SERS: Materials, applications, and the future

Surface enhanced Raman spectroscopy (SERS) is a powerful vibrational spectroscopy technique that allows for highly sensitive structural detection of low concentration analytes through the amplification of electromagnetic fields generated by the excitation of localized surface plasmons. SERS has progressed from studies of model systems on roughened electrodes to highly sophisticated studies, such as single molecule spectroscopy. We summarize the current state of knowledge concerning the mechanism of SERS and new substrate materials. We highlight recent applications of SERS including sensing, spectroelectrochemistry, single molecule SERS, and real-world applications. We also discuss contributions to the field from the Van Duyne group. This review concludes with a discussion of future directions for this field including biological probing with UV-SERS, tip-enhanced Raman spectroscopy, and ultrafast SERS.

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The first observations of the Raman spectra of pyridine on roughened silver were made in 1974[1]; however, at this time the authors did not recognize that these spectra were due to any unusual, enhanced, or new phenomena. Since its discovery in 1977[2], interest in and the use of surface enhanced Raman spectroscopy (SERS) has grown exponentially (Fig. 1). The SERS field has dramatically progressed from the originally observed enhancement on roughened silver electrodes to the current fields of sensing and imaging applications, single molecule detection, and extensions to ultrahigh vacuum and ultrafast science[3-6]. At the most basic level, SERS is a way to significantly increase the signal from the weak yet structurally rich technique of Raman scattering. Researchers have implemented several methods to increase the Raman scattering efficiency, including using stimulated Raman processes and electronic resonance enhancement; however, the most significant amplification of the Raman signal comes from SERS[7-10]. At its most complex level, single molecules are now routinely observed due to the large enhancement. Additionally, SERS is an exceptional technique for the characterization of small numbers of molecules bound to or near plasmonic surfaces.

As SERS enters its fourth decade, we review here several of the most exciting findings and new avenues in this field. In this article, we
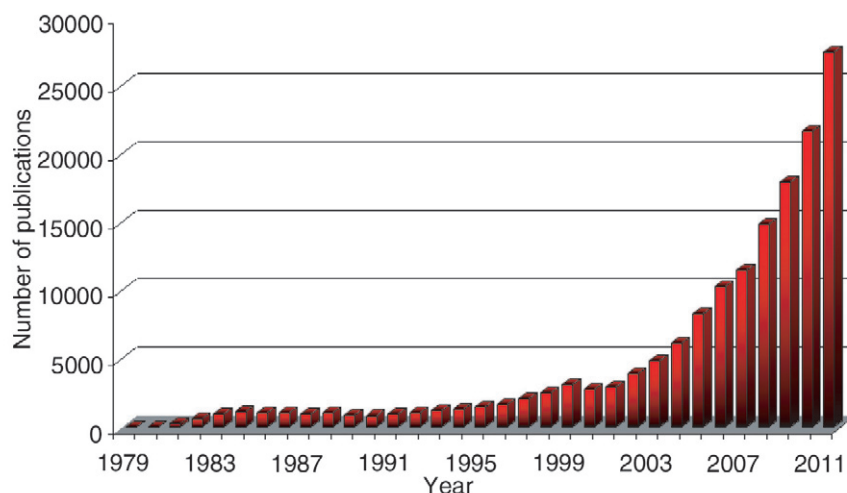
Fig. 1 Growing popularity of the surface enhanced Raman technique. This plot shows citation data in Web of Science for the term "surface enhanced Raman", as accessed on September 30th, 2011. Citations for 2011 are predicted based on year-to-date values.

briefly discuss the background and mechanism of SERS, highlight the important role of understanding the structure-function relationships of plasmonic materials, and evaluate its applications to sensing and detection, including single molecule detection and uses for SERS outside of the laboratory environment. We conclude with several exciting new developments in the SERS field, including extension to the ultraviolet regime for biological applications, tip enhanced Raman spectroscopy (TERS), and SERS integration with ultrafast spectroscopies.

Background and mechanism

After decades of debate, it is now generally agreed that the dominant contributor to most SERS processes is the electromagnetic enhancement mechanism[10]. The enhancement results from the amplification of the light by the excitation of localized surface plasmon resonances (LSPRs). This light concentration occurs preferentially in the gaps, crevices, or sharp features of plasmonic materials, which are traditionally noble and coinage metals (e.g., silver, gold, and copper) with nanoscale features. Reproducible and robust structures that strongly enhance the electromagnetic field are most desirable for SERS, and will be discussed below. Depending on the structure of the supporting plasmonic material, electromagnetic enhancement for SERS is theoretically calculated to reach factors of $\sim 10^{10} - 10^{11}$.[11] In most circumstances the enhancement factor can be well approximated by the magnitude of the localized electromagnetic field to the fourth power[10].

The other mechanism involved in signal enhancement is chemical enhancement, which primarily involves charge transfer mechanisms, where the excitation wavelength is resonant with the metal-molecule charge transfer electronic states[12]. Theoretically, chemical enhancement factors up to 10^3 were calculated using time dependent density functional theory for *para*- and *meta*-substituted pyridine interacting with a silver cluster.

The authors found that the magnitudes of enhancement through charge transfer transitions are highly molecule specific[12,13]. Our group and the Schatz group at Northwestern are currently working at experimentally and theoretically determining the chemical enhancement by examining various substituted benzenethiols. Presently, we have experimentally obtained chemical enhancement factors of only $\sim 5 - 10$.[14]

The total SERS enhancement factor is the product of the electromagnetic and chemical enhancement mechanisms. For highly optimized surfaces, it may approach $\sim 10^{10} - 10^{11}$.[15] In addition, resonance Raman effects have traditionally played a large role in SERS experiments, as dye molecules with extremely large resonance Raman cross sections[16] are often used in SERS. Development of SERS substrates with high enhancement factors remains an active area of SERS research.

Experimental considerations

Although performing a SERS experiment requires careful consideration of sample and optical setup to ensure maximum signal generation and enhancement, it is a powerful and non-destructive technique for determining chemical identity and structural information from small numbers of molecules. The first parameter to take into account is the choice of enhancing substrate. Substrates range in structure from nanorods to three-dimensional colloidal solutions, with tunable plasmon resonances and a range of average enhancement factors. Additionally, as the maximum SERS enhancing region decreases extremely rapidly with distance (r^{-10} for spheres),[10] the largest enhancements are found in the few nanometers closest to the substrate surface.

Next to consider is an appropriate excitation source, which should enable efficient excitation of the plasmon resonance. Simplified theories of SERS predict a maximum enhancement when the laser is tuned to the peak of the plasmon resonance, for a substrate with a single peak in

its LSPR spectrum. While this has been shown experimentally to lead to high enhancements, the maximum enhancement factors are found when the laser wavelength is shifted to the blue of the plasmon resonance, ideally shifted by one-half of the Raman vibrational frequency[17]. This most efficiently maximizes enhancement on both the excitation and emission parts of the Raman process, leading to the highest SERS signals. Thus, maximum signal is found when the plasmon frequency is tuned to be slightly red-shifted from the laser wavelength.

Following excitation of the plasmon resonance and generation of the SERS signal, the detection process is identical to normal Raman experiments. A notch or long-pass filter is used to absorb or reflect any Rayleigh scattering while allowing for transmission of the Raman signal, and a spectrograph and detector are used to image Raman spectra across a wide spectral region. Complete handheld commercial Raman systems are easy to integrate with SERS experiments, as described below.

Plasmonic materials

The success of SERS is highly dependent on the interaction between adsorbed molecules and the surface of plasmonic nanostructures, often the classic SERS substrates of gold (Au), silver (Ag), or copper (Cu). In general, Au and Ag are most often used as SERS substrates because they are air stable materials, while Cu is more reactive. All three metals have LSPRs that cover most of the visible and near infrared wavelength range, where most Raman measurements occur, also making them convenient to use (Fig. 2). Over the last 30 years, researchers strived to optimize substrate structure and configuration to maximize enhancement factors. Recently efforts have been made to identify new plasmonic materials[18-20], as well as different shapes that support increased SERS enhancement.

Advances have been made in the development of SERS substrates[21], including Ag and Au nanoparticles with various shapes and with coatings resulting in structures such as Shell-isolated nanoparticle-enhanced Raman spectroscopy (SHINERS)[22], SiO_2-encapsulated Au particles[23], 2D Au nano-mushroom arrays[24], polyhedral Ag mesocages[25], Si wafers with Ag or Au

coating[26], atomic layer deposition (ALD)-coated plasmonic nanoparticles[8] and film over nanospheres (FONs).[27] The ALD coating on nanoparticles is intriguing because it allows for the determination of the distance dependence for SERS, protects the nanoparticle surface, provides temperature stability, enables functionalization of the nanoparticle and improves the stability of the surface for use with femtosecond pulses[8,28]. FONs are created by vapor deposition of thin films of either silver or gold over spheres (polystyrene or silica) and are optimal SERS substrates in that they are easily made, cost-effect, and extremely reproducible over a large area.

Moving beyond Ag and Au, metals including the alkali metals (Li, Na, K, Rb, and Cs), Al, Ga, In, Pt, Rh, and metal alloys[20] have all been explored as plasmonic substrates for SERS. Al is discussed in more detail as a substrate material for UV SERS (*vide infra*). Some of these materials are highly reactive in air making them difficult to use; however, if methodologies can be developed to overcome this reactivity, new avenues for the development of metallic SERS substrates would be opened.

Novel materials such as graphene[29,30], semiconductors such as TiO_2[31], and quantum dots[32-34] have recently been reported to show SERS, although they do not fit traditional definitions of SERS substrates. Many factors need to be considered when classifying a material as a reliable and highly enhancing SERS substrate. First, a plasmon resonance spectrum that is separate from the charge transfer and absorption spectra must be acquired, because plasmonic materials support electromagnetic SERS enhancement, while excitation through the chemical enhancement mechanism of charge transfer alone does not result in a SERS spectrum, by the conventional definition of SERS. In order for a material to be described as plasmonic, it must have a negative real component of the dielectric constant and a small, positive imaginary component of the dielectric constant. SERS should be measured on a number of different molecules, to confirm that various types of molecule are enhanced. In order to assure the system is not undergoing a resonance Raman effect, SERS spectra are collected for non-resonant molecules. Establishing collaborations with theoreticians is important for finding an agreement
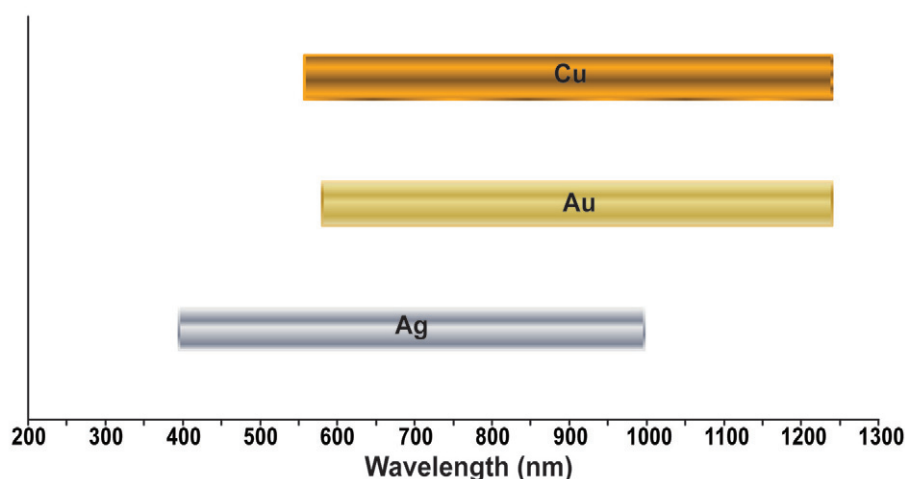

Fig. 2 Approximate wavelength ranges where Ag, Au, and Cu have been well-characterized and are established to support SERS.
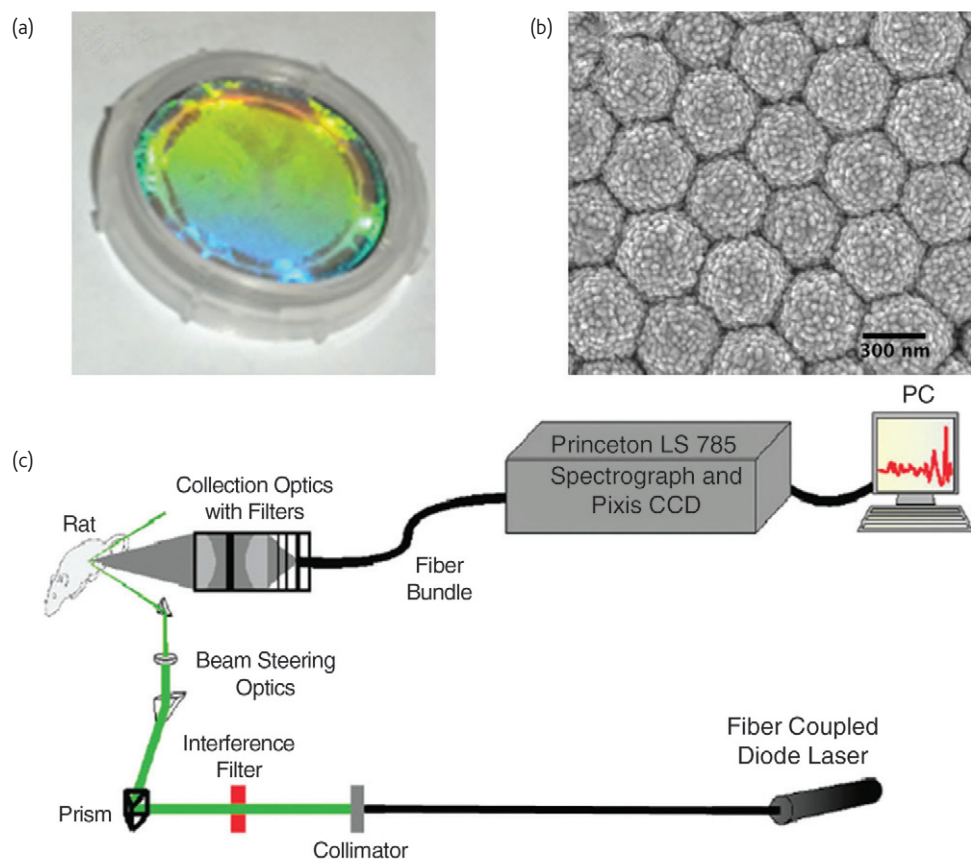
Fig. 3 (a) Silver film (200nm) over 880 nm Si nanospheres (AgFONs) on 1 inch coverslip (courtesy of N. G. Greeneltch). (b) SEM image of an AgFON (N. G. Greeneltch and A.-I. Henry); (c) Schematic of SESORS apparatus (courtesy of J. M. Yuen).

between theory and experimental work. Finally, a methodology needs to be developed to establish coverage of molecules on the surface. These requirements allow for a material to be well-characterized and clearly established as a SERS substrate.

A few groups[29-34] have begun to explore semiconductors, quantum dots, and graphene as substrates for SERS for use in characterizing exciting new materials and devices. These groups acknowledge that these substrates involve purely chemical enhancements, attributed to charge transfer bands, resonances with interband transitions, and π-π stacking interactions. There is no evidence of electromagnetic enhancement and therefore, these substrates are unlikely to achieve enhancement factors greater than 10^3. Progress is being made in establishing graphene as a plasmonic material in the infrared[35], leading to the future possibility of SERS on graphene. Further exploration of novel substrates will open up new avenues of research for SERS.

Applications

The power of SERS lies in its ability to identify chemical species and obtain structural information in a wide variety of fields including polymer and materials science, biochemistry and biosensing, catalysis, and electrochemistry. We highlight here a few exciting applications of SERS.

Biosensors

SERS is a highly sensitive and selective technique for use in the detection of biological samples. SERS biosensing, a vast topic, has been reviewed in great detail elsewhere[36-38]. SERS biosensors are used in detection of various biological samples and diseases, including various cancers[39-42], Alzheimer's disease[43,44], and Parkinson's disease[45,46]. Here, we will focus on the progress made in the use of SERS biosensors for glucose detection.

A significant medical problem of the 21st century is the growing incidence of diabetes mellitus, a disease in which the body either does not produce its own insulin (Type I) or cells become insulin resistant (Type II). Patients with diabetes are often required to check their blood glucose levels 3 – 10 times/day. Development of an *in vivo* glucose sensor that allows for real-time measurement of blood glucose levels without having to draw blood would greatly improve the quality of life of diabetic patients. The Van Duyne group has made significant progress in the development of a SERS-based *in vivo* glucose sensor. A AgFON surface functionalized with a decanethiol and mercaptohexanol (DT/MH) self-assembled monolayer (SAM) (Figs. 3a,b) can accurately detect blood glucose concentrations even in the presence of additional bioanalytes[8,47-49]. Significant progress has been made in combining this
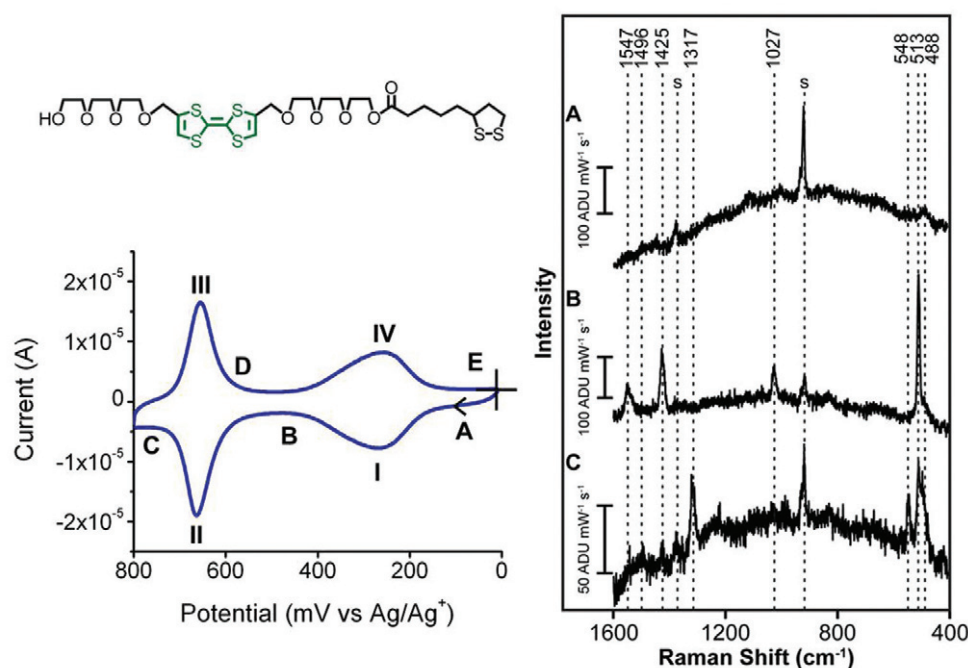
Fig. 4 Spectroelectrochemistry of TTF-derivative 1. Top left: structure of 1, bottom left: cyclic voltammogram of 1 in MeCN on a Au FON, right: SER spectra at different potential, as labeled in the bottom left panel. Note that the spectrum at D is equivalent to B, and E is equivalent to A. Reproduced with permission from[61] © 2011 American Chemical Society.

AgFON DT/MH functionalized SERS sensor with spatially offset Raman spectroscopy (SORS), resulting in surface enhanced SORS (SESORS) which allows for measurement of the blood glucose through the skin of living rats (Fig. 3c) [50,51]. The implanted sensors are highly accurate and consistent, while also able to accurately measure low concentrations of blood glucose. The glucose concentrations measured are less than the currently accepted lower limit established by the International Organization Standard requirements[50]. These results are highly promising for the future of SERS-based *in vivo* glucose sensors and for improving the quality of life of diabetic patients.

Chemical warfare agents

Gas phase chemical detection is of critical importance for the sensing of highly toxic molecules, such as chemical warfare agents (CWAs) and toxic industrial chemicals (TICs). The key challenge in detecting such analytes with SERS is to overcome the typical lack of interaction of the molecules with the substrate, allowing for detection of a SERS signal. Despite this difficulty, explosives such as the half-mustard agent[52] and dinitrobenzenethiol[53] have been successfully detected by SERS. One way to circumvent the surface interaction challenge is to use water-soluble analytes that are converted from the gas phase to the liquid phase and can be detected using a device such as a combined microfluidics-SERS sensor[54], that has allowed for the detection of most explosives.

Beyond the ability to detect CWAs in a laboratory, i.e., in the context of large, technical, and relatively expensive apparatus, of significant interest is the detection of CWAs with SERS in the field. The advent of

small, portable Raman spectrometers with dimensions close to that of a smartphone such as the ReporteR spectrometer (Intavec, Inc.) or the FirstDefender (Thermo Scientific, Inc.), and the development of stand-off SERS detection[55,56] has begun the transition from the lab to the field. Overall, SERS is a promising method for the ultrasensitive detection of chemical species that are relevant to homeland security[57].

Spectroelectrochemistry

Moving beyond mechanisms for detection, SERS has also been developed for use in conjunction with electrochemistry to detect and unravel the behavior of molecules in different oxidation states. SERS substrates and electrochemical electrodes are typically metal surfaces, allowing for these techniques to be combined for studying electrochemically active molecules spectroscopically. Chemical information during a potential sweep was obtained in real-time for a derivative of the molecule tetrathiafulvalene (TTF, compound 1, Fig. 4), an electron rich compound extensively used in mechanostereochemistry and molecular electronic devices[58,59]. The electrochemistry of TTF in nonaqueous solvents is well known, displaying two reversible one-electron processes at around 0.34 and 0.68 eV (vs SCE)[60]. The structural changes and redox properties of compound 1 were investigated using a AuFON as the SERS-active working electrode[61]. A series of SERS spectra of a monolayer of 1 were acquired concomitant with cyclic voltammetry measurements (Fig. 4). The results show a change in vibrational frequencies as a result of a change in oxidation state. Additionally, dramatic changes in signal were observed as the potential was swept. Overall, the capability to observe
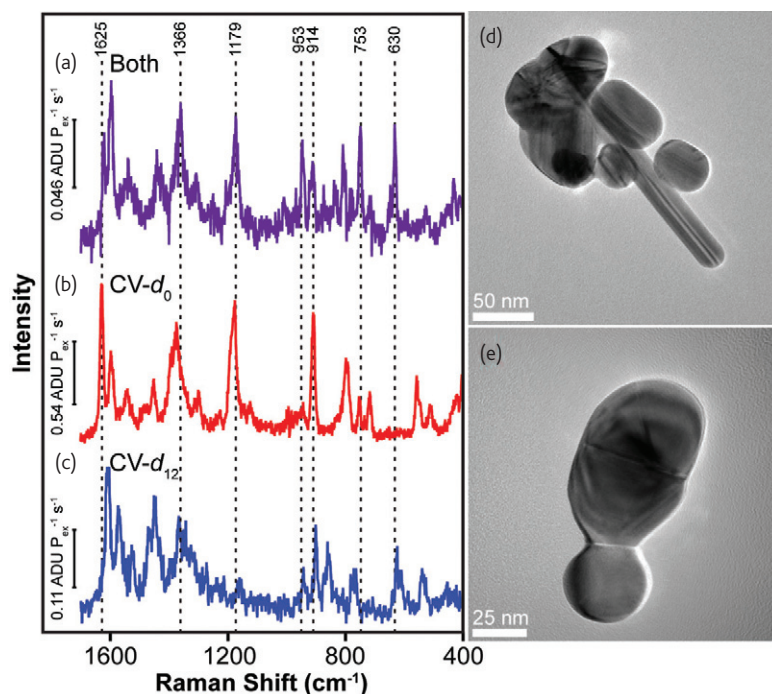
Fig. 5 Representative SMSERS spectra of crystal violet isotopologues. (a) both deuterated and undeuterated, (b) undeuterated, (c) deuterated, (d-e) TEM images of Ag colloid aggregates which support SMSERS. Reproduced with permission from[66] © 2011 American Chemical Society.

electrochemical changes spectroscopically as they occur is a powerful tool, applicable to molecular switches and electronic stimulation.

Single molecule SERS

Nearly 15 years ago, SERS began progressing from bulk samples to single molecule sensing; often considered to be the ultimate limit of detection[62,63]. The concept of single molecule detection revitalized the field and rejuvenated interest in SERS. Single molecule SERS (SMSERS) offers significant advantages when compared to single molecule fluorescence, in particular due to decreased sample bleaching and richer, fingerprint-like chemical information. Our interest in SMSERS stems from its power to detect and identify analytes down to the single molecule level.

Our group pioneered the isotopologue approach, which is a variant of the bianalyte method introduced by Le Ru *et al.*,[64] to confirm the single molecule nature of an observed signal. Using a pair of molecules that have contrasting isotopic vibrational signatures, it is possible to distinguish signals that originate from either of the adsorbates, even at very low concentrations. Rhodamine 6G and crystal violet were both characterized separately using this approach by comparing 50:50 mixtures of their isotopologues (H vs D-terminated; Figs. 5a-c). For each spectrum, only the vibrational signature of either the deuterated or non-deuterated samples was predominantly detected, confirming the SMSERS nature of the experiment[65,66].

All single molecule observations in the literature originate from random aggregates of colloidal silver nanoparticles. Recently, correlated

approaches have allowed us to obtain the SMSERS signal, LSPR spectrum, and structure of the enhancing aggregates[66]. The single molecule nature of the signal was proven using the isotopologue approach, and the structural correlation was obtained by using a TEM grid as a nanoparticle support (Figs. 5d,e). Two important conclusions were drawn from the ~ 40 aggregates studied: first, a large variety of structures were observed, from dimers to clusters containing over 10 nanoparticles; no single particle gave rise to SMSERS signal[66]. Second, no correlation exists between the number of nanoparticles in an aggregate and the intensity of the SMSERS signal.

Despite a better understanding of the molecular and structural requirements for enhancement obtained through our recent studies, challenges in SMSERS remain numerous. Although it has been demonstrated for non-resonant molecules[67], to date the technique has mostly been applied to resonant dyes for fundamental research. Many potential applications are also hindered by the lack of reproducible substrates, as currently only random aggregates of silver colloids have been shown to produce SMSERS. Learning about such structures and their enhancement factors however, provides a route towards the rational design of surfaces for single molecule spectroscopy.

Real world SERS applications

Although SERS was first observed and interpreted in 1977[2], its application to other scientific fields and application to fields outside the laboratory is quite recent. The technique has greatly benefited from progress made since the 1990s in the controlled fabrication of nanostructured
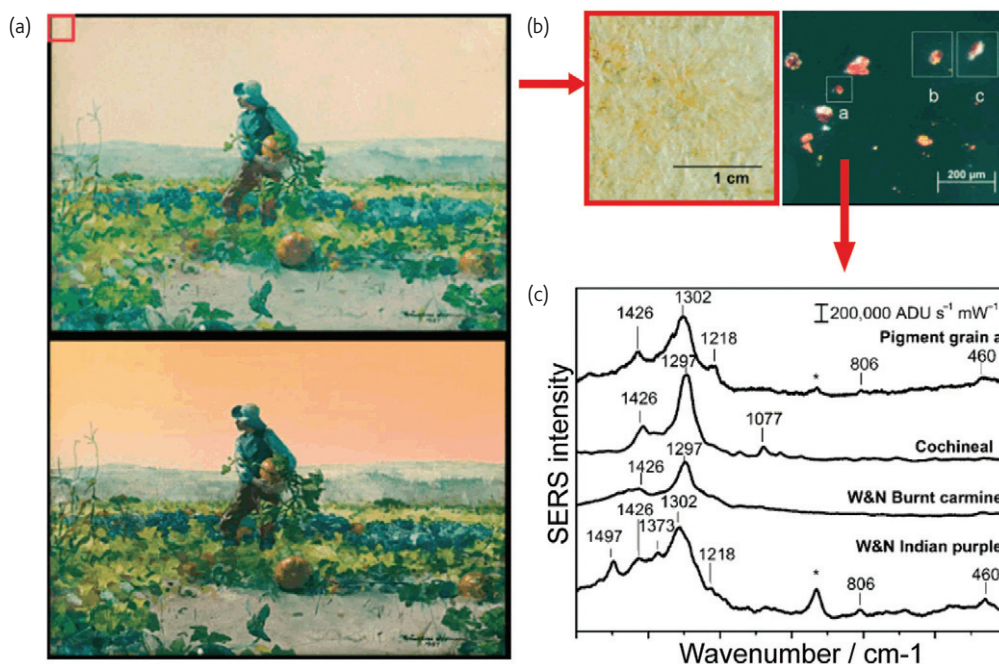
Fig. 6 Identification of a pigment from the Winslow Homer watercolor 'For to be a farmer's boy' Art Institute of Chicago 1963.760. (a) Painting as it appears today (top) and how it appeared after completion (bottom), based on SERS analysis of (b) pigments (shown in the photomicrographs) taken from the top left corner of the artwork (red box), and (c) analyzed by SERS and compared to dye standards allowing for the pigment to be identified as most likely composed of Indian purple. Adapted and reproduced from[68] with permission from Wiley.

substrates. In the following, we give two examples of applications of SERS outside the laboratory.

Detecting chemicals in very low concentration from very small material quantities is of great interest in the area of art preservation, where sample uptake from works of art must be kept to a minimum when allowed. SERS is an adequate technique for the identification of natural dyes and glazes that are often found in art materials and present a highly fluorescent background in the visible and NIR in standard Raman measurements. The metal surfaces used in SERS experiments act quenchers for the fluorescence, thus facilitating the study and identification of the analytes present in art objects. Sample uptake for SERS experiments is kept at a minimum though, and samples in the sub-μg to pg range have been successfully analyzed[68,69] in a variety of supports ranging from oil[70] and pastel[71] paintings to textiles and even wood sculptures[72]. A general preparation protocol consists of using aggregated Ag colloids incubated in a suspension of the dye extracted from the art medium. Following the detection of a dye in pigments, it is identified by comparing the experimental spectrum to a SERS spectral database. Fig. 6 illustrates how SERS measurements on a pigment-extracted dye enabled the elucidation of the colors originally used in a faded painting. SERS allows for the characterization of art works in many ways: tracing the origin dyes and thus the history of the art work, authenticating the work by comparison to other works from the same artist, and rendering the initial colors of a faded painting. The tracing of material is also of interest to areas outside of the art domain, such as in the context of counterfeit goods and currency.

SERS nanotags, Au spheres functionalized with reporter molecules and encased in a silica shell, can be incorporated in a variety of supports and be used for the labeling and authentication of different objects[73]. These nanotags are used in the field of brand security, for example, to encode jewelry or luxury goods. Nanotags can also be embedded in currency or bank notes[74] during the printing process.

The development of novel uses for SERS goes hand-in-hand with developments in instrumentation, which accounts for special technical considerations, and allows for SERS to be performed in the field. This includes portability of instrumentation. Portable Raman spectrometers are now available from several manufacturers, making it possible to measure SERS in the field for real-time chemical detection of environmental pollutants[75], CWAs, or in forensic science[76]. An example of a SERS experimental set-up with a portable spectrometer is presented in Fig. 7. Furthermore, stand-off detection by SERS is a reality made possible with optical fiber probes[77], greatly relevant for *in vivo* measurements or biomedical applications involving offset measurements through the skin, and long-focus collecting optics for the stand-off detection from samples at distances of 15 – 20 m.[55,56] Overall, SERS has successfully transitioned from a purely laboratory based technique to a valuable method for the ultrasensitive detection of molecules in the field. As such, it is very likely that its use will be extended to future field applications.

Future directions

SERS has been demonstrated to be an exciting field with applications not only to laboratory research problems but, also real-life situations.

Fig. 7 Example of experimental set-up for performing SERS on the field. SERS measurements can be easily taken by using a palm-size hand held spectrometer (here, ReporteR™ from Intevac, Inc.) while holding the sample, i.e., the SERS substrate incubated with the molecular species to be analyzed. Note that while measurements are being carried out, the sample is kept closer to sample attachment part (focal length: 6.25 mm) than shown. Image courtesy of Dr. J. M. Yuen.
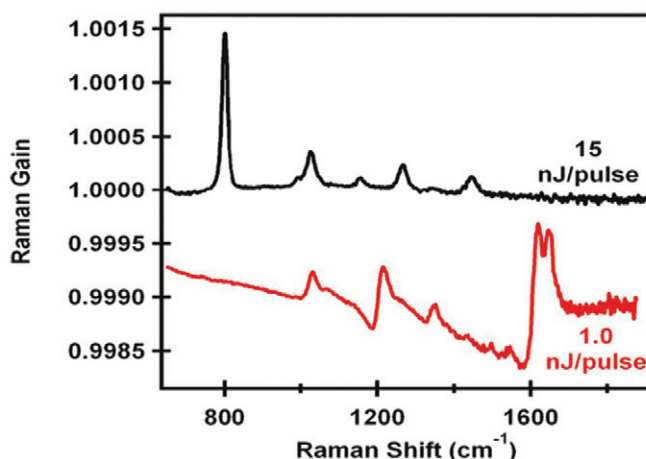

Fig. 8 Surface enhanced femtosecond stimulated Raman spectroscopy (SE-FSRS). The signal magnitude of neat cyclohexane with 15 nJ/pulse Raman pump power is similar to that of the dilute BPE nanoantennas taken with only 1 nJ/power. The surface enhancement is estimated to be $10^4 - 10^6$. Reproduced with permission from[94] © 2011 American Chemical Society.

Two attempts have been made at SERS in the DUV: exciting at 244 nm on an Al substrate[79] and at 266 nm on an Al coated Si tip[84], with the latter having an enhancement factor of ~ 210.

Aside from finding appropriate substrates for SERS, other challenges of working in the UV include avoiding photodegradation of samples; increasing efficiency of optical elements, including optics, spectrometer throughput, and the quantum efficiency of CCD cameras. These are not, however, insurmountable challenges. There is great potential in the development of UV SERS as a technique to further the scope of SERS.

Ultrafast and stimulated SERS

Combining all of the advantages afforded by the SERS technique with existing ultrafast spectroscopies is an active area of SERS research. There are several strong motivators for these kinds of investigations. Mechanistic studies on stimulated SERS are relatively unexplored, and some predict that enhancement factors could exceed 10^{20}.[85] Additionally, surface enhancement could be used as a method to simply increase the signal magnitudes of existing ultrafast spectroscopies, leading to investigations of ultrafast reaction dynamics on metal surfaces, including plasmon-enhanced photocatalytic and photovoltaic reactions. Although there have been many attempts to observe highly enhanced Raman signal using ultrafast and stimulated spectroscopies[86-88], many of these were limited to one vibrational peak with surface enhancement factors estimated to be well under 10^4.

Recently we demonstrated the incorporation of surface enhancement effects with the technique of femtosecond stimulated Raman spectroscopy (FSRS). FSRS is a coherent and stimulated vibrational technique capable of attaining highly resolved structural information on the femtosecond timescale[87,89]. FSRS has been used to probe the structural dynamics of a wide variety of photodriven reactions[90-93]. With

We feel, however, that researchers have only begun to realize the true potential of SERS. Some future directions for SERS that hold great promise for elevating SERS to new levels are discussed (below).

UV SERS

The excitation of SERS in the ultraviolet frequency range is relatively uncharted territory, but is highly desirable, as it would enable resonant detection of many biological molecules, including protein residues and DNA bases. For most metals, including the common SERS substrates of Ag and Au, the strongest enhancements are found in the visible or near infrared (NIR). Few groups have attempted to obtain UV SERS[78,79], often with much difficulty, indicating that achieving surface enhancement in the UV presents challenges that are not found in the visible or NIR. However, we believe the potential benefits of achieving SERS in the deep UV (DUV) outweigh the challenges. DUV SERS would be highly useful for investigating biological molecules, which have electronic resonances in this wavelength range, resulting in both electronic resonance and SERS enhancements.

The first challenge is finding plasmonic materials that support surface enhancement in the UV. Researchers have explored various metals as plasmonic materials, including Pd/Pt[78,80], Ru[81,82], Rh[78,81,82], Co[81,83], and Al[79]. Enhancement factors for the transition metals are on the order of ~ 10^2, which are considerably weaker than for Au and Ag in the visible[28,81].
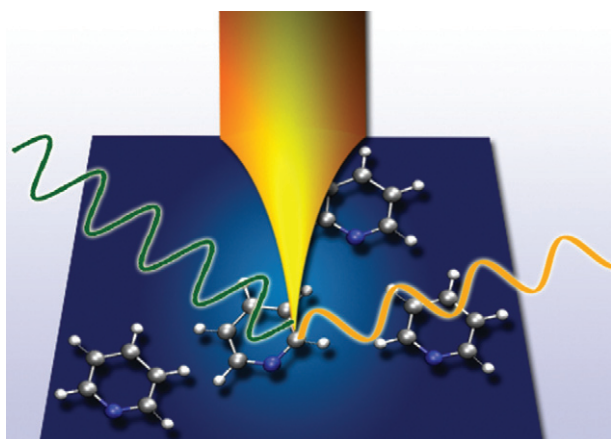
Fig. 9 Schematic depiction of tip enhanced Raman spectroscopy (TERS). Incoming light excites plasmons confined to the nanometer scale tip, enabling localized Raman probing of molecules below the tip.

the use of strongly enhancing plasmonic systems, we obtained ground state vibrational spectra in a variation of the technique called surface enhanced-femtosecond stimulated Raman spectroscopy (SE-FSRS)[94].

Our recent SE-FSRS experiments achieved enhancement factors estimated to be between 10^4 and 10^6, using SERS nanotags consisting of multiple gold cores, adsorbed *bis*-pyridyl-ethylene molecules, and a silica capping layer[23,94]. Using a picosecond Raman pump pulse and a femtosecond broadband Raman probe pulse, we obtained high signal-to-noise SE-FSRS spectra spanning $600 - 1800$ cm^{-1} (Fig. 8). The mechanism of enhancement in SE-FSRS is still unknown, and theoretical studies are needed to understand the interaction between the long-lived molecular vibrational coherences and adjacent plasmonic resonances.

Coupling ultrafast and surface enhanced spectroscopies is an exciting new field which should lead to greater insight on the interaction between molecules and metal surfaces. Additionally, the successful demonstrations of surface enhancement with coherent and time-resolved techniques should guide several directions of future research, including dynamic measurements on signal molecules or small homogeneous subsets, as well as investigations into ultrafast chemical reaction dynamics on surfaces.

Tip-enhanced Raman spectroscopy

Tip enhanced Raman spectroscopy (TERS) has been proposed as a method to spectroscopically interrogate a wide variety of chemical, biological, and material samples, with sub-diffraction-limited imaging capabilities[95,96]. In TERS, the electromagnetic field enhancement is located at a sharp metallic tip (Fig. 9) that is irradiated with laser light. When the tip is brought close to the sample of interest, it provides a localized region of SERS enhancement, which enables structural and compositional characterization with spatial resolution of a few nanometers. TERS experiments are typically performed by modifying a scanning tunneling microscope (STM) or atomic force microscope (AFM) with optical excitation and collection optics.

TERS experiments have been performed for over a decade, with initial studies on strong Raman scatterers such as dye molecules and buckyballs[97]. The field has rapidly grown to include samples as diverse as single stranded RNA[98], an individual single walled carbon nanotube[99], single particle dye sensitized solar cells[100], and hydrogen bonding in DNA bases[101], amongst others.

Two issues need to be addressed to achieve the extraordinary promise of TERS as a robust analytical technique for imaging on the nanometer length scale[102]. First, it is extremely challenging to calculate the area of the enhancing region, and thus the intrinsic resolution and enhancement factor in TERS. Further work on single molecule TERS should narrow estimates of the range of enhancement factors and spatial resolution achievable[103,104].

A second challenge to making TERS a robust analytical technique relies on developing a method to reliably generate enhancing TERS tips, just as scanning tunneling microscopists have developed tip conditioning methods for STM scanning. Innovative solutions including focused ion beam milling to etch a light-coupling grating into the wire above the tip[105], coinage metal deposition[106], or directly measuring tip plasmons[107], are a significant step in this direction.

TERS is a nascent field with largely unexplored areas of future potential[108]. UV-TERS would bring the TERS process into electronic resonance with a wide variety of biological samples, potentially enabling the non-invasive imaging of biological membranes or proteins with chemical specificity. Initial work on deep UV-TERS of crystal violet and adenine with aluminum coated tips has already been achieved[84]. Great potential also exists for the development of ultrahigh vacuum (UHV) TERS, in which molecules can be simultaneously imaged with sub-atomic resolution by STM on well-defined single crystal surfaces while their structure is interrogated spectroscopically. Obtaining time-resolved structural information with the addition of a photochemically gated laser pulse would achieve the ultimate dream of watching a single molecule undergo a chemical reaction.

Conclusions

SERS is a highly sensitive technique that allows for the detection of molecules in very low concentrations and provides rich structural information. We have highlighted some of the numerous applications for SERS both inside and outside the lab, demonstrating the versatility of the technique. With the advent of UV SERS, SE-FSRS, and TERS, we envision greater extension of the SERS technique into the realms of materials imaging, highly sensitive biological sensing, and probing of chemical reaction dynamics. mt

Acknowledgment

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