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Jürgen Popp *et al.* Recent progress in surface-enhanced Raman spectroscopy for biological and biomedical applications: from cells to clinics

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Introduction

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Tip-enhanced Raman spectroscopy (TERS) is a technique that couples the imaging capabilities of scanning probe microscopy (SPM) with the chemical structure analysis of Raman spectroscopy by taking advantage of the strong signal enhancement generated at a metallic tip apex. The basic principle relies on the resonance of surface plasmons, which are collective electron oscillations in the conduction band of a metal at the dielectric interface, causing a significant amplification of the

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Mastering high resolution tip-enhanced Raman spectroscopy: towards a shift of perception

Recent years have seen tremendous improvement of our understanding of high resolution reachable in TERS experiments, forcing us to re-evaluate our understanding of the intrinsic limits of this field, but also exposing several inconsistencies. On the one hand, more and more recent experimental results have provided us with clear indications of spatial resolutions down to a few nanometres or even on the subnanometre scale. Moreover, lessons learned from recent theoretical investigations clearly support such high resolutions, and vice versa the obvious theoretical impossibility to evade high resolution from a purely plasmonic point of view. On the other hand, most of the published TERS results still, to date, claim a resolution on the order of tens of nanometres that would be somehow limited by the tip apex, a statement well accepted for the past 2 decades. Overall, this now leads the field to a fundamental question: how can this divergence be justified? The answer to this question brings up an equally critical one: how can this gap be bridged? This review aims at raising a fundamental discussion related to the resolution limits of tip-enhanced Raman spectroscopy, at revisiting our comprehension of the factors limiting it both from a theoretical and an experimental point of view and at providing indications on how to move the field ahead. It is our belief that a much deeper understanding of the real accessible lateral resolution in TERS and the practical factors that limit them will simultaneously help us to fully explore the potential of this technique for studying nanoscale features in organic, inorganic and biological systems, and also to improve both the reproducibility and the accuracy of routine TERS studies. A significant improvement of our comprehension of the accessible resolution in TERS is thus critical for a broad audience, even in certain contexts where high resolution TERS is not the desired outcome.

Raman signal when excited by an external electromagnetic field. In the simplest scenario, in surface-enhanced Raman spectroscopy (SERS), small particles and/or noble metal surfaces with a typical roughness of a few nanometres confine the plasmons in the area surrounding the curvature, leading to a tremendous enhancement of the Raman signal, up to 10¹¹, depending on the experimental conditions.¹

The basic concept of TERS was developed about 2 decades ago, first by coupling a Raman spectrometer with an atomic force microscope $(AFM)^{2-4}$ set up (and quickly extended to a scanning tunneling microscope $(STM)^{5,6}$) in order to circumvent some of the issues encountered in SERS, namely: (1) the *a priori* unknown "hot spot" distribution on a metallic substrate (the heterogeneous distribution of enhancement factors) leading to a lack of spatial resolution of the probed molecules, and (2) the intrinsic difficulties at extracting quantitative information. TERS thus had the aim of using a single particle or edge feature as an antenna that scans a substrate with the help of SPM techniques and spatially resolves vibrational signatures at a scale that could eventually reach the size of a single molecule, no matter how many molecules are surrounding it. Since the beginning of the

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2000s, SERS- and TERS-based systems have evolved together due to the common physical principles that give rise to signal enhancement. Active research of SERS since the late 1990s has revealed that the technique is sensitive enough to reach single molecule detection,^{7,8} a conclusion that naturally should also apply to TERS. Nevertheless, the crucial issue of the specific size of the enhanced area under the tip remains a major subject of debate and is of course of utmost importance to discuss the lateral resolution aspects of TERS.

In conventional Raman spectroscopy, the resolution is limited by the Abbe diffraction limit, which is about half the wavelength (typically a few hundred nanometres). Therefore, for any specific experimental setup, one has a clear image of the spatial limitation of the system. Even though the diffraction limit does not play a role in a near-field optical technique like TERS, the situation is still more complex. Since the beginning of the development of TERS, the main question has been: what lateral resolution can be achieved and what is/are the limiting factor/s? The simplest scenario is the case where the resolution is related to the tip apex, just as is the case for SPM techniques. In such a context, the sole possible conclusion is that the lateral resolution in TERS is limited by the methodology used to produce the probe and, indirectly, by the maximum enhancement factor it generates. The latter enables measuring a satisfying signal from such a small area. For a while, different groups have reported lateral resolutions of ~ 10 to 80 nm, a range commonly accepted by the field and generally in accordance with the typical tip apex diameter. In contradiction with this, recent experimental results highlighted the possibility of performing subnanometre TERS, both with AFM and STM based techniques.9-12 Those results seem surprising at first glance and cannot be justified by a simple description of the tip size and shape, which forces us to



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question and revisit our vision of the real accessible lateral resolution in TERS. The latest results have pushed the development of theoretical investigations that will lead to a satisfying explanation and provide us with reliable predictions concerning the lateral resolution. In this context, the task of the theoretical investigation is: (1) to develop justifications for the subnanometre resolution observed in experimental results and (2) to work towards a generalised concept that will lead to a clear and general image of the physical basis behind high resolution TERS. To date, the most recent and promising avenue has looked towards the presence of atomic scale effects on the surface of the metallic particles that cover the tips. Furthermore, the formation of picocavities and the additional chemical effects on the enhancement factor that would justify an extremely localised field enhancement are an area of great interest.

Gaining a deeper understanding of our possibility of accessing high resolution in routine experiments is critical. TERS is currently unique in terms of its combined advantages regarding the wealth of information that can be extracted from vibrational spectra, the accessibility and the impressive spatial resolution it provides. Other techniques giving access to similar spatial resolution are fluorescence-based techniques such as stimulated emission depletion microscopy (STED),^{13,14} stochastic optical reconstruction microscopy (STORM)^{15,16} and photoactivated localisation microscopy (PALM).^{17,18} The development of super-resolved fluorescence microscopy represents a major breakthrough, ultimately addressing single molecules and consequently leading to the Nobel Prize of Chemistry in 2014. All the same, the main drawback of this technique is the necessity of actively labelling the specimen. Several other SPM-probe-based spectroscopic techniques have also demonstrated spatial resolutions close to TERS, namely, AFM-IR and infrared scatteringscanning near-field microscopy (IR s-SNOM). AFM-IR is based on thermomechanical expansion of the sample when absorbing infrared radiation.¹⁹ Its more recent implementation, mainly known as resonance enhanced (RE)-AFM-IR,²⁰ reported a spatial resolution of 20 nm.²¹ IR s-SNOM is similar to TERS in view of the fact that it detects the scattered IR signal under resonant conditions, bringing the advantage of separately measuring amplitude and phase of the signal. Admittedly, it requires more complex instrumentation and spectral reconstruction based on specific models.²²

Accordingly, several fields of chemistry, biology and physics are now considering TERS as a medium to obtain hitherto inaccessible information. It must be stressed that the direct application of TERS in the field of material characterisation currently remains limited. Anyhow, it is our belief that the expansion of its direct routine use for such an application is closely related to further development of the field in terms of control and comprehension of spatial resolution, because it implies a more efficient and quantitatively reliable analysis at various scales. Indeed, at the smallest possible scale, the potential ability to map single molecules enables accessing new fundamental properties. Thus, it provides new possibilities, such as direct sequencing of polymers, single molecule localisation in complex materials or probing events occurring at the interface, with a precision that was impossible to reach just a few years ago. At the same time, by being conscious of the real resolution, one has the ability to choose wisely the appropriate sampling steps at which data should be acquired, which ensure both a higher imaging quality and, most importantly, the avoidance of reproducibility issues that are the direct consequences of under-sampling heterogeneous samples.

This review is divided into 3 sections: the first critically reviews the key examples of state-of-the-art high resolution TERS. The second section surveys some of the recent major advances to theoretically explain the high spatial resolution, *e.g.* by simulation of localised plasmons and TERS tip/sample interaction. Finally, the third section intends to provide a fundamental discussion related to the practical parameters that affect resolution.

What has been achieved so far?

1.1. Model systems

The history of TERS, as any near- and far-field optical microscopy technique, is correlated with the search for the resolution limitations and the development of experimental strategies to constantly improve it. As stated in the introduction, from the very first TERS paper, it was reckoned that the size and shape of the tip were the main limiting factors. Thus, TERS studies were conducted in close proximity to tip production development, where the main concept was to reduce the tip apex in order to further improve resolution. A detailed description of the specific tip production strategies developed with time is beyond the aim of this review and interested readers are referred to the general TERS review of this issue. Here, our focus is solely on the evolution of high resolution TERS conducted in the past years by discussing selected TERS studies that indicate a resolution much higher than expected.

One of the first model systems used for such studies were carbon nanotubes, mainly due to the simplicity of the interpretation of the Raman signal, their intrinsically large crosssection and their structural stability. In 2003, Hartschuh et al.²³ first investigated a single walled carbon nanotube (SWNT) and concluded a spatial resolution of ~ 25 nm, based on near-field Raman imaging of the G' band intensity. Interestingly, by comparing the results with the AFM imaging, they concluded that the AFM topography showed a slightly lower resolution (~30 nm). And erson et al.²⁴ also mapped the lateral cross section of a SWNT and concluded a resolution of the same order of magnitude. The same group, however, later reported a resolution of 10 nm by mapping the lateral cross section of a similar sample.^{25,26} In the same period other experiments concluded that the lateral resolution was as low as \sim 75 nm, with cross section mapping of multi-walled carbon nanotubes (MWCTs), illustrating the significant differences observed for a similar system in different experimental configurations.²⁷ The variability of the results extracted from these different measurements

on fairly similar samples illustrates well why the resolution has been associated with the tip apex size.

In 2005, Pettinger et al. used an original way to study TERS lateral resolution using a side illumination setup to perform a detailed analysis of the bleaching effect of malachite green isothiocyanate deposited on an Au(111) crystal surface. The decay of the TERS intensities during the bleaching provided insights into the distribution of the enhanced electromagnetic field underneath the tip. From the data, they argued that the spatial resolution, in this particular context, was on the order of 25 nm, again slightly smaller than what could have been estimated from the tip apex.²⁸ A few years later, the same group developed the first ultra-high vacuum STM-based configuration and demonstrated an improved resolution of ~ 15 nm by investigating single brilliant cresyl blue molecules (an organic blue dye).^{29,30} It is noteworthy that, again, these resolution values correspond fairly well to the tip apex size, showing that the use of ultra-high vacuum or STM-based apparatus, as such, does not seem to be critical. In contrast, Stadler et al., in 2010, used an STM setup to image a flat highly ordered pyrolytic graphite (HOPG) surface and graphene, showing that the lateral resolution could be as high as 12-15 nm,^{31,32} close to the STM imaging resolution of the experimental configuration used, and in a context where the tip apex was as large as \sim 75 nm.³¹ It should be stressed here that the observation of an experimental resolution higher than expected on the basis of the tip apex has been one of the first direct experimental indications that simple models might not be sufficient to explain the lateral resolution.

1.2. Experimental strategies to overcome the lateral resolution limitations

The principle of extraordinary high resolution TERS was initially studied by the Kawata group at the end of the 2000s with the development of several experimental strategies that aimed at overcoming some of the limitations that were, for a while, believed to be inherently related to TERS. The first one was tipenhanced coherent anti-Stokes Raman scattering (TE-CARS).³³ The third order non-linearity was believed to improve simultaneously the sensitivity and lateral resolution of the techniques. Section 2.2.2 deals with the theoretical description of the entire TERS process and exposes how it is expected to influence the lateral resolution. The proof-of-concept experiment was made on poly-adenine DNA clusters, and indeed showed an improved sensitivity. In terms of lateral resolution, however, the results were less conclusive.

The same group also developed the concept of a time-gated detection scheme. As will be exposed in Section 3, most of the AFM-based TERS measurements are done in an intermittent mode (with an oscillating cantilever) to improve the lifetime of the tips and to avoid too strong interaction with the sample. However, a portion of the signal is sacrificed due to the intrinsically varying tip-to-sample distance, a factor that is exposed in Section 2 to be critical for both lateral resolution and enhancement factor. The time-gated illumination setup essentially allows separating signals detected at various tip–sample distances, and consequently

eliminates far-field artefacts and directly reveals distance effects.^{34,35} A demonstration of lateral resolution improvement has not been established yet, but in Section 3, we discuss how this type of detection scheme can help in improving it.

The Kawata group has also developed the so-called pressurized-TERS, in which an external pressure is applied on a nanoscale volume of the sample with the help of the tip apex, in order to create a local distortion. This distortion is felt only by a small number of molecules in a limited area, therefore improving the lateral resolution. The proof-of-concept experiment was made using adenine crystals and single walled carbon nanotubes (SWNTs), and led to a resolution down to the range of several nanometres.35-37 Fig. 1a illustrates a schematic representation of a TERS tip laterally mapping a SWNT by applying a force of 2.4 nN at each selected point. The lateral resolution was extracted using a step scan of 1 nm, by mapping the shift of the high frequency band of the G mode (noted here as mode B) and by evaluating the full width at half maximum (FWHM) of the TERS profile (Fig. 1b). A resolution of 4 nm was obtained by this procedure, a value much smaller than the one simultaneously extracted from the STM topographic image (Fig. 1c). It is, however, noteworthy that this method requires alteration of the samples in order to probe it, and therefore, implies modifying the spectral response of the compounds studied. Nevertheless, those results are especially significant because they can be considered as the first demonstration of high lateral resolution TERS in the nanometre range (at least well beyond the limitations of the actual tip apex size of 35 nm).

Remote excitation-TERS (RE-TERS) has been developed with a similar aim: increasing the sensitivity, eliminating far-field artefacts and, eventually, increasing the lateral resolution. The main principle is again to create a localised plasmon at the tip apex, but one that is formed by a propagating surface plasmon. By focussing a laser beam far from the apex, for instance on a grating or metallic wire, the plasmon propagates towards the tip apex and no far-field light contribution obscures the probed area. This concept was first realised with the use of a grating (written by focussed ion beam lithography) at the shaft of a metal tip.³⁸⁻⁴⁰ It was later adapted by using a single groove situated close to the tip apex,⁴¹ and by attaching a silver wire at the end of a tip apex.⁴² Although these strategies have, indeed, demonstrated their efficiency in increasing the overall sensitivity and reducing far field background contributions, the experiments often were not actually designed to prove a lateral resolution improvement. Therefore, even though none of the latter techniques are an intrinsic requirement for drastic improvement of TERS lateral resolution and haven't played a major role for reaching subnanometre resolution, it should be acknowledged that they all represent interesting perspectives for further instrumental development.

1.3. High resolution TERS of biopolymers

In the meantime, and in parallel to the development made through the study of simple systems such as carbon nanotubes, a few groups have focused their interest on the biological applications of TERS. Deckert *et al.*, in particular, have used



Fig. 1 High spatial resolution STM-TERS of a SWNT by pressurized TERS. (a) STM imaging of an isolated SWNT using 1 nm steps (represented by the white dashes) under a constant tip-applied force of 2.4 nN. (b) Peak shifts of the high frequency band of the G mode caused by the mechanical deformation of the tube (black dots) as a function of the tip position for line (i) in (A). The FWHM of the line profile is defined as the lateral resolution (4 nm). (c) Topographic profile of the SWNT showing a FWHM five times larger than that of the TERS mapping profile presented in (b). Reprinted with permission from Macmillan Publishers Ltd: [Nat. Photonics], (T.-A. Yano, P. Verma, Y. Saito, T. Ichimura and S. Kawata, *Nat. Photonics*, 2009, **3**, 473–477). Copyright (2009).³⁶

natural polymers such as DNA, RNA strands and fibrils, both for characterisation purposes and for evaluating the sequencing capabilities of the technique.

In 2008, Bailo and Deckert illustrated the potential to distinguish single bases on a RNA strand and the possibility of sequencing it, by TERS mapping of a single poly(cytosine) RNA strand.⁴³ With a conservative assumption that the signal at each point comes from a maximum of 30–60 bases

(based on the approximation of the tip apex) and that all bases were equally contributing to the signal, individual base signals could be potentially extracted from a deconvolution of the signal measured at each point.^{44,45} Based on the size of the tip apex (~ 20 nm) obtained by scanning electron microscopy, the estimated lateral resolution was ~ 10 nm. It is worth mentioning that it, nevertheless, was already considered high enough to enable sequencing of the strand. A similar conclusion was drawn by Treffer *et al.* in their study of single strands of uracil and adenine copolymers.⁴⁶

In 2012, in an attempt to investigate the limits of the lateral resolution, Deckert–Gaudig *et al.*⁴⁷ have first reported a lateral resolution between 1 and 2 nm by investigating the molecular structure of fibril surfaces immobilised on ultra-flat gold crystals (see the schematic representation of the fibrils in Fig. 2). By applying a very small step size of 0.5 nm between each point, large differences in terms of both the spectral intensities and the band positions were observed (Fig. 2, lower panel). These results evidence that different amino acids of the peptide chain



Fig. 2 Schematic representation of a TERS tip scanning an intertwined peptide chain. Representative examples of TERS spectra measured at different locations (*Y* axis) on an insulin fibril using a step size of 0.5 nm. The bands highlighted by color bars correspond to marker bands for histidine (H – pink), phenylalanine (F – green), proline (P – grey), tyrosine (Y – orange) and cysteine (C – purple). Adapted with permission from (T. Deckert-Gaudig, E. Kämmer and V. Deckert, *J. Biophotonics*, 2012, **5**, 215–219). Copyright Wiley-VCH Verlag GmbH & Co. KGaA.⁴⁷

dominate the respective signals. They thus clearly expose that the chemical composition probed by the tip differs even at a 5 Å step size, indicating a lateral resolution certainly beyond the assumed tip size. These extreme position dependent changes of the spectral features enabled the identification of specific amino acid contributions on a scale corresponding to ~1.5 nm and were interpreted as direct proof of the accessible lateral resolution.⁴⁷ It is important in this context to stress that a protein is usually considered as a complete molecular entity and thus typical Raman spectra provide averaged information on the entire structure.

At that time in 2012, those results were interpreted as originating from either an additional confinement of the electric field due to the gap-mode (i.e. where the metallic tip is situated in close proximity to an atomically flat metallic surface on which the molecules are either chemically or physically adsorbed), a tip size smaller than expected, an additional contribution to the enhancement factor caused by the so-called "chemical effect" or a combination of such effects. Nevertheless, it was the first study strongly indicating subnanometre resolution with AFM-based TERS setups and under ambient conditions. Recently, a similar experimental strategy was used in order to investigate the possibility of sequencing DNA strands composed of a defined (ACAC3AC5AC10 AC)8 sequence (where A refers to adenine and C refers to cytosine moieties), but using an even smaller step size of 0.3 nm. Again, a clear distinction from one base to the next could be shown, leading to the conclusion that the effective lateral resolution in those experimental conditions is comparable to or smaller than that of a single nucleobase.¹² The strategy described here was used from a more applied point of view later for an in-depth characterisation of the alternating hydrophobic/hydrophilic nanometre-sized domains on insulin fibrils.¹¹ Similar strategies were also used for detailed characterisation of the insulin fibril surface by quantitatively determining amino acid residue composition and protein secondary structure relations on protein systems.48 They also enabled extracting further fundamental information related to the self-assembly mechanism and the polymorph formation on such materials.⁴⁹ It should be stressed that the interpretation of those results is still subject to discussion as theoretical studies pointing in this direction are just starting to emerge. A comprehensive justification of how recent results from near-field optical and quantum chemical models support those experimental findings is provided in Section 2.

Interestingly, and as described in Section 1.1, when going through the literature different research groups present quite different statements regarding their achieved lateral resolution. Pashaee *et al.*,⁵⁰ for instance, recently investigated β2AR DNA plasmid embedded and plasmid free strands deposited onto gold nanoplates. In contrast to the above mentioned experimental demonstrations, by mapping the strands with a step size of 1 nm, they concluded a resolution of 8 nm, smaller than that dictated by the tip apex (10 nm), but still much larger than what was reported previously. In this case, the lateral resolution was estimated from mapping with a single band and by evaluating the full width at half maximum (FWHM). It should also be mentioned that the intensity of the most intense bands in the spectra was used to estimate the resolution. Those bands are not necessarily the most specific marker bands and relying on their intensity (affected *e.g.* by distance fluctuations) is less accurate than utilising well-defined structurally related band shifts. Nevertheless, Najjar *et al.*⁵¹ observed a similar behaviour in their TERS investigation of DNA strands of a λ -phage virus and evaluated their resolution as being ~8–10 nm in comparison to 28 nm evaluated from their AFM imaging from the same tip. In Section 3, we will discuss how different methodologies can lead to different interpretations (and potential artefacts) of the resolution. Those arguments can, to a certain extent, address the discrepancies raised above.

1.4. Ultimate lateral resolution: single molecule mapping

The initial studies of TERS were developed by coupling a Raman spectrometer with an AFM setup.² The concept was quickly adapted and extended to STM by Pettinger *et al.*, who were aiming at single molecule sensitivity with the help of the tunnelling mode.⁵² A few years later in 2007, Pettinger's group was also the first to implement a STM-based system with ultrahigh vacuum (UHV-TERS).³⁰ As mentioned above, TERS mapping was used to demonstrate a lateral resolution of ~15 nm, which was claimed to be sufficient for the imaging of a single BCB molecule but did not represent a net improvement of the lateral resolution.

Later, Chen *et al.*⁵³ revisited carbon nanotube mapping with an STM-TERS setup used in the gap-mode (with a gold tip and carbon nanotubes deposited on a flat gold substrate), but under ambient conditions. They achieved a 1.7 nm resolution and extracted subnanometre scale information of defect distribution, showing that ultra-high vacuum is not a requirement for nanometre lateral resolution in TERS. Recently, Liao *et al.*⁵⁴ investigated a similar system with an ultra-high vacuum STM setup at low temperatures. Here individual carbon nanotubes were deposited on silver substrates and mapped using a silver tip. Again, it was expected that the gap-mode will further confine the plasmon and, consequently, improve the resolution. By imaging the lateral cross section, they estimated an impressive spatial resolution of 0.7 nm.⁵³

In fact, and in sharp contrast to the initial demonstration of Pettinger, such UHV setups have recently led to several clear demonstrations of single molecule detection^{55,56} and direct imaging.^{10,57-59} Zhang et al.,9 in a pioneer study published in 2013, were the first to obtain structural imaging of a single molecule using a low-temperature UHV TERS setup. Fig. 3 shows the TERS mapping of a single meso-tetrakis(3,5di-tertiarybutylphenyl)porphyrin (H₂TBPP) molecule deposited on a Ag(111) surface. A clear distinction can be made between the Raman spectral features observed when the tip is situated on the lobes as compared to the center of the molecule (Fig. 3a). No signal could be detected away from the molecule, illustrating the absence of contamination of the tip and/or of the substrate in the course of the experiment. The spectral images reconstructed for extracted individual modes (associated with their respective grey zone) are shown in the upper panel of Fig. 3b, where the



Fig. 3 TERS mapping of a single H_2 TBPP molecule deposited on Ag(111). (a) Representative single-molecule TERS spectra obtained from the lobe (red) and centre (blue) of the molecule and about 1 nm away from the molecule (black). (b) The top panels show experimental TERS mapping of a single molecule for different Raman peaks (0.16 nm per pixel), processed from all individual TERS spectra acquired at each pixel (see the grey zones exposing the Raman mode associated with each spectral image). The bottom panels show the theoretical simulation of the TERS mapping. (c) Height profile of a line trace in the inset STM topograph. (d) TERS mapping of the 817 cm⁻¹ intensity for the line shown in c. Reprinted with permission from Macmillan Publishers Ltd: [Nature], (R. Zhang, Y. Zhang, Z. C. Dong, S. Jiang, C. Zhang, L. G. Chen, L. Zhang, Y. Liao, J. Aizpurua, Y. Luo, J. L. Yang and J. G. Hou, *Nature*, 2013, **498**, 82–86). Copyright (2013).⁹

high signal-to-noise ratio for most modes enabled extracting experimental results that matched fairly well with the theoretical simulation (lower panel of Fig. 3b). Fig. 3c shows the STM imaging height profile in comparison to the profile extracted from the mapping of the 817 cm^{-1} mode. The subnanometer lateral resolution determined from the spectral imaging is obvious. The same group recently carried out another experiment using the same STM-controlled TERS system and demonstrated the possibility of distinguishing two adjacent molecules with very similar structural skeletons, namely the H₂TBPP and its metal (Zn) centered homologue.⁵⁷ Section 2.2.2 exposes how non-linear optical effects are expected to further improve the confinement of the electric field and how it can be exploited in order to increase the lateral resolution. In the context of the study mentioned above, however, it has been concluded that the signal was largely dominated by the linear TERS contribution.

In a series of recent papers, the van Duyne group also emerged as a leading group for single molecule mapping with their UHV STM-TERS system.^{10,58,60} Fig. 4 shows an example of their high resolution study of H₂TBPP deposited on a Cu(111) ultra-flat surface.¹⁰ The 1502 cm⁻¹ mode was identified as a discriminating feature between two conformers, namely the bowl-down and bowl-up which switch from one to another by surface-mediation (upper panel of Fig. 4). From the point-by-point mapping of this mode and using a step size of 0.25 nm, they estimated a lateral resolution on the order of the step size (see the comparison of the middle and lower panels in Fig. 4), emphasising that TERS systems enable the investigation of structural features on a molecular scale. Ultimately, those ultra-high resolution experiments expose an interesting aspect of TERS. In STM, the feedback signal is related to the electron tunneling between the last few atoms of the tip apex and the sample.⁶¹ Therefore, if the STM and TERS signals can be directly correlated, as is the case in Fig. 4, the TERS signal may also arise from the presence of such small atomic scale features.

In summary, the results presented in this section illustrate several facts that have to be considered when discussing lateral resolution in TERS: (1) even when using similar samples such as carbon nanotubes or DNA strand samples, the claimed resolution can be extremely different, illustrating the importance of several purely experimental parameters on the lateral resolution. (2) Based on several recent results, it is physically impossible that the curvature radius of the tip apex is the major limiting factor and thus, ultra-high resolution must rely on different physical parameters. (3) Both high-vacuum STM-based



Fig. 4 High-resolution STM mapping of tetrakis(3,5-ditertiarybutylphenyl)porphyrin (H₂TBPP) on Cu(111) prior to the TERS imaging experiment. The top panel is a schematic representation of buckled up/down H₂TBPP conformers. Middle: STM line scan, bottom: TERS line scan with a step size of 0.25 nm of the integrated 1502 cm⁻¹ band (associated with the bowldown conformer) from which the lateral resolution is extracted. Adapted with permission from (N. Chiang, X. Chen, G. Goubert, D. V. Chulhai, X. Chen, E. A. Pozzi, N. Jiang, M. C. Hersam, T. Seideman, L. Jensen and R. P. Van Duyne, *Nano Lett.*, 2016, DOI: 10.1021/acs.nanolett.6b03958). Copyright (2016) American Chemical Society.¹⁰

and AFM-based setups have demonstrated strong evidence for the ultra-high subnanometre resolution capabilities of TERS. The question now is simply the following: how does one achieve subnanometre resolution and why? With this in mind, the next section discusses recent theoretical developments in this direction.

2. Theory

The spatial resolution of TERS can be influenced by many factors, including physical origins and purely experimental parameters. Details of the latter will be discussed in Section 3. In this section we mainly focus on the physical mechanisms of the TERS spatial resolution. Briefly speaking, two aspects related to the local electric field can be considered responsible for the resolution: the confinement of the local plasmonic field and the molecular response to this local field. For the plasmonic response, the local field can be analysed from classical and quantum theories, while for the molecular response both linear and non-linear processes can affect the spatial resolution and generally require quantum chemical calculations. These two aspects are discussed here in detail in Sections 2.1 and 2.2 respectively. Section 2.3 gives a critical point of view of the current remaining limitations.

2.1. Plasmonic response

2.1.1 Classical theory of the local electromagnetic field near a plasmonic tip. Surface plasmon resonance is the collective oscillation behavior of the surface electrons in metallic nanostructures, whose properties are usually determined by the types of metals they are composed of and their geometrical parameters. In classical theory, the plasmonic properties include the electromagnetic field distributions and the spectral responses of a plasmonic nanostructure. They can be calculated by various methods and most of them deal with solving Maxwell's equations analytically or numerically. For simple geometries such as spheres, ellipsoids, and cylinders, exact analytical solutions can be obtained by the use of, for example, Mie's theory⁶² or plasmonic hybridisation methods.⁶³ If the geometry of the

plasmonic structures is more complex, numerical treatments are adopted to discretise the boundaries, the spatial domains or the time domains. Numerical solutions can thus be obtained according to different numerical treatments, which can be specified by the method's names such as the finite difference time domain (FDTD) method,⁶⁴ finite element method (FEM),⁶⁵ boundary element method (BEM),⁶⁶ discrete dipole approximation (DDA)⁶⁷ or multiple multipole (MMP) method,⁶⁸ just to mention a few.

Let us first evaluate the local field intensity by assuming that the metal tip is a sphere with radius *R* (as shown in Fig. 5a). The optical response of the metal sphere can be described by its polarisability $\alpha_{\rm m} = 4\pi\epsilon_0 R^3 \frac{\varepsilon_{\rm m} - 1}{\varepsilon_{\rm m} + 2}$, where ε_0 is the permittivity of the vacuum, and $\varepsilon_{\rm m}$ is the permittivity of the metal sphere. For an incident electric field, **E**_{inc}, the local electric field at a distance **r** near the metal sphere can be obtained from the polarised dipole moment (**p**_m = $\alpha_{\rm m} \mathbf{E}_{\rm inc}$) as follows:⁶⁹

$$\mathbf{E}_{\text{loc}} = \mathbf{E}_{\text{inc}} + \frac{1}{4\pi\varepsilon_0} \frac{3(\mathbf{p}\cdot\hat{\mathbf{r}})\hat{\mathbf{r}} - \mathbf{p}}{r^3}$$

$$= \mathbf{E}_{\text{inc}} + \frac{\varepsilon_{\text{m}} - 1}{\varepsilon_{\text{m}} + 2} \left(\frac{R}{r}\right)^3 [3(\mathbf{E}_{\text{inc}}\cdot\hat{\mathbf{r}})\hat{\mathbf{r}} - \mathbf{E}_{\text{inc}}].$$
(1)

For a test point right beneath the tip apex, the local field intensity can be simplified as:

$$\frac{|\mathbf{E}_{\rm loc}|}{|\mathbf{E}_{\rm inc}|} = 1 + 2\left(\frac{R}{R+d}\right)^3 \frac{\varepsilon_{\rm m} - 1}{\varepsilon_{\rm m} + 1}.$$
 (2)

For a perfect conductor $(\varepsilon_{\rm m} \rightarrow -\infty)$, the maximum local field can be obtained for d = 0, and the local field intensity decreases dramatically, with a proportionality of $(R/r)^3$, when the tip moves far away from the test point. If the permittivity $\varepsilon_{\rm m}(\omega)$ of the metal is considered, the plasmonic resonance frequency can be obtained by imposing the condition $\varepsilon_{\rm m}(\omega) + 2 = 0$. If the tested point is laterally shifted from the center position by *x*, the parameters concerning the second term of eqn (2) changes from 2 to $\sqrt{3(R+d)^2/[(R+d)^2+x^2]+1}$. The full width at half maximum (FWHM), *w*, when the local field decreases to



Fig. 5 Schematic representations of the geometric structure and local field distribution of (a) an individual metal tip as well as its analogue as a single metal sphere and (b) metal tip-substrate structure as well as its analogue as a metal-sphere dimer.

half of its maximum value, can be defined as $w \approx 1.346(R + d)$, giving rise to an ultimate confined region of the local field that is determined by the sphere radius *R* for the closest distance d = 0. Therefore, in order to get a more confined region of the local electric field, the sphere diameter (or the curvature radius of the tip) should be very small. In other words, a very sharp tip (that could eventually imply even an atomic scale sharpness) is required to experimentally achieve high spatial resolution.

The local field enhancement and the corresponding field confinement in the metallic nanostructures can be improved by introducing a nano-gap (and the resultant gap-mode plasmon) in the tip-substrate system (as shown in Fig. 5b), which can be regarded as a dimer system composed of a metal sphere and its image.⁷⁰ This system is typical for almost all STM and many AFM based experiments where the substrate is a conductive metal. It should be noted that while this is an important case and it is extremely useful to improve the SNR, a gap is not necessarily required since high resolution has also been demonstrated with non-metallic substrates. Nevertheless, as it is generally used whenever possible, this gap-mode plasmon will be discussed in detail. In the electrostatic limit, Xu et al. proposed a simple method to estimate the local electric field in the gap of the dimer from the drop in potential for the incident field E_{inc} using a simple geometrical argument.^{71,72} For the geometries shown in the right panel of Fig. 5b, the drop in potential from one sphere to another can be expressed as $\Delta V = |E_{loc}|d$ if they are composed of perfect conductors. On the other hand, the potential drop in the absence of the spheres between the two sites would be $\Delta V = |E_{inc}|(2R + d)$. Considering the two spheres as

equipotential bodies, the local field can be related to the incident field by $\Delta V = |E_{\text{loc}}|(d = |E_{\text{inc}}|(2R + d))$, which leads to:^{71,72}

$$\frac{|E_{\rm loc}|}{|E_{\rm inc}|} \approx \frac{2R+d}{d},\tag{3}$$

from which the field enhancement can be estimated as a function of 2R/d for very small d values. Therefore, as the two spheres get closer, the local field intensity increases dramatically. According to the same reasoning, the local electric field laterally offset from the center can be described as $|E_{\rm loc}(x)| = \Delta V / (2R + d - 2\sqrt{R^2 - x^2})$. The FWHM of the local field could thus be given by:

$$w = 2\sqrt{Rd},\tag{4}$$

which is similar to the accurate calculations⁷³ predicted for the sphere-substrate structure shown in Fig. 5b. More exact simulations from analytical or numerical calculations lead to an *n*th-power $(\mathbf{E}_{loc} \sim 1/(R + d)^n)$ or an exponential dependence⁷⁴ [$\mathbf{E}_{loc} \sim \exp(kd)$] of the local electric field for the gap distance d. In this case, the local field is usually confined in a region proportional to \sqrt{Rd} for tip-substrate configurations,⁷⁵ as typically shown in Fig. 6. For large gap distances (see the field distribution of \mathbf{E}_7 in Fig. 6a–d and field intensity $|\mathbf{E}|^2$ in Fig. 6g–j), the field distribution is not influenced by the gap and only determined by the tip radius. As the gap distance decreases (see the field distribution of E_z in Fig. 6e and f and the field intensity $|\mathbf{E}|^2$ in Fig. 6k and l), the gap-mode plasmonic field becomes dramatically enhanced and highly localised within a confined region substantially below the tip radius. Therefore, both the local field enhancement and the



Fig. 6 FEM calculations of the field distribution (\mathbf{E}_z for panels (a–f) and $|\mathbf{E}|^2$ for panels g–l) around a metallic tip with different gap distances varying from 500 to 1 nm indicated below the panels. The numbers in the lower left corners of panels (g–l) indicate the multiplying factors applied to the data. Adapted with permission from (S. F. Becker, M. Esmann, K. Yoo, P. Gross, R. Vogelgesang, N. Park and C. Lienau, *ACS Photonics*, 2016, **3**, 223–232). Copyright (2016) American Chemical Society.⁷⁵

lateral confined region can be improved by decreasing the gap distance, which provides additional flexibility to control the local field in experiments, apart from the tip radius.

2.1.2 Quantum and atomistic effects on the plasmonic response. From the classical theory (either from the simple analysis mentioned above or from more precise analytical/ numerical calculations), the plasmonic field would be extremely enhanced, almost to infinity, and highly localised to an ideal mathematical point when the gap distance approaches zero, which is obviously unphysical. In order to avoid this problem, many modifications are adopted (for example using hydrodynamic^{76,77} or surface screening models⁷⁸). In fact, when the gap distance enters the subnanometre scale, the classical electromagnetic model is not suitable anymore to account for the actual localisation of the surface changes induced by the incident light. Quantum effects, including electron tunneling and nonlocal screening, become important and influence the optical response of the plasmonic nanostructures.⁷⁹⁻⁸¹ As described in the latest review article by W. Zhu et al.⁷⁹ (and as shown in Fig. 7), for gap distances larger than $10\delta_{\rm F}$ (2–5 nm), where $\delta_{\rm F}$ is the Feibelman parameter related to the surface charge positions and usually in the Ångström range,82 the classical theory can describe the optical response in a fairly satisfactory manner. However, when the gap distance becomes small enough, the non-local screening effect would spill the surface charges out of the classical boundaries, and the plasmonic response deviates from the classical predictions.^{76,83-86} If the gap distance is smaller than 1 nm, electron tunneling effects appear with the quenching of the local field enhancement and the appearance of a new charge-transfer plasmon mode.^{80,81,87} Therefore, because of the transition from the classical to the quantum regime with



Fig. 7 Schematic representation of the different regimes for the plasmon resonances of a sphere-dimer in vacuum as a function of the gap distance *d*. These regimes are illustrated by the energies of the plasmonic modes predicted by the classical (red dashed line) and quantum calculations (solid lines). See the main text for details. Reproduced with permission from (W. Zhu, R. Esteban, A. G. Borisov, J. J. Baumberg, P. Nordlander, H. J. Lezec, J. Aizpurua and K. B. Crozier, *Nat. Commun.*, 2016, **7**, 11495). Copyright 2016 Nature Publishing Group.⁷⁹

decreasing gap distances, there exists an optimal gap distance $(d_{\rm QR})$ for the field enhancement and confinement. For example, for the Au dimer, $d_{\rm QR} \approx 3$ Å,^{80,81} the plasmonic field enhancement reaches ~500 and the field confinement is improved to an ultra-small localised region described by $w_{\rm QR} \geq \sqrt{Rd_{\rm QR}}$.⁸¹

As a matter of fact, for very small gap distances (e.g., d < 1 nm), the nanostructure cannot be described by a classical smooth boundary, considering that the nearest neighbor distance for two metal atoms is usually on the Ångström scale (e.g., d_{Ag-Ag} = 2.89 Å and $d_{Au-Au} = 2.88$ Å).⁸⁸ The real atomistic structures of the nanostructures, rather than classical smooth boundaries, have to be considered to describe the optical response of such a system.^{89,90} For example, M. Barby et al. have calculated the local electric field distributions of a sodium nanocluster dimer for different gap distances based on time-dependent density functional theory (TDDFT) calculations.⁸⁹ It was found that the strongest field enhancement occurs when the gap distance is about 6 Å (Fig. 8a), with the minimum confinement of the local field below 1 nm. A further decrease in the gap distance leads to smaller field enhancement and broader field confinement owing to the emergence of quantum tunneling. Therefore, on one hand, the quantum effect provides insights into the limit of the spatial resolution; on the other hand, the consideration of the atomistic details of the tip could drive the spatial resolution down to the subnanometre scale, which may even result in the appearance of a "pico-cavity" with a mode volume of only a few nm^{3.91} It should be noted that the atomistic feature of the tip could also be described by the classical theory, in which the contributions from a protrusion or defect as small as a single atom are considered to account for the ultra-high spatial resolution.92 In fact, even the whole atomistic structure can be described classically if each atom is treated as a polarised dipole and interacts with each other.93 It is noteworthy that Fig. 8a exposes different cases of the electric field confinement and enhancement between 2 metallic structures, a case that is analogous to a typical SERS experiment.

In TERS, the closest equivalent configuration is brought by the use of the gap-mode, because it implies the close contact of two metallic structures. It was recently demonstrated, using a classical approach including atomic scale substructures on smooth particle surfaces, that the electric field enhancement and confinement is also very large in the nanogap between the apex of a TERS tip and a non-conductive glass substrate (Fig. 8b top panel).⁹² Even though the use of a non-metallic substrate does reduce the enhancement factor, these results indicate that a metal-metal gap is not a specific requirement to achieve subnanometre resolution (Fig. 8b, bottom panel). In fact, for any configuration, one has to consider whether the enhancement factor in the spatially confined region is high enough for probing the molecular response. In 2008, Etchegoin and Le Ru have stated that the minimum enhancement factor required to observe a single molecule evaluated from the $|E|^4$ -approximation should be on the order of $\sim 10^8$ for resonant molecules and $\sim 10^{11}$ for nonresonant molecules, values much smaller than the initial approximation and considered as fairly commonly encountered in real experimental situations.94 It has been shown in the



Fig. 8 (a) Local induced-field enhancement in the *yz* and *xy* planes of the Na cluster dimer for the case of a tip-to-facet configuration. The incident plane wave is polarised along the dimer axis. From top to bottom, three cases of decreasing separation distances are shown for each configuration: $d_{sep} = 20$ Å, 6 Å and 1 Å. The field is always plotted at the frequency of the most intense resonance in the absorption cross-section of the dimer. Adapted with permission from (M. Barbry, P. Koval, F. Marchesin, R. Esteban, A. Borisov, J. Aizpurua and D. Sánchez-Portal, *Nano Lett.*, 2015, **15**, 3410–3419). Copyright (2015) American Chemical Society.⁸⁹ (b) Top panel: Local field enhancement factor induced for a particle–substrate configuration of a resonantly enhanced Ag nanoparticle/glass system with a substructure protrusion size of 3 Å. Bottom panel: Axial local-field distribution normalised to the incident field amplitude $|\mathbf{E}_{ind}/\mathbf{E}_0|$ for the Ag particle/glass system described in the top panel. Results are plotted for a distance from the particle with atomic scale protrusions between 0 and 3 Å. The axial field distribution clearly shows a peak on top of a baseline background. [S. Trautmann, J. Aizpurua, I. Götz, A. Undisz, J. Dellith, H. Schneidewind, M. Rettenmayr and V. Deckert, *Nanoscale*, 2016, **9**, 391.] – Published by The Royal Society of Chemistry.⁹²

context of two independent studies that, in the absence of gapmode, the amplitude of the enhanced field is reduced by a factor of 5 to 10 (in worst case scenario).^{89,92} Following the $|E|^4$ -approximation, one can thus state a reduction of enhancement factor of $\sim 10^3$ to 10^4 . Therefore, even if considering a maximal potential enhancement factor of 10^{12} in the gap-mode, the absence of gap-mode would still lead to single molecule sensitivity, at least for resonant molecules. This is supported by experimental evidence for such high resolution and the clear dominance of a single compound in the detected signal.^{12,95}

2.2. Molecular response in an inhomogeneous plasmonic field

2.2.1 Linear optical response of a molecule. In most electromagnetic calculations, the molecule is regarded as a point dipole \mathbf{p}_{mol} and the linear optical response of the molecule is described by the polarisability (α_{mol}) as $\mathbf{p}_{mol} = \alpha_{mol} \mathbf{E}_{loc}(\mathbf{r}_{mol})$, where $\mathbf{E}_{loc}(\mathbf{r}_{mol})$ is the local electric field at the molecular position \mathbf{r}_{mol} , and is assumed to be uniform over the molecule within the point dipole approximation. For a sample composed of different types of molecules, the polarisability $\alpha_{mol}(\mathbf{r}')$ is different at different positions (\mathbf{r}') corresponding to specific species of the sample, resulting in a position-dependent response and thus to the ability to spatially resolve chemical species. When the tip scans over the sample, the confinement area of the local electric field would play a critical role in determining the spatial resolution of

the TERS mapping according to the expression describing the TERS intensity:⁶⁹

$$I_{\text{TERS}}(\mathbf{r}_{0};\mathbf{r}_{\text{tip}}) = \left| \int \vec{\mathbf{G}}(\mathbf{r}_{0},\mathbf{r}';\mathbf{r}_{\text{tip}}) \cdot \alpha_{\text{mol}}(\mathbf{r}') \mathbf{E}_{\text{loc}}(\mathbf{r}';\mathbf{r}_{\text{tip}}) \mathrm{d}^{3}\mathbf{r}' \right|^{2}$$
(5)

where $\mathbf{G}(\mathbf{r}_0, \mathbf{r}'; \mathbf{r}_{tip})$ is the Green's function correlating the electric field at the detection position \mathbf{r}_0 with a dipole located at \mathbf{r}' for a given tip position \mathbf{r}_{tip} .

However, if the size of the local electric field is comparable to the size of the molecule, the optical response of the molecule significantly differs from the point-dipole approximation described above. Under such a condition, the electric field is not uniform over the molecule and different atoms inside the molecule may experience different polarisation changes induced by the position-dependent field. The polarisability defined previously for an incident plane wave is no longer a well-defined physical quantity. Thus, the quantum theory has to be adopted to address the optical response of a single molecule to an inhomogeneous field. In a quantum chemistry approach proposed by S. Duan *et al.*,^{96–98} the inhomogeneous field can be regarded as a perturbation that influences the polarisability of the molecule, resulting in different Raman intensities at different locations of the inhomogeneous field for a given vibrational mode.96,98 The situation would also be different for resonant and non-resonant Raman scattering configurations.98



Fig. 9 (a) Calculated TERS spectra of an allylcarbinol molecule adsorbed on an Au(111) surface when the tip is located at different positions: PL for left side, PC for center and PR for right side, respectively. (b) Calculated Raman mapping images for vibrational modes v_{CC} , v_{CH} and v_{OH} , respectively. Adapted with permission from (S. Duan, G. Tian and Y. Luo, *J. Chem. Theory Comput.*, 2016, **12**, 4986–4995). Copyright (2016) American Chemical Society.⁹⁸

Fig. 9a shows an example of the calculated TERS spectra of the allylcarbinol molecule when the tip is located at different positions, and the spatial mapping images for C—C, C–H and O–H stretching modes are shown in Fig. 9b, which reveals well-confined regions corresponding to different chemical bonds.⁹⁸

In the above discussions treating inhomogeneous fields, the molecular optical response is considered to be linear, thus the spatial resolution is mainly determined by the confinement of the local plasmonic field, as described in Section 2.1. However, when the local field is dramatically enhanced and highly confined, other non-linear effects associated with the higher order response of the molecules could appear and affect the spatial resolution of the TERS mapping, which will be briefly overviewed below.

2.2.2 Non-linear optical response of a molecule. One of the typical examples of non-linear optical responses is the non-linear optical process, including two-photon excitation,⁹⁹ coherent anti-Stokes Raman scattering (CARS),¹⁰⁰ stimulated Raman scattering (SRS),¹⁰¹ *etc.* Generally speaking, the total dipole moment of a single molecule in an electric field can be expressed as

$$\mathbf{p} = \mathbf{p}_0 + \alpha \cdot \mathbf{E} + \frac{1}{2}\beta : \mathbf{E}\mathbf{E} + \frac{1}{6}\gamma \vdots \mathbf{E}\mathbf{E}\mathbf{E} + \dots,$$
(6)

where \mathbf{p}_0 is the intrinsic dipole moment of the molecule, α is the molecular polarisability tensor, β is the hyper-polarisability tensor and γ is the second-hyper-polarisability tensor. For the traditional Raman scattering process, only the linear response (*i.e.* the second term in eqn (6)) is considered, and the polarisability α is usually expanded in normal coordinates of vibrations Q_k as:

$$\alpha = \alpha_0 + \sum_k \left(\frac{\partial \alpha}{\partial Q_k}\right)_0 Q_k + \frac{1}{2} \sum_k \sum_l \left(\frac{\partial^2 \alpha}{\partial Q_k \partial Q_l}\right)_0 Q_k Q_l + \dots,$$
(7)

in which the first term corresponds to the Raleigh scattering, and the second term is related to the Raman scattering process. In conventional treatments, the higher order dependencies on the normal coordinates are usually ignored. Therefore, the spatial resolution of the Raman signals in this case is mainly determined by the resolution of the electric field E. However, if the hyper-Raman process is considered, then the non-linear dependence on the electric field E appears and affects the spatial resolution (as shown in Fig. 10a). For example, in the CARS process, as described by S. Kawata *et al.*,¹⁰⁰ two pump photons (at the frequency ω_1) and one probe photon (at the frequency ω_2) "mix" together (known as "four-wave mixing"¹⁰²) and result in a coherent radiation at the anti-Stokes frequency $\omega_3 = \omega_1 - \omega_2 + \omega_1 = 2\omega_1 - \omega_2$, as shown in the energy level diagram in Fig. 10b. The resultant polarised dipole would be $p_{\text{CARS}} \propto \gamma(Q_k) E_2 E_1^{2.101}$ The SRS process also exhibits a similar trend, with the resultant frequency at $\omega_3 = \omega_1 + \omega_2 - \omega_1 = \omega_2$ and the polarised dipole as $p_{\text{SRS}} \propto \gamma(Q_k) E_2 E_1^{-2}$.^{9,101,103} Therefore, for the non-linear optical process, the optical response of the molecule is theoretically much more sensitive to the electric field, providing an additional contribution to improve the spatial resolution.

2.2.3 Influence of the local field gradient. In fact, if the electric field is inhomogeneous, the gradient of the field also contributes to the polarisation process and we need to consider the additional quadrupole response apart from the dipole response discussed in Section 2.2.1.^{104–107} In this case, the total dipole moment can be described as:¹⁰⁸

$$p_{\rho} = p_{\rho}^{0} + \sum_{\sigma} \alpha_{\rho\sigma} E_{\sigma} + \frac{1}{3} \sum_{\sigma,\phi} A_{\rho\sigma\phi} \frac{\partial E_{\sigma}}{\partial \phi} + \dots, \qquad (8)$$

where $\alpha_{\rho\sigma}$ is the tensor element of the dipolar polarisability (ρ , σ and φ are permutations of the coordinates *x*, *y* and *z*), $A_{\rho\sigma\varphi}$ is a parameter related to the quadrupole polarisation and the ratio $|A_{\rho\sigma\varphi}|/|\alpha_{\rho\sigma}|$ is of the same order of magnitude as the ratio



Fig. 10 Spatial confinement of the excitation efficiency of the higher order non-linear effect (a), and the energy diagram of a non-linear CARS process (b). Reproduced with permission from (S. Kawata and P. Verma, *CHIMIA*, 2006, **60**, 770–776). Copyright 2006 Swiss Chemical Society.¹⁰⁰

of the polarised quadrupole moment to the polarised dipole moment.¹⁰⁸ Thus, apart from the hyper-polarisability related to the higher order optical process in eqn (6), the appearance of higher order multipoles originating from the gradient of the inhomogeneous electric field could also affect the final polarised dipoles. Similar to eqn (7), this dipole can also be expanded into the normal coordinates Q_k as:¹⁰⁶

$$p_{\rho} = p_{\rho}^{0} + \sum_{\sigma} \alpha_{\rho\sigma}^{0} E_{\sigma} + \frac{1}{3} \sum_{\sigma,\phi} A_{\rho\sigma\phi}^{0} \frac{\partial E_{\sigma}}{\partial \phi} + \sum_{k} \left[\left(\frac{\mathrm{d}p_{\rho}^{0}}{\mathrm{d}Q_{k}} \right)_{0} + \sum_{\sigma} \left(\frac{\partial \alpha_{\sigma\rho}}{\partial Q_{k}} \right)_{0} E_{\sigma} + \frac{1}{3} \sum_{\sigma,\phi} \left(\frac{\partial A_{\rho\sigma\phi}}{\partial Q_{k}} \right)_{0} \frac{\partial E_{\sigma}}{\partial \phi} \right] Q_{k} + \dots$$
(9)

The fourth term in eqn (9) is related to the vibration-dependent scattering (including infrared-active and Raman-active modes) in the inhomogeneous field. As proposed by L. Meng *et al.*,¹⁰⁷ the typical electric field distribution in the tip–substrate system and the corresponding field gradient images are shown in Fig. 11. The spatial distribution of the field gradient is usually confined in a tighter region and the resulting spectrum is much more sensitive to the infrared-active vibration modes of the molecule.¹⁰⁴ Therefore, the combination of the local electric field and its gradient could contribute to the spatial resolution and even change the Raman selection rules because of the introduction of the electric quadrupoles and magnetic dipoles.

2.2.4 Self-interaction process. Zhang *et al.* have proposed another mechanism to explain the high spatial resolution of TERS mapping, in which the self-interaction of the molecule *via* the plasmonic nanostructures is considered.¹⁰⁹ In eqn (6) and (8), the electric field **E** is usually regarded as the plasmon enhanced local field resulting from the incident electric field **E**₀, as depicted in Fig. 12a. The molecular response to this local field would produce the polarised dipole μ and the emission of this dipole would be further enhanced by the TERS configuration, as shown in Fig. 12c, where **G** is again the Green's function as in eqn (5). The processes in Fig. 12a and c are just the common plasmon enhanced Raman process. However, by considering that the molecule itself could also be polarised and emit photons at the same frequency ω as the incident light through multiple elastic



Fig. 11 Schematic representation of the spatial distributions of electric field intensity (a) and electric field gradient (b) at the plane between tip and substrate in TERS configuration. Reproduced with permission from (L. Meng, Z. Yang, J. Chen and M. Sun, *Sci. Rep.*, 2015, **5**, 9240). Copyright 2015, Nature Publishing Group.¹⁰⁷



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Fig. 12 Schematic diagram for normal spontaneous Raman enhancement and molecule self-interaction assisted Raman enhancement. See main text for details. Adapted with permission from (C. Zhang, B.-Q. Chen and Z.-Y. Li, *J. Phys. Chem. C*, 2015, **119**, 11858–11871). Copyright (2015) American Chemical Society.¹⁰⁹

scattering (white arrows in Fig. 12b, abbreviated as E.S.), the authors express the electric field acting on the molecule as:¹⁰⁹

$$\mathbf{E} = \mathbf{E}_0 + \mathbf{E}_s + \mathbf{E}_{m,s} \tag{10}$$

where E_0 is the incident electric field, E_s is the enhanced local field by the plasmonic nanostructure, and $E_{m,s}$ is the induced local field by the polarised molecule itself. The radiation process would also be modified by the multiple elastic scattering process when considering the molecular self-interaction process (as shown in Fig. 12d). The introduction of the extra self-interaction effect modulates the Raman excitation and radiation processes, leading to an improvement in the spatial resolution of TERS mapping. The induced local field can be viewed to be distributed in a much more local region because the interaction between the emitter and the plasmon would excite the so-called "pseudo-plasmon" mode,^{110,111} in which the higher order multipole modes would contribute to the improvement of the spatial resolution.

2.2.5 Vibration–plasmon coupling. In the above discussions, the molecular response is calculated with classical or quantum theory while the plasmonic field is always treated as a classical perturbation. In other words, the enhancement of the Raman responses is treated as a weak coupling. However, the interaction between the molecule and the tip may be already beyond the weak coupling regime, especially for a single molecule. From this point of view, the population of each energy level as well as the number of photons interacting with it would further affect the Raman response. In order to take into account the coupling between the molecular vibrations and the plasmon (or related photons), one possible solution is the optomechanical model proposed by P. Roelli *et al.*¹¹² and M. K. Schmidt *et al.*¹¹³ In this model, the plasmonic field is treated using the cavity quantum electrodynamics

(cavity-QED) theory, where the molecular vibration is described by a mechanical displacement. The dynamic back-action of the plasmon on the molecular vibrational modes can lead to the amplification of the Raman signals and the emergence of non-linear responses. Although this model, at its current stage, cannot directly describe the real chemical structure of a molecule and the related Raman mapping, it provides a new approach to take into account the vibration–plasmon coupling, beyond the simple amplification of the Raman signals described above.

2.2.6 Orbital overlap between the sample and the TERS probe - "chemical" effects. Besides the electromagnetic effects mentioned above, there are also chemical effects in which chemical structures of the molecule will be influenced by the existence of the tip and the substrate, leading to symmetry breakdowns.¹¹⁴ This can be understood as the formation of compounds that exists as long as there is an overlap between the respective wave functions of the tip and the sample. Consequently, a full quantum description of the whole molecule-tip model system provides additional information about such "chemical effects" on the TERS signals, especially when the distance between the tip and the molecule is very small. In this situation, the local electronic densities and even the geometric structure of a molecule might be influenced because of the interaction with the tip, resulting in changes in the TERS spectra when the tip is located at different positions within a molecule volume. According to such a scenario, F. Latorre et al. used DFT calculations to obtain a full 3-dimensional Raman map of an adenine molecule by modeling the tip either as a single silver atom or as a small silver cluster and so far neglecting all plasmon specific effects.¹¹⁵ Pronounced changes in the Raman spectra can be found, and the related intensities depend on the conformation of the tip-molecule system, particularly on the distance and lateral position. Fig. 13a shows the schematic representation of the adenine orientation and the computational grid for Raman mapping calculations. An example of an intensity mapping image for the silver-cluster tip with a tip–sample gap distance of 4 Å (still in the attractive region, so the actual minimum distance in scanning probe experiments will be even smaller) is shown in Fig. 13b. The observed variations in the Raman spectra are predominantly accounted by amplification of all C–H and N–H out-of-plane modes of the molecule. Therefore, by considering the chemical interaction between the molecule and the tip, the spatial resolution can also reach the subnanometre range. Consequently, on top of the plasmon induced resolution aspect, an additional resolution enhancement, purely based on the polarisability changes, was predicted for a model tip consisting only of a single silver atom or a small Ag cluster.

2.3. Lessons from theory - hints on future challenges

In summary, all the mentioned theoretical aspects point towards a resolution beyond the geometrical parameters of TERS tips generally used. It will be interesting to see how this field will further develop and which parameters are truly crucial. Surely, future TERS experiments can be designed to address the different aspects of the respective models and lead to a refinement and potentially a unification of the models. Most importantly, the models show that subnanometre resolution is physically feasible and can explain experimental results, an aspect that was challenged not too long ago.

Yet, there is no conclusive common vision in the field that combines the different approaches in a clear way. At this early stage, it is difficult to predict which models will prevail. If one considers that the TERS resolution originates primarily from the plasmonic response, the major mechanism is the strong confinement of the local electric field, explainable either *via* classical or quantum theory. In all cases, the development of atomistic descriptions of the tip apex structure and response to the electromagnetic field (or any model taking into account the



Fig. 13 (a) Schematic representation of the adenine orientation and the computational grid for Raman mapping calculation. An Ag₂₀ cluster is scanned with a step size of 0.5 Å over the fixed adenine molecule. (b) Simulated signal amplification of the entire Raman spectrum along the grid at a gap distance of 4 Å for the silver-cluster tip. [F. Latorre, S. Kupfer, T. Bocklitz, D. Kinzel, S. Trautmann, S. Gräfe and V. Deckert, *Nanoscale*, 2016, **8**, 10229–10239.] – Published by The Royal Society of Chemistry.¹¹⁵

atomic-scale surface roughness) rather than the initial classical models involving smooth structures appears more realistic and in line with the experimental observation of resolution.

However, if the TERS resolution mainly originates from the molecular response, the mechanism varies from the non-linear effect to orbital overlapping, and is likely to vary for different types of molecules. Under most circumstances the strong spatial confinement of the local plasmonic field is believed to be the dominant mechanism to explain the TERS resolution. In this situation, the molecular response is regarded as linear. Anyhow, if the molecule has special responses to (1) the strong field intensity (non-linear optical process), (2) the field gradient, (3) the higher order plasmonic mode (self-interaction process), (4) strong vibration-plasmon coupling, or even (5) the orbital overlap between the molecule and tip states (chemical effect), the situation differs significantly and the TERS resolution is influenced accordingly. In most cases, one can argue that a juxtaposition of all 5 factors exists, of course, depending on the experimental configurations and molecules under investigation. From this perspective, the major challenge will be to develop experimental designs that allow a deconvolution of the distinct parameters.

It is worth emphasizing that most of the models presented in this section were not developed specifically for TERS and, as such, often do not consider its specific characteristics. Most of the discussions raised above treat the general cases of two metallic structures of different sizes and shapes approaching each other and their respective response to the electromagnetic field (and/or of the molecule response in the context). As a consequence, several aspects typically applicable to TERS still remain unclear, especially the impact of the tip morphology on the resolution. This includes aspects such as the relative lateral resolution expected from tips formed via different procedures like chemical etching or covering tip templates by rough or smooth gold or silver layers, respectively. Consequently, the corresponding geometric parameters including the size of the islands, the thickness of the metal layer, the additional coating or refractive index modifications must play a role. As mentioned in Section 1, initially the improvement of TERS lateral resolution was believed to be closely related to the ability to produce tips with a smaller apex. Now that this statement is no longer valid, the optimisation of tip production methodologies most likely is going to move in a different direction. This includes the investigation of the plasmon resonance of those tips and of course the spatial confinement, an aspect closely related to resolution optimisation. Several experimental methodologies such as dark-field microscopic imaging with far-field excitation,^{116,117} evanescent-wave excitation¹¹⁸ and electron energy loss spectroscopy (EELS) combined with scanning transmission electron microscopy (STEM)⁴¹ have been used for such applications. To date, however, none of these techniques have been capable of providing real atomic scale spatial evaluation of the phenomenon. A best-case scenario will eventually allow the evaluation of the theoretical models considering the detailed tip morphology as well as experimental results like plasmon resonance and spatial distribution. This in turn will then lead

to a deterministic tip design for high resolution and high sensitivity investigations.

3. What influences the lateral resolution experimentally and how can we control it?

Considering the literature related to high resolution TERS in Section 1 several questions arise: (1) why was the field convinced for so long that the resolution was limited by the tip apex only and (2) what experimental factors justify such a discrepancy for resolution evaluation when working on systems such as carbon nanotubes or DNA strands? Section 2 shows that, among other factors, the tip-to-sample distance is a critical factor and that an atomistic view of the tip apex can explain the extreme lateral resolution reported by several groups in the past years. This section targets the purely experimental factors that can affect resolution, highlights some of the main current experimental challenges, provides guidelines and perspectives on how to achieve high resolution TERS and, last but not least, how to evaluate the experiments. It first covers AFM-TERS and then specifically treats STM-TERS and ultra-high vacuum systems.

3.1. How to evaluate the lateral resolution?

As exposed in Section 1, different research groups use different approaches to define lateral resolution and/or use different experimental methodologies for its evaluation. The most widely used convention so far for resolution assessment was defined in 2005 by Pettinger as being half of the radius of the tip apex,²⁸ a definition that had the advantage of being particularly clear and that led to a straightforward evaluation of the limitations. Considering the theoretical developments discussed in the previous section, sensitivity and lateral resolution estimations based solely on the tip size not only lead to an underestimation of the lateral resolution, but also to an underestimation of the enhancement factor (due to the overestimation of the number of molecules contributing to the signal). Consequently, any attempt to perform quantitative experiments based on the tip diameter can only be considered as an approximation, at best. On the other hand, if, for instance, atomic scale protrusions need to be considered, the evaluation of the optimal lateral resolution based strictly on tip imaging (for instance by SEM) becomes a significant challenge. Thus, the most reliable method to draw accurate conclusions is the direct experimental evaluation of the resolution through TERS spectral imaging or point by point mapping.

As exposed in Section 1, two experimental methods for quantitatively extracting the lateral resolution are generally used, and can be summarised as follows: (1) most groups laterally scan a sample or the edge of a sample, deposited on a flat metallic surface, and extract the resolution from the width (or more specifically FWHM) of the spectral intensity of a given mode (used as a marker band) as a function of the position. (2) It has been proposed that the resolution could be evaluated by reducing the steps between two probed points as much as

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possible and by analysing at which scale spectral heterogeneities clearly lead to the conclusion of a different chemical composition under the tip. The main consequence of the purely experimental demonstration of high resolution is that it often implies measuring the "apparent" resolution because it is subject to experimental errors and artefacts caused by the imaging methodology used. It is worth mentioning that most of the aspects discussed here were already discussed in a very similar context two decades ago in an important article by Hecht *et al.*,¹¹⁹ when the resolution aspects became important in near-field optics. Interestingly, this time the discussion seems to be the "other way around".

3.2. Edge effects

Fig. 14 shows a schematic representation of a TERS tip covered by silver particles and laterally mapping a sample such as a carbon nanotube in order to evaluate lateral resolution. The panel on the right illustrates a closer zoom of the particle at the tip apex which is surrounded by atomic scale protrusions. In a perfect scenario (and based on the hypothesis that the enhancement factor is much stronger for a close tip-to-sample contact, at each point of the mapping) the signal is dominated only by the electric field enhancement arising from the protrusion at the very end of the particle in the tip-to-sample axis, with a small contribution from the ones that are just beside. In reality, when laterally mapping a sample, protrusions from the right side of the particles are first in contact with the sample and lead to the appearance of a TERS signal. It is expected that this signal is lower than its maximum value because the protrusion-to-sample axis is not optimal. However, this effect contributes to the broadening of the mapped signal as a function of the position and thus leads an overestimation of the FWHM used for resolution quantification. The measured resolution can thus become truly limited by the nanometre scale size of the tip apex (or the size of the particle at the tip apex) and is therefore determined by the imaging methodology rather than the protrusion size. This effect can also be extended and amplified by the analysis of a sample showing a nanometre scale roughness and/or absorbed on a nanometre scale rough substrate: those imperfections can act as edges that interact with the protrusion surrounding the tip apex in a way that is similar to what has been described above. In addition, one of the well-known artefacts in the field of near-field optics is the increase of the scattering due to the presence of edges.¹¹⁹ Therefore, resolution studies using solely the lateral mapping of band intensities as a function of the tip position can lead to misinterpretations. From this point of view, it is clear that carbon nanotubes are not ideal candidates for ultra-high resolution investigations due to their intrinsic height. In a perfect scenario, only samples of atomic scale roughness should be used for such applications. Another interesting option, in contexts where this criterion cannot be met, is to avoid lateral mapping and rather investigate the longitudinal chemical heterogeneity, as long as the sample does not present nanometre scale roughness along this axis.



Fig. 14 Scheme of a typical TERS experiment with a silver coated AFM tip laterally scanning a sample. The right panel shows a zoom to the tip apex with atomic scale protrusions surrounding the metallic particles. When mapping the carbon nanotube laterally, protrusion from the right side of the particles interacts with the sample while the one directly situated in the tip-to-sample axis is still far away.

Besides the edge effect itself, roughness from the substrate can critically lower the resolution, especially when TERS experiments are conducted in the gap-mode, *i.e.* when the sample is adsorbed or chemically bonded to an ultra-thin flat metallic surface such as gold or silver nanoplates. For such surfaces, any nanometre or even subnanometre roughness is likely to produce local "hot spots" in the macroscopic region irradiated by the incident beam. It was shown that the presence of 2 nm edges generates an undesired contribution to the signal in the form of a SERS contribution that increases the signal by as much as an order of magnitude, while 1 nm larger protrusions were not interfering significantly with the TERS signal.¹²⁰ Those contributions, which can be considered as a "far-field background" (because this signal does not arise from the hotspot under the tip), are more likely encountered when working with ultra-thin films prepared by vacuum deposition methods. Measuring the far field Raman spectra with the tip retracted should give an indication of the absence of such contributions.

3.3. Incident beam polarisation

From a purely theoretical point of view, the polarisation of the incident beam only plays an indirect role in the accessible resolution. In a typical experiment, in order to optimise the enhancement of the electric field, one must optimise the amplitude of the incident beam with a polarisation along the tip-to-sample axis (*z*-axis, see the reference axis in Fig. 13). In close proximity to the edge effect described in the previous section, the confinement of the electric field at the very end of the tip apex and the capacity to excite a Raman mode that is not in this axis rely partially on the quality of the incident polarisation. However, this also relies on the geometry of the setup used. Here, we give a brief overview of the most common cases, discuss possible consequences on high resolution experiments and propose strategies to control it. For a detailed description of

the possible setup geometries, interested readers are referred to the general TERS review of this issue.

Let us first consider the case of bottom illumination (*i.e.* with the excitation and signal collection through an objective situated under the sample) in combination to linearly polarised light (x or y-incident polarisation). In a perfect scenario, light should reach the sample with its polarisation parallel to the propagation direction to create a localised plasmon that is strongly interacting in the tip-to-sample axis. Experimentally, Fig. 15a shows that when using a low numerical aperture objective, light preserves its original polarisation and therefore, only x-polarised plasmons are generated at the tip apex. The most popular (and simplest) approach is to solve this issue through the use of large numerical aperture objectives. Linearly polarised light passing through such objectives is partially tilted in the tip-tosample axis (from x to z), although an important fraction of the incident field remains in the initial x- (or y-) polarisation due to geometrical factors and physical limitations upon increasing the numerical aperture to an infinite extent.^{121,122} The relative importance of the z vs. x (or y) component can be quantified with the knowledge of the numerical aperture.^{121,122} When reaching the sample surface, a spatial distribution of the electric field polarisation is formed, as schematised in Fig. 15b. In a typical TERS experiment, one scans this micron scale "heterogeneous polarisation" region with the tip in order to find the specific nanoscale region where the Raman signal is the most intense. Since the purely x-polarised region is detrimental to the tip-to-sample interaction, the signal is, in general, higher closer to the side bands, which are z-polarised. However, given the low amplitude of the side bands, it is likely that the spatial region that gave rise to

the higher signal is an intermediate one, *i.e.* in the region where a mixture of x- and z-polarisation exists. Therefore, the tip apex can (and does) interact with the sample in both the z and x directions, causing the situation described in the previous section regarding the edge effects (and applicable for any substrate or sample roughness), thus significantly reducing the measured resolution. This general conclusion can be extended for side illumination setups (i.e. with incident and collected beams situated at right angle with respect to the tip-to-sample axis). Fig. 15c illustrates the typical case of an initially purely z-polarised beam that is tilted by the use of a parabolic mirror with the direct consequence of inducing an x component of the electric field. The higher the tilt angle of the beam with respect to the substrate axis, the higher the x-polarisation contribution.^{30,123} In this geometry, the effect of high numerical apertures to focus tightly on the sample surface is the same as previously described: it tilts the polarisation in the propagation direction. Therefore, here, it decreases the z-polarised amplitude and increases its component perpendicular to it (x or y), which is the exact opposite of what is generally desired.

For bottom illumination, an elegant way to circumvent the polarisation issue is the use of radially polarised incident beams, which enable cancelling any component of the electric field in the *xy* plane of the sample once the surface is reached.¹²⁴ The spatial distribution, as represented in Fig. 15d, presents an amplitude heterogeneous distribution, but a homogeneous and close to perfect *z*-polarisation.^{125,126} Besides the direct effect on the lateral resolution, it has recently been demonstrated that the signal enhancement increases by the use of radial polarisation.¹²⁷ A detailed description of the formation of radially polarised light is beyond the scope of this review. Interested readers are referred to



Fig. 15 Schematic qualitative representations of polarisation at the surface of the sample for different TERS setup geometries. (a) Light propagating in the *z* direction (tip-to-sample axis) from below. The incident beam is *x*-polarised and focused by a low numerical aperture objective. The black arrows represent the polarisation of the field of the incoming beam and at the sample surface. The blue arrows represent the induced polarisation of the plasmon on the metallic particles covering the tip. (b) Bottom illumination with high numerical aperture. A spatially dependent distribution of *x*- and *z*-polarisation is generated at the sample surface. (c) Side-illumination where the incident beam polarisation is partially tilted and the induced polarisation of the plasmons at the tip is a mixture of *x* and *z*. (d) Bottom illumination using radially polarised light that yields exclusively a *z*-polarisation at the surface of the sample.

the theoretical and experimental description of the spatial field distribution described in ref. 125.

For the general case of linearly polarised light illumination, the residual polarisation in the plane of the sample axis has two major consequences on high resolution experiments. One of them can be understood in correlation with the edge effect mentioned above, where the probability of exciting the sample from the side is increased by the excitation of the plasmon perpendicular to the tip axis. The other is that, even for perfectly flat surfaces, the imperfect polarisation lowers the enhancement factor and thus, the sensibility of the technique, which can possibly be detrimental to the signal detection arising from an atomic scale surface of the sample of interest.

When considering solely polarisation and signal collection efficiency arguments, one could argue that bottom illumination setups are ideally suited for high resolution experiments. However, it is worth emphasising that for practical reasons, side illumination schemes are very common and have also proved their capability of high resolution TERS, particularly for opaque samples. Specifically, the fact that a side illumination TERS setup demonstrated single molecule mapping speaks for itself. Nevertheless, there is always potential for improvement and it is definitely worthwhile considering illumination aspects before starting a TERS experiment.

3.4. AFM feedback modes

Fig. 6 of Section 2 has clearly exposed that both the sensitivity and lateral resolution of any TERS experiment dramatically relies on the tip/sample distance, for a given experimental context. Most importantly, the resolution is directly influenced by the field distribution at the tip apex and consequently by the tip-to-sample distance. Therefore, it is expected that the imaging mode (i.e. AFM feed-back mode) used during the spectral acquisition strongly influences both the strength of the signal for a given acquisition time and the overall determined resolution. A detailed description of the different possible imaging modes in AFM-TERS and STM-TERS is beyond the scope of this review and they are summarised in another article in this special issue. Here, we only intent to comment on their impact on the lateral resolution. In AFM-TERS, contact and intermittent contact modes are generally used for imaging/ or mapping of single points along a line or a grid. The intermittent mode implies that the tip-to-sample distance is oscillating at a constant frequency, generating an oscillating gradient of enhancing factors as a function of time. Hence, large oscillation amplitudes refer to a shorter time frame for the tip apex to be close to the sample and thus, lower the signal for a given acquisition time. Small oscillation amplitudes (<10 nm), in particular in air, tend to lead to an unstable feedback. Therefore, one has to find a suitable compromise between high enhancement/resolution and experimental practicalities. Having this in mind, a contact mode should be more advantageous because it intrinsically enables a constant tip-tosample distance that should help at (1) the uniformity of the Raman enhancement factor and (2) a constant spatial confinement area/volume of the electric field as a function of time.

It is therefore expected that it leads to a much stronger signal for a given acquisition time. This feedback was successfully applied; however, this mode has its disadvantages when it comes to tip and sample damage. In particular, if the subnanometre scale features mentioned in Section 2 are responsible for the field confinement, such features can easily be destroyed by the use of contact mode due to friction, excessive forces or roughness. One must also consider the increasing risk of tip contamination when using contact mode, which induces artefacts that are even more detrimental in TERS as compared to AFM imaging. Indeed, here the contamination is directly bonded and thus in "contact" with the tip apex, i.e. where the enhancement factor is the largest. With this in mind, the time-gated detection scheme proposed by the Kawata group^{34,35} (see Section 1.2) appears as an interesting future avenue because it allows working in intermittent contact mode while collecting the signal only at the same tip-to-sample distance. From this point of view, TERS could benefit from lessons from IR-s-SNOM that uses similar approaches,¹²⁸ although the overall detection scheme in TERS remains more straightforward.

3.5. Thermal drift and step sizes

One of the most annoying factors that contribute to lowering the resolution in ambient AFM-TERS experiments is also one of the most difficult to avoid: namely the thermal drift. For instance, our AFM system generally operates under ambient conditions and shows a thermal drift of $\sim 30 \text{ nm h}^{-1}$, which is not too bad.^{12,53} However, it means that even for a typical 5 min full imaging experiment, the drift can be already as big as 5 nm. It quickly becomes the limiting factor, even if theoretically a 0.5 nm resolution is possible. Thermal drift is unavoidable under most conditions, but from this example, it is clear that high resolution TERS measurements particularly rely on the improvement (and/or the development) of the technical aspects of the apparatus.^{129,130}

The problem of the thermal drift for resolution purposes is intrinsically coupled with two other factors, namely, the enhancement factor (the technical sensitivity in a given experimental context) and the sampling step size. First, the sampling step must be chosen in order to extract the best possible resolution without under-sampling. It is our belief that the use of too large step sizes has, for a while, prevented us from understanding the lateral resolution correctly. In a given experimental context, one has to select the acquisition time for each spectrum, based on the minimal time necessary to obtain a satisfactory signal-to-noise ratio. Obviously, shorter acquisition times lead to a lower signal-to-noise ratio, but can avoid drift related problems. Finally, the overall time required for an experiment is related to the sample size. Let us consider a hypothetical TERS investigation of the sequence of a DNA strand composed of 100 bases. If the acquisition time necessary to reach a satisfying signal to noise ratio is 1000 ms, a standard value in most Raman experiments, and the required step size is 0.5 nm (dictated by the size of a unit), a minimum of 100 spectra will be measured in ~ 100 s. Thus, by the end of the strand, a localisation uncertainty of 0.5-1 nm must be expected, which refers to a mismatch size of 1–2 bases. In this case, information obtained from every measurement will allow for correcting some of the effects, but the general problem still remains.

For most experiments in TERS, ultimate high resolution is not necessarily desired, but it, nevertheless, affects the analysis. For any experiment, one must consider the scale of the chemical heterogeneity as compared to the resolution of the technique. In the context of the characterisation of micron scale samples, a proper comprehension of the resolution thus is also critical because it enables choosing the sampling steps wisely and thus, avoiding under-sampling that can lead to misinterpretation and reproducibility issues. If a heterogeneous sample is mapped for identification purposes using sampling steps bigger than the small feature size, it is likely that the average spectra extracted will lack reproducibility from one experiment to the other. However, for a full coverage of all data points, the experiment time becomes prohibitively long and the thermal drift quickly becomes the limiting factor. One could argue that the enhancement factor is the limiting factor, because, as mentioned above, the experiment time is also defined by the sensitivity of the techniques. This conclusion is very general and applies to all TERS experiments. Regarding ultra-high resolution investigations, in particular regarding experiments conducted under ambient conditions, the ideal sampling step should be small, as the information on structural or chemical heterogeneities might otherwise be lost and might lead to misinterpretations.

3.6. Near-field heating and molecular movements

Another aspect that is rarely raised is the possible modification of the sample or tip morphology during the experiment due to heat effects arising from the near-field. According to Zhang et al., the Joule effect in the nanogap between the tip apex and a metallic substrate could locally increase the temperature by tens of Kelvins, therefore inducing morphology changes of the substrate.¹³¹ The demonstration was made by comparing the AFM images of a gold substrate morphology before and after a typical TERS experiment, and significant morphological changes were observed. The absence of any changes when using only laser illumination for the same amount of time (with a retracted tip) led to the conclusion of a significant near-field heating effect on the substrate. This conclusion is important for two aspects in TERS. First, if the metallic substrate can be annealed during the course of a routine experiment, the same can happen for the tip apex. This could cause, for instance, small changes of atomic organisation during the measurement that could lead to a dynamic formation and destruction of atomic scale protrusions that eventually create fluctuations in the measured enhancement or, at the extreme, contribute to the tip apex destruction. Recently, Benz et al. reported the improved stability of picocavities in the gap-mode, when working at cryogenic temperatures as compared to room temperature,⁹¹ therefore reinforcing the conclusion that small morphological changes may arise at the tip apex during routine TERS experiments. Furthermore, local near-field heating can amplify local molecule movements such as orientational changes,

conformation changes or lateral diffusion that complicate signal interpretation and lead to misinterpretation of the lateral resolution. Consequently, for high resolution experiments under ambient conditions, rigid samples adsorbed at multiple locations on the substrate are preferred. Under low temperature conditions, where most temperature effects can be avoided, this does not apply. In any case, it is a good idea to keep an eye on temperature induced effects and, in doubt, to investigate power dependencies and/or consider different temperature experiments.

3.7. Advantages of STM-TERS and low-temperature ultra-high-vacuum conditions

As overviewed above, the lateral resolution of a TERS experiment is mainly affected by two important factors: tip quality and system stability. In this regard, the STM-TERS setups, 29,52,53 particularly those operating under low temperature and ultrahigh vacuum conditions,^{9,60} appear advantageous in terms of the control of these two factors when compared with the ambient AFM-TERS. As addressed in Sections 2 and 3.2, the signal intensity and spatial resolution of a TERS-active tip are associated with the morphology of the tip apex or even the atomic scale protrusion at the tip apex. In STM-TERS, the structure of the tip apex or the atomic scale protrusion can be modified in situ by applying voltage pulses or by tip indentation (namely, crashing to the metal substrate).^{9,57,132,133} The tip status or the plasmonic resonance mode can be monitored by STM induced luminescence^{9,57,70,132–134} or photon scattering signals from the tunnel junction. The combination of such tip modification and mode monitoring allows tuning the spectral matching of the local plasmon resonance with the incident laser and/or molecular optical transitions so that favorable tip conditions can be achieved for TERS experiments. Such active modification of the tip status is hard to fulfill in ambient AFM-TERS.

Furthermore, in STM-TERS, the substrate is necessarily conductive and the gap-mode plasmon between the metal tip and the metal substrate can always be exploited to enhance the Raman signals. As described in Section 2.1, the introduction of the gap-mode plasmon can dramatically improve the spatial confinement and the local field enhancement through additional control of the gap distance (beyond the control of tip radius alone). In contrast to the intermittent mode in AFM-TERS where the gap distance oscillates, the gap distance in STM-TERS can be precisely controlled through the tunneling current of the STM feedback loop with stability down to sub-Ångström levels. This impressive accuracy is achieved by means of highly sensitive exponential dependency of the tunneling current on the gap distance in STM. As an advantageous side effect, the fluorescence background that limits conventional Raman studies is, for most molecules, no longer a serious issue when using a gap-mode scheme since the fluorescence signal is usually strongly quenched when molecules are adsorbed directly on metallic substrates.

The junction stability of the TERS systems based on STM or AFM can be further improved by using ultra-high-vacuum and low-temperature conditions. As opposed to ambient conditions, low temperature can significantly suppress the thermal drift of the system (see Section 3.5) as well as the diffusion and desorption of molecules on surfaces (see Section 3.6), facilitating the detection of a single molecule. The ultra-high-vacuum condition can dramatically improve the contamination issue both for the tip and for the sample. It is also helpful for the preparation of clean substrate surfaces and molecular samples with controlled coverage. In particular, under ultra-high vacuum conditions, air-sensitive materials such as silver (Ag) can be used more efficiently as tips or substrates to generate strong plasmonic enhancements, because of their improved lifetime in those conditions.²² Furthermore, the photobleaching problem can also be suppressed. Thanks to the improved system stability and tip quality in low-temperature ultra-high-vacuum STM, TERS measurements can also be carried out with smaller step sizes, allowing exploration of a resolution down to the subnanometre scale. Finally, high-resolution STM topographic imaging can provide a convenient way to monitor and control the adsorption configurations of molecules on surfaces, which can also facilitate the analysis of the TERS measurements. Ultra-high-vacuum lowtemperature systems imply technical challenges that are worth mentioning, but thanks to the factors mentioned here, they have brought the most impressive results in terms of resolution so far.

Conclusion and outlook

In this review, we specifically covered high resolution TERS. In recent years, this field has evolved impressively, both from an experimental and a technical point of view and by an increasingly detailed and accurate theoretical description of the parameters related to such experimentally achieved resolutions. Section 1 has exposed how, within two decades of TERS development, the resolution has improved by 1 to 2 orders of magnitude. Surprisingly, the experimental methodologies are still similar and the physical parameters behind high resolution are thus identical. Interestingly, the increasing evidence for experimentally achieved ultra-high lateral resolution have finally required the development of novel theoretical description approaches, as simple models were insufficient. The recent development of ultra-high-vacuum and low-temperature STM-based TERS systems has propelled the field towards the ultimate "resolution" dream experiment: chemically mapping single molecules and spectroscopically reaching the resolution of an STM. So far, such systems have been confined to STM-TERS, but can just as well be applied to AFM-based experiments with minimal modifications. Interestingly, AFM-based TERS conducted under ambient conditions reaches almost the same resolution and allows discriminating chemical compounds on the subnanometre scale. This observation is critical for the field because it suggests a democratisation of high resolution experiments by making it accessible to most robust SPM-TERS instruments when used in the right configurations.

From a theoretical point of view, and as covered in Section 2, two intrinsically related phenomena are important: the confinement of the local plasmon and the respective molecular response, when the electric field is so confined that its area/volume is comparable to the investigated molecule. The atomistic descriptions of metallic particles in close contact with a sample and the investigation of quantum effects provide insights into how the spatial resolution can reach values down to the subnanometre scale. Atomic scale protrusions or even the appearance of "picocavities" when two metallic objects are brought into close contact have been identified as the driving factors. These conclusions can be directly applied for TERS; namely when the experiment is conducted in the gap-mode to reproduce the close interaction of metallic structures. It is important to emphasise here that any enhancement of the Raman signal (resonance Raman effect, non-linear effects, gap-mode, etc.) is welcomed due to a better signal-to-noise ratio which also makes experiments easier. However, the basic principle also works without such mechanisms. In particular recent theoretical and experimental investigations highlighted that the gap-mode is not a critical criterion for reaching high resolution. Therefore access to subnanometre lateral resolution is possible for compounds that cannot be deposited on metal substrates, or are simply too thick for STM or for a gap-mode to be effective. Chemical effects and non-linear response of the molecule in the electric field can also contribute to the optimisation of spatial resolution. It simultaneously opens a new door to experimentally investigate the response of the molecule to an inhomogeneous electric and magnetic field.

As most of the high-resolution experiments and theoretical arguments are still very recent, it is not surprising that the matter is still under discussion. Reproducibility is still an issue; different groups investigating fairly similar samples are coming to different conclusions. Our general comprehension is that the problem is based, at least partially, on the definition of resolution and the experimental strategies adopted to study it. Section 3 discussed edge effects (including nanoscale topographic heterogeneities) and how they can lead to underestimation and misinterpretation of resolution. It also provides guidelines for optimising resolution experiments and avoiding misinterpretations. Currently, the main limitations are purely technical and can be reduced to (1) the unavoidable thermal drift and (2) the ability to control an ultra-close and stable tip-to-sample distance while avoiding alteration of the sample or the tip. The current state can be summarised as follows: molecular level resolution has been experimentally achieved and theoretical models are supporting the experimental results. Now, the challenge will be to transform those initial experiments into routine and accessible applications. It is our belief that the instrumental improvements in the years to come will eventually enable fulfilling this goal.

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