs.4140>.
162. Li, D.W.; Qu, L.L.; Zhai, W.L.; Xue, J.Q.; Fossey, J.S.; Long, Y.T. Facile On-Site Detection of Substituted Aromatic Pollutants in Water Using Thin Layer Chromatography Combined with Surface-Enhanced Raman Spectroscopy. *Environ. Sci. Technol.* **2011**, *45*, 4046–4052. <https://doi.org/10.1021/es104155r>.
163. Kong, X.M.; Squire, K.; Chong, X.Y.; Wang, A.X. Ultra-sensitive lab-on-a-chip detection of Sudan I in food using plasmonics-enhanced diatomaceous thin film. *Food Control* **2017**, *79*, 258–265. <https://doi.org/10.1016/j.foodcont.2017.04.007>.
164. Kong, X.M.; Li, E.W.; Squire, K.; Liu, Y.; Wu, B.; Cheng, L.J.; Wang, A.X. Plasmonic nanoparticles-decorated diatomite biosilica: Extending the horizon of on-chip chromatography and label-free biosensing. *J. Biophotonics* **2017**, *10*, 1473–1484. <https://doi.org/10.1002/jbio.201700045>.
165. Liu, S.; Xu, D.; Chen, J.; Peng, N.; Ma, T.; Liang, F. Nanozymatic magnetic nanomotors for enhancing photothermal therapy and targeting intracellular SERS sensing. *Nanoscale* **2023**, *15*, 12944–12953. <https://doi.org/10.1039/d3nr02739b>.
166. Lian, B.; Li, H.; Guo, J.; Fan, D.E. Optoelectric Raman Nanosensors: Overcoming Intrinsic Limit in Nano-biosensing. *Res. Sq.* **2024**. <https://doi.org/10.21203/rs.3.rs-4732904/v1>.
167. Liu, J.; Guo, J.; Meng, G.; Fan, D. Superstructural Raman Nanosensors with Integrated Dual Functions for Ultrasensitive Detection and Tunable Release of Molecules. *Chem. Mater.* **2018**, *30*, 5256–5263. <https://doi.org/10.1021/acs.chemmater.8b01979>.
168. Huang, Y.; Gu, Y.; Liu, X.; Deng, T.; Dai, S.; Qu, J.; Yang, G.; Qu, L. Reusable ring-like Fe₃O₄/Au nanozymes with enhanced peroxidase-like activities for colorimetric-SERS dual-mode sensing of biomolecules in human blood. *Biosens. Bioelectron.* **2022**, *209*, 114253. <https://doi.org/10.1016/j.bios.2022.114253>.
169. Jiang, S.; Li, Q.; Wang, C.; Pang, Y.; Sun, Z.; Xiao, R. *In Situ* Exosomal MicroRNA Determination by Target-Triggered SERS and Fe₃O₄@TiO₂-Based Exosome Accumulation. *ACS Sens.* **2021**, *6*, 852–862. <https://doi.org/10.1021/acssensors.0c01900>.
170. Bai, X.; Wang, L.; Ren, J.; Bai, X.; Zeng, L.; Shen, A.; Hu, J. Accurate Clinical Diagnosis of Liver Cancer Based on Simultaneous Detection of Ternary Specific Antigens by Magnetic Induced Mixing Surface-Enhanced Raman Scattering Emissions. *Anal. Chem.* **2019**, *91*, 2955–2963. <https://doi.org/10.1021/acs.analchem.8b05153>.
171. Han, L.; Zhu, C.; Tan, Z.; Wang, J.; Liao, X.; Xia, X.; Wang, C. Integrated separation and detection of exosomes via a label-free magnetic SERS platform. *Chem. Commun.* **2023**, *59*, 7967–7970. <https://doi.org/10.1039/d3cc01530k>.
172. Kim, H.; Lee, S.; Seo, H.; Kang, B.; Moon, J.; Lee, K.; Yong, D.; Kang, H.; Jung, J.; Lim, E.; et al. Clustered Regularly Interspaced Short Palindromic Repeats-Mediated Surface-Enhanced Raman Scattering Assay for Multidrug-Resistant Bacteria. *ACS Nano* **2020**, *14*, 17241–17253. <https://doi.org/10.1021/acsnano.0c07264>.
173. Zhou, J.; Xiong, Q.; Ma, J.; Ren, J.; Messersmith, P.; Chen, P.; Duan, H. Polydopamine-Enabled Approach toward Tailored Plasmonic Nanogapped Nanoparticles: From Nanogap Engineering to Multifunctionality. *ACS Nano* **2016**, *10*, 11066–11075. <https://doi.org/10.1021/acsnano.6b05951>.
174. Duan, W.; Liu, R.; Sen, A. Transition between Collective Behaviors of Micromotors in Response to Different Stimuli. *J. Am. Chem. Soc.* **2013**, *135*, 1280–1283. <https://doi.org/10.1021/ja3120357>.
175. Kim, K.; Guo, J.; Liang, Z.; Fan, D. Artificial Micro/Nanomachines for Bioapplications: Biochemical Delivery and Diagnostic Sensing. *Adv. Funct. Mater.* **2018**, *28*, 1705867. <https://doi.org/10.1002/adfm.201705867>.
176. Wu, J.; Balasubramanian, S.; Kagan, D.; Manesh, K.M.; Campuzano, S.; Wang, J. Motion-based DNA detection using catalytic nanomotors. *Nat. Commun.* **2010**, *1*, 36. <https://doi.org/10.1038/ncomms1035>.
177. Chen, C.; Ding, S.; Wang, J. Materials consideration for the design, fabrication and operation of microscale robots. *Nat. Rev. Mater.* **2024**, *9*, 159–172. <https://doi.org/10.1038/s41578-023-00641-2>.
178. Pacheco, M.; López, M.; Jurado-Sánchez, B.; Escarpa, A. Self-propelled micromachines for analytical sensing: A critical review. *Anal. Bioanal. Chem.* **2019**, *411*, 6561–6573. <https://doi.org/10.1007/s00216-019-02070-z>.

179. Akolpoglu, M.B.; Dogan, N.O.; Bozuyuk, U.; Ceylan, H.; Kizilel, S.; Sitti, M. High-Yield Production of Biohybrid Microalgae for On-Demand Cargo Delivery. *Adv. Sci.* **2020**, *7*, 2001256. <https://doi.org/10.1002/adv.202001256>.
180. Shih, K.; Zaidi, N.; Lee, S.H.; Li, H.; Fan, D.E. Nanotweezers for Manipulating Untethered Micro/Nanoscale Bio-Tools: Principles, Performance, and Highlighted Applications. *Adv. NanoBiomed Res.* **2025**, *5*, 2400130. <https://doi.org/10.1002/anbr.202400130>.
181. Liang, Z.; Teal, D.; Fan, D. Light programmable micro/nanomotors with optically tunable in-phase electric polarization. *Nat. Commun.* **2019**, *10*, 5275. <https://doi.org/10.1038/s41467-019-13255-6>.
182. Joh, H.; Fan, D.E. Materials and Schemes of Multimodal Reconfigurable Micro/Nanomachines and Robots: Review and Perspective. *Adv. Mater.* **2021**, *33*, 2101965. <https://doi.org/10.1002/adma.202101965>.
183. Liang, Z.X.; Fan, D.L. Visible light-gated reconfigurable rotary actuation of electric nanomotors. *Sci. Adv.* **2018**, *4*, eaau0981. <https://doi.org/10.1126/sciadv.aau0981>.
184. Xu, X.; Kim, K.; Li, H.; Fan, D.L. Ordered Arrays of Raman Nanosensors for Ultrasensitive and Location Predictable Biochemical Detection. *Adv. Mater.* **2012**, *24*, 5457–5463. <https://doi.org/10.1002/adma.201201820>.
185. Lai, H.; Xu, F.; Wang, L. A review of the preparation and application of magnetic nanoparticles for surface-enhanced Raman scattering. *J. Mater. Sci.* **2018**, *53*, 8677–8698. <https://doi.org/10.1007/s10853-018-2095-9>.
186. Wang, Z.; Zong, S.; Wang, Y.; Li, N.; Li, L.; Lu, J.; Wang, Z.; Chen, B.; Cui, Y. Screening and multiple detection of cancer exosomes using an SERS-based method. *Nanoscale* **2018**, *10*, 9053–9062. <https://doi.org/10.1039/c7nr09162a>.
187. Huang, X.; Wu, S.; Hu, H.; Sun, J. AuNanostar@4-MBA@Au Core-Shell Nanostructure Coupled with Exonuclease III-Assisted Cycling Amplification for Ultrasensitive SERS Detection of Ochratoxin A. *ACS Sens.* **2020**, *5*, 2636–2643. <https://doi.org/10.1021/acssensors.0c01162>.
188. Zhang, W.; Tang, S.; Jin, Y.; Yang, C.; He, L.; Wang, J.; Chen, Y. Multiplex SERS-based lateral flow immunosensor for the detection of major mycotoxins in maize utilizing dual Raman labels and triple test lines. *J. Hazard. Mater.* **2020**, *393*, 122348. <https://doi.org/10.1016/j.jhazmat.2020.122348>.
189. Bell, S.E.J.; Charron, G.; Cortés, E.; Kneipp, J.; de la Chapelle, M.L.; Langer, J.; Procházka, M.; Tran, V.; Schlücker, S. Towards Reliable and Quantitative Surface-Enhanced Raman Scattering (SERS): From Key Parameters to Good Analytical Practice. *Angew. Chem. Int. Ed.* **2020**, *59*, 5454–5462. <https://doi.org/10.1002/anie.201908154>.
190. Qian, X.M.; Nie, S.M. Single-molecule and single-nanoparticle SERS: From fundamental mechanisms to biomedical applications. *Chem. Soc. Rev.* **2008**, *37*, 912–920. <https://doi.org/10.1039/B708839F>.
191. Bi, X.; He, Z.; Luo, Z.; Huang, W.; Diao, X.; Ye, J. Digital colloid-enhanced Raman spectroscopy for the pharmacokinetic detection of bioorthogonal drugs. *Chem. Sci.* **2024**, *15*, 13998–14008. <https://doi.org/10.1039/D4SC02553A>.
192. Bi, X.; Czajkowsky, D.M.; Shao, Z.; Ye, J. Digital colloid-enhanced Raman spectroscopy by single-molecule counting. *Nature* **2024**, *628*, 771–775. <https://doi.org/10.1038/s41586-024-07218-1>.
193. Ando, J.; Murai, K.; Michiyuki, T.; Takahashi, I.; Iida, T.; Kogo, Y.; Toyoda, M.; Saito, Y.; Murayama, S.; Kurihara, M.; et al. Digital SERS bioanalysis of single-enzyme biomarkers. *Proc. Natl. Acad. Sci. USA* **2025**, *122*, e2510559122. <https://doi.org/10.1073/pnas.2510559122>.
194. Li, J.; Wuethrich, A.; Sina, A.A.I.; Cheng, H.-H.; Wang, Y.; Behren, A.; Mainwaring, P.N.; Trau, M. A digital single-molecule nanopillar SERS platform for predicting and monitoring immune toxicities in immunotherapy. *Nat. Commun.* **2021**, *12*, 1087. <https://doi.org/10.1038/s41467-021-21431-w>.
195. Wen, P.; Yang, F.; Zhao, H.; Li, S.; Xu, Y.; Chen, L. Microcavity Array-Based Digital SERS Chip for Rapid and Accurate Label-free Quantitative Detection of Live Bacteria. *ACS Sens.* **2024**, *9*, 6167–6173. <https://doi.org/10.1021/acssensors.4c02007>.
196. Liu, W.; Wang, Z.; Liu, Z.; Chen, J.; Shi, L.; Huang, L.; Liu, Y.; Cui, S.; He, X. Utilizing an Automated SERS-Digital Microfluidic System for High-Throughput Detection of Explosives. *ACS Sens.* **2023**, *8*, 1733–1741. <https://doi.org/10.1021/acssensors.3c00012>.
197. Kim, W.; Han, J.; Kim, Y.J.; Lee, H.; Kim, T.G.; Shin, J.-H.; Kim, D.-H.; Jung, H.S.; Moon, S.W.; Choi, S. Molybdenum Disulfide-Assisted Spontaneous Formation of Multistacked Gold Nanoparticles for Deep Learning-Integrated Surface-Enhanced Raman Scattering. *ACS Nano* **2024**, *18*, 17557–17569. <https://doi.org/10.1021/acsnano.4c00978>.
198. Kim, M.G.; Jue, M.; Lee, K.H.; Lee, E.Y.; Roh, Y.; Lee, M.; Lee, H.J.; Lee, S.; Liu, H.; Koo, B.; et al. Deep Learning Assisted Surface-Enhanced Raman Spectroscopy (SERS) for Rapid and Direct Nucleic Acid Amplification and Detection: Toward Enhanced Molecular Diagnostics. *ACS Nano* **2023**, *17*, 18332–18345. <https://doi.org/10.1021/acsnano.3c05633>.
199. Zhao, Y.; Zhan, K.; Xin, P.-L.; Chen, Z.; Li, S.; De Angelis, F.; Huang, J.-A. Single-Molecule SERS Discrimination of Proline from Hydroxyproline Assisted by a Deep Learning Model. *Nano Lett.* **2025**, *25*, 7499–7506. <https://doi.org/10.1021/acs.nanolett.5c01177>.
200. Bi, X.; Lin, L.; Chen, Z.; Ye, J. Artificial Intelligence for Surface-Enhanced Raman Spectroscopy. *Small Methods* **2024**, *8*, 2301243. <https://doi.org/10.1002/smt.202301243>.

201. Xue, B.; Bi, X.; Dong, Z.; Xu, Y.; Liang, M.; Fang, X.; Yuan, Y.; Wang, R.; Liu, S.; Jiao, R.; et al. Deep spectral component filtering as a foundation model for spectral analysis demonstrated in metabolic profiling. *Nat. Mach. Intell.* **2025**, 7, 743–757. <https://doi.org/10.1038/s42256-025-01027-5>.
202. Xie, Y.; Su, X.; Wen, Y.; Zheng, C.; Li, M. Artificial Intelligent Label-Free SERS Profiling of Serum Exosomes for Breast Cancer Diagnosis and Postoperative Assessment. *Nano Lett.* **2022**, 22, 7910–7918. <https://doi.org/10.1021/acs.nanolett.2c02928>.
203. Sjöberg, J.; Siminea, N.; Păun, A.; Lita, A.; Larion, M.; Petre, I. RADAR: Raman Spectral Analysis Using Deep Learning for Artifact Removal. *Adv. Opt. Mater.* **2025**, 13, 2500736. <https://doi.org/10.1002/adom.202500736>.
204. Luo, S.-H.; Xu, J.; Wang, W.-L.; Xiong, C.-R.; Wang, L.-P.; Tian, Z.-Q.; Liu, G.-K. SSNet: A Spectral Unmixing Framework for Enhancing the Qualitative Sensitivity of SERS to Trace Targets in Complex Mixtures. *J. Am. Chem. Soc.* **2025**, 147, 43964–43972. <https://doi.org/10.1021/jacs.5c16529>.
205. Pavlou, E.; Kourkoumelis, N. PyFasma: An open-source, modular Python package for preprocessing and multivariate analysis of Raman spectroscopy data. *Analyst* **2025**, 150, 3112–3122. <https://doi.org/10.1039/D5AN00452G>.
206. Georgiev, D.; Pedersen, S.V.; Xie, R.; Fernández-Galiana, Á.; Stevens, M.M.; Barahona, M. RamanSPy: An Open-Source Python Package for Integrative Raman Spectroscopy Data Analysis. *Anal. Chem.* **2024**, 96, 8492–8500. <https://doi.org/10.1021/acs.analchem.4c00383>.
207. Wang, Z.; Ranasinghe, J.C.; Wu, W.; Chan, D.C.Y.; Gomm, A.; Tanzi, R.E.; Zhang, C.; Zhang, N.; Allen, G.I.; Huang, S. Machine Learning Interpretation of Optical Spectroscopy Using Peak-Sensitive Logistic Regression. *ACS Nano* **2025**, 19, 15457–15473. <https://doi.org/10.1021/acsnano.4c16037>.
208. Song, Y.; Zhang, M.; Jiang, X.; Zhang, F.; Ju, C.; Huang, S.; Lau, A.P.T.; Wang, D. SRS-Net: A universal framework for solving stimulated Raman scattering in nonlinear fiber-optic systems by physics-informed deep learning. *Commun. Eng.* **2024**, 3, 109. <https://doi.org/10.1038/s44172-024-00253-w>.
209. Huang, L.; Sun, H.; Sun, L.; Shi, K.; Chen, Y.; Ren, X.; Ge, Y.; Jiang, D.; Liu, X.; Knoll, W.; et al. Rapid, label-free histopathological diagnosis of liver cancer based on Raman spectroscopy and deep learning. *Nat. Commun.* **2023**, 14, 48. <https://doi.org/10.1038/s41467-022-35696-2>.
210. Zheng, P.; Wu, L.; Lee, M.K.H.; Nelson, A.; Betenbaugh, M.; Barman, I. Deep Learning-Powered Colloidal Digital SERS for Precise Monitoring of Cell Culture Media. *Nano Lett.* **2025**, 25, 6284–6291. <https://doi.org/10.1021/acs.nanolett.5c01071>.
211. Zheng, P.; Semancik, S.; Barman, I. Deep Learning-Assisted SERS for Therapeutic Drug Monitoring of Clozapine in Serum on Plasmonic Metasurfaces. *Nano Lett.* **2025**, 25, 5342–5349. <https://doi.org/10.1021/acs.nanolett.5c00391>.
212. Zhang, D.; Cheng, Z.; Song, Y.; Li, H.; Shi, L.; Wang, N.; Peng, Y.; Chen, R.; Sun, N.; Han, M.; et al. Rapid and sensitive acute leukemia classification and diagnosis platform using deep learning-assisted SERS detection. *Cell Rep. Med.* **2025**, 6, 102320. <https://doi.org/10.1016/j.xcrm.2025.102320>.
213. Zaki, J.K.; Tomasik, J.; McCune, J.A.; Bahn, S.; Lió, P.; Scherman, O.A. Explainable Deep Learning Framework for SERS Bioquantification. *ACS Sens.* **2025**, 10, 6597–6606. <https://doi.org/10.1021/acssensors.5c01058>.
214. Li, M.; He, X.; Wu, C.; Wang, L.; Zhang, X.; Gong, X.; Zeng, X.; Huang, Y. Deep Learning Enabled SERS Identification of Gaseous Molecules on Flexible Plasmonic MOF Nanowire Films. *ACS Sens.* **2024**, 9, 979–987. <https://doi.org/10.1021/acssensors.3c02519>.
215. Lin, X.; Lin, D.; Chen, Y.; Lin, J.; Weng, S.; Song, J.; Feng, S. High Throughput Blood Analysis Based on Deep Learning Algorithm and Self-Positioning Super-Hydrophobic SERS Platform for Non-Invasive Multi-Disease Screening. *Adv. Funct. Mater.* **2021**, 31, 2103382. <https://doi.org/10.1002/adfm.202103382>.