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Optical fiber SERS sensors: Unveiling advances, challenges, and applications in a miniaturized technology

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Abstract: In both the scientific and technological fields, there is a fundamental need for highly sensitive and specific detection of chemical traces or biological targets at the single molecule level. To achieve this, sensor technology based on surface-enhanced Raman scattering (SERS) is a promising approach due to its extremely narrow linewidth, high sensitivity and signal-to-noise ratio, target specificity and ability for non-destructive and multiplexed monitoring of chemical or biological species. Raman scattering is a phenomenon that occurs due to the interaction between photons and molecules depending on the kinetic modes of the analytes, providing unique fingerprints that enable real-time detection of chemical or biological species. By monitoring molecular activity in the vicinity of nanostructured surfaces, SERS-based sensors not only provide valuable insight into molecular interaction or binding, but also serve as a reference for the further development of powerful and optimized detection methods. While the existing reviews on SERS devices mainly focus on classical planar or chip-based substrates, a detailed review covering various strategies for highly sensitive SERS sensors based on optical fibers, nanostructuring of the fiber surface, their working mechanisms and practical applications is still pending. Only recent advances in nanotechnology and related equipment have made it possible to effectively and reliably use optical fibers as SERS substrates. Our aim is therefore to report on the current status of SERS fiber technologies, their detection mechanisms, the different fiber geometries used so far to develop miniaturized lab-on-fiber devices, and the extensive range of applications associated with these advances by highlighting the advantages, limitations and future perspectives in this field.

Keywords: Surface enhanced Raman scattering (SERS), nanomaterials, surface nanostructuring, fiber optics, and plasmonics.

1. Introduction

Raman spectroscopy is a powerful analytical tool with the ability to provide useful information about the molecular vibrations and structural characteristics of a sample, all without the need for extensive sample preparation and manipulation. It has garnered significant attention due to its unique ability to offer a distinctive "fingerprint" of molecular structures [1]. However, the Raman spectroscopy potential is somewhat hidden by the modest Raman scattering cross-section and the presence of stronger fluorescence or chemiluminescence signals, which often overshadow the Raman signal. Nevertheless, since its discovery in 1974

and subsequent confirmation in 1977, SERS has widely been employed to greatly amplify the Raman scattering signal emitted by molecules that are adsorbed on or near metallic nanostructures, such as gold (Au), silver (Ag), and copper (Cu) [2,3]. Surface enhanced Raman scattering (SERS) takes Raman spectroscopy a step forward by exploiting metallic nanoparticles or nanostructures that enable to unveil the Raman signals [4,5]. When a molecule undergoes adsorption on the surface of a metallic nanoparticle, the incident laser light prompts the surface electrons of the nanoparticle to oscillate, producing a localized electric field due to light-matter interactions. This localized effect dramatically enhances the intensity of Raman signals of the adsorbed molecule. SERS offers a valuable capability in the identification and quantification of minuscule amounts of chemicals and biomolecules, as well as for investigating molecular interactions and dynamics at the nanoscale level [6].

This technique has undergone significant advances in the development of new substrates, characterization methods, and theoretical models. In terms of substrates, researchers have developed a wide range of materials that exhibit strong SERS signals. The most commonly used substrates are based on metal nanoparticles, such as Ag and Au, which are functionalized with organic molecules to enhance their SERS activity. Other materials used for SERS substrates include carbon nanotubes, graphene, and metal-organic frameworks [7–10]. A wide range of SERS-active substrates have been utilized, encompassing Ag films, electrochemically roughened electrodes, produced through acid-etched Ag foils, sputtering or evaporation as well as colloidal metal nanoparticles [11]. In terms of characterization methods, researchers have developed new techniques for imaging and analyzing SERS signals. Tip-enhanced Raman spectroscopy (TERS) can be considered as one of the examples of such advanced techniques that enable the study of single molecules and surfaces with sub nanometer resolution [12]. To augment the sensitivity and spatial resolution of SERS, additional techniques such as confocal Raman microscopy and surface plasmon resonance (SPR) imaging have been developed [13]. Theoretical modeling and computational methods have been devised to simulate spectra of SERS and better understand the underlying physical, chemical and biological behaviors involving SERS. These models have aided in explaining the enhancement mechanism of SERS and designing new substrates with improved sensitivity and selectivity. Nowadays SERS is becoming increasingly important, in areas such as monitoring the environment analyzing pharmaceuticals ensuring food safety and imaging, for purposes [14,15].

However, the growing range of users on Raman spectroscopy has also brought attention to its drawbacks, which mainly stem from the limited signal strength of Raman platforms. Other constraints include difficulties of working in label-free mode with biological samples and with tiny volumes, of entirely removing the fluorescence signal or other interfering signals, and of developing remote sensing platforms operating in real time. Another significant limitation of mostly SERS sensors is associated with their rigid and bulky design, which can hinder their deployment in complex or hard-to-reach environments. The lack of flexibility and compactness in conventional SERS setups dramatically limits their domain of applications where *in-situ* and real-time monitoring is required. Additionally, traditional SERS sensors may face challenges in optimizing the delivery and collection of light, impacting sensitivity, signal stability and signal-to-noise ratio (SNR). All these limitations underscore the need for more innovative and adaptable sensing solutions using a different SERS substrate.

In this scenario, the advent of optical fibers as novel SERS substrate is providing new chances to get around the existing problems. Optical fibers possess unique features in guiding, managing and collecting light that the other sensing platforms can hardly attain [8]. Those also enable to keep costs within a reasonable threshold. In order to efficiently stimulate and collect Raman scattering while obstructing unwanted photons, optical fibers have the direct capability of filtering and focusing light via embedded lenses needed at the distal end of the fibers [16]. In addition, a considerable amplification of the Raman signal is feasible and effective when using specialty optical fibers, such as hollow core fibers, since light can be confined into tiny regions of the fiber, leading to intense light-matter interaction over long distances. Furthermore, fiber flexibility allows easy integration into diverse and challenging settings, with the possibility for *in situ* measurements and real-time monitoring, and the miniaturization of the system enables the creation of compact and portable devices, expanding the applicative domain of SERS technology to fields such as environmental monitoring, medical diagnostics, and point-of-care testing. Last but not least, the efficient transmission of light through optical fibers enhances sensitivity and signal quality, with a better SNR. Therefore, the combination of SERS with optical fibers seems representing a perfect marriage that has led to the rise of a new class of SERS sensors, which have garnered significant interest over the past decade owing to the peculiarities of optical fibers that can overcome many drawbacks associated with conventional SERS sensors.

SERS-based optical fiber sensors have witnessed high demand across a diverse range of applications, including environmental monitoring, food safety, biological diagnostics, and chemical sensing, due to their exceptional sensitivity, specificity, and selectivity [17–20]. The capacity to remotely measure analytes in real-time through optical fibers is a key benefit, allowing for the creation of dispersed sensing systems for continuous monitoring. In order to increase the Raman signal of the surface adsorbed analytes, the metallic nanoparticles or nanostructured surfaces are typically used in the coating of the fiber used in SERS-based optical fiber sensors. The laser is used to excite the analytes molecules, and the resulting scattered light are collected and analyzed with a Raman spectrometer. Recent advances in materials science, nanotechnology, and fiber optic technology have made it possible to create more sensitive and robust SERS-based optical fiber sensors. The plasmonic nanoparticles e.g., Au, Ag, and Cu, have shown considerable gains in SERS signal amplification. Furthermore, the use of microstructured optical fibers has permitted the construction of very sensitive sensors with enormous surface areas. SERS-based optical fiber sensors provide several benefits over traditional sensing approaches, including real-time monitoring with ultrahigh sensitivity and specificity. The ongoing advancements in these sensors undoubtedly promise their extensive adoption across diverse domains in the future, including chemical sensing, environmental monitoring, and biological diagnostics [21]. Figure 1 exhibits the key information of proposed review work, which encompasses several applications. [22–27].

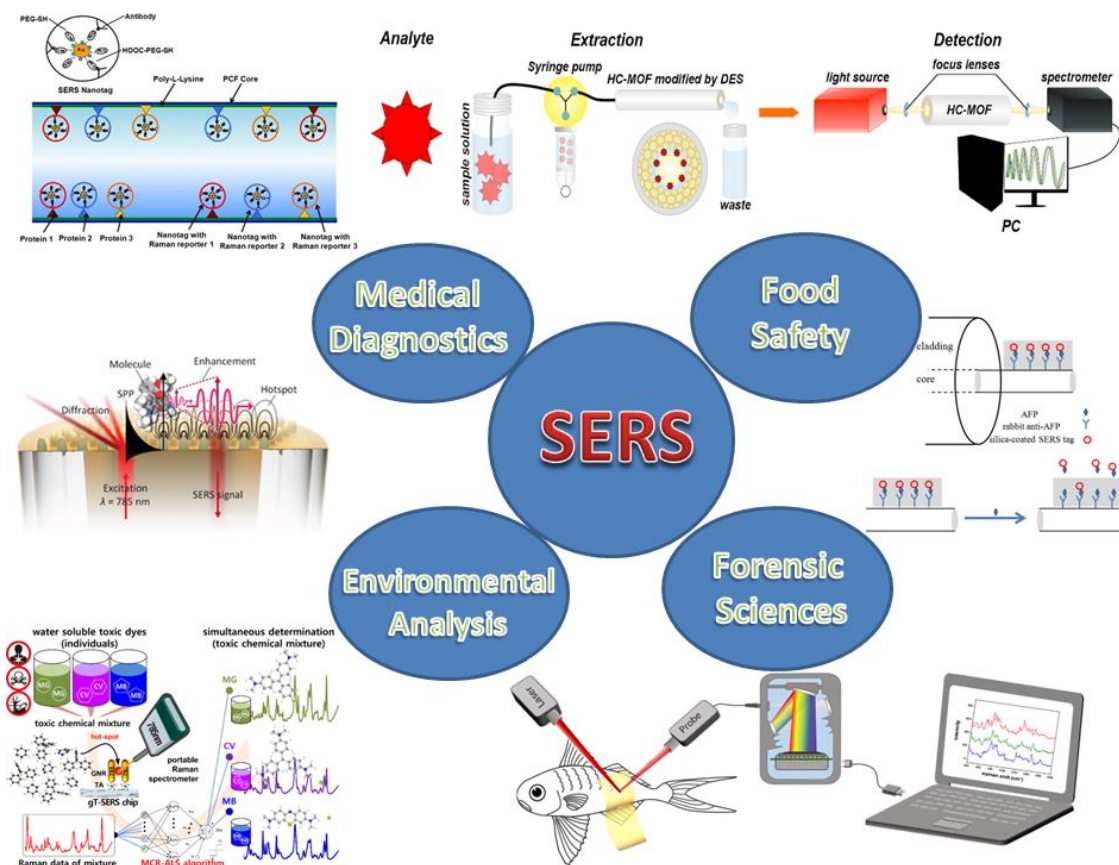


Fig. 1. An overview of conventional and emerging SERS based optical fiber sensors for various sensing applications (Reprinted/adapted from [22–27]).

The main novelty of the review lies in the various types of SERS based optical fiber sensors which are not available in the literature review. In this review article, we have covered most promising and latest technologies developed in the past decade based on the SERS. Also, for the ease of the scientific community, the present review is categorized in four different application areas so that one can easily identify the area of interest based on their expertise. The selected published articles are also summarized in tabulated form at the end of the each section to compare the sensing performance for better understanding. The present review is organized as follows. It starts with a brief introduction on SERS mechanism and a technique used for electromagnetic and chemical enhancements (Section 2) and then goes on with the different geometries used to implement fiber-based SERS sensors (Section 3). Later, Section 4 highlights application domains of SERS sensors, such as chemical sensing, biosensing, drug delivery, and agricultural and food quality monitoring. This section not only provides a detailed discussion of the most significant examples of SERS sensors, but also aims at covering the recent development in the respective domain with advantages and limitations. Finally, Section 5 will emphasize the future perspectives and challenges of the SERS fiber-based sensors and, in Section 6, an overall conclusion is drawn.

2. SERS mechanism

The basic SERS mechanism involves the enhancement of Raman scattering signal by the interaction of the analytes molecule with a roughened metal surface or metal colloidal nanoparticles. Metallic nanoparticles involving conventional choices i.e., Au and Ag have been extensively used as SERS substrates because of their unique plasmonic characteristics. The

resonance peak of Ag nanoparticles has better sharpness and intensity compared to Au [28]. However, Ag is prone to oxidization and has strong toxicity, making it less suitable for applications involving organic samples [29,30]. In such a situation, the stability and biocompatibility of Au nanoparticles are more desirable [31].

When a molecule adsorbs on the surface of metallic nanostructures, it leverages on localized electromagnetic field generated in the proximity of the metal clusters due to light-matter interactions. This highly localized electromagnetic field termed as hotspot can significantly improve the Raman signal, leading to a much stronger and more easily detectable Raman signal than would be observed in conventional Raman spectroscopy. Optimization of the substrates involves modification in terms of surface morphology and metal deposition parameters to produce well-distributed hotspots [32]. The Raman scattering signal can be significantly enhanced via two different approaches (i) electromagnetic, and the (ii) chemical, enhancement approach. The electromagnetic enhancement arises from the interaction of the molecule with the localized electromagnetic field generated by the metal surface. The chemical enhancement, on the other hand, arises from the formation of a charge transfer complex between the molecule and the metal surface. In actual, both enhancements work in tandem, and the separation of the effects has largely been unsuccessful [33].

Electromagnetic enhancement is one of the primary mechanisms responsible for the large signal enhancement observed in SERS [34]. Interaction of light with strong localized electromagnetic field in the vicinity of the analytes molecule induces Raman process in the molecule and the scattered radiation is transmitted back into the plasmon with its frequency changed by the energy transferred to the nuclei in the Raman process.

Electromagnetic enhancement is typically viewed as the product of local field enhancement and radiation enhancement. Local field enhancement relies on effects such as local surface plasmon resonance (LSPR) arises from the collective oscillation of conduction electrons in the metal nanoparticle in response to the incident electromagnetic field. The presence of LSPR strengthens the local electric field that subsequently enhances the power radiated by the molecule oscillating at Raman scattering frequency. The resulting local field enhancement factor (M_{loc}) at laser angular frequency (ω_L) is then viewed as the average of the enhanced electric field amplitude (E_{loc}) over the incident electric field amplitude (E_0) as expressed in Equation 1 [35]:

$$M_{loc}(\omega_L) = \left[\frac{E_{loc}(\omega_L)}{E_0(\omega_L)} \right]^2 \quad (1)$$

The concept of radiation enhancement comes from the fact that radiation from a dipole is dependent on the surrounding dielectric material and its interactions. This consequently affects Raman scattering leading to the combination of local field and radiation enhancements. The enhancement factor at Raman frequency, $M_{Rad}(\omega_r)$ is expressed by Equation 2, which takes into account the ratio of radiated power, P_{rad} to radiated power in a vacuum (P_0) dielectric constant in vacuum (ϵ_0), wavenumber (k), and complex amplitude of the dipole (p_0):

$$M_{Rad}(\omega_r) = \frac{P_{Rad}}{P_0} = 1 + \frac{6\pi\epsilon_0}{|p_0|} \frac{1}{k^3} \text{Im}\{p_0^* \cdot E_{SR-0}\} \quad (2)$$

In a vacuum, the self-reaction field, E_{SR-0} is equal to zero while P_{Rad} is equivalent to P_0 . This is of course different if the molecules are placed near plasmonic materials, which changes the value of E_{SR-0} , and subsequently the radiated power, P_{Rad} . Based on the optical reciprocity theorem and under some conditions, radiation enhancement can be represented as local field enhancement at frequency, ω_r . $M_{Rad}(\omega_r)$ is then equivalent to $M_{loc}(\omega_r)$ and the SERS enhancement factor is expressed as [36]:

$$EF(\omega_L, \omega_r) = M_{loc}(\omega_L) \cdot M_{loc}(\omega_r) = \left[\frac{E_{loc}(\omega_L)}{E_0(\omega_L)} \right]^2 \cdot \left[\frac{E_{loc}(\omega_r)}{E_0(\omega_r)} \right]^2 \quad (3)$$

This $|E|^4$ expression is a standard SERS approximation that is applied in general SERS application with a small Raman shift. By taking Stokes shift into account, a more elaborate expression, $|E(\omega)|^2 |E(\omega')|^2 / |E_0|^4$, where ω' is the Raman emitted frequency was acquired [37]. Correction to the $|E(\omega')|^2$ factors to include emission from the inelastic emission dipole was also able to obtain a more accurate approximation.

In addition to the electromagnetic enhancement, SERS is also influenced by chemical enhancement, which can further increase the Raman signal intensity of the analyte molecule. The chemical enhancement arises due to the formation of a charge transfer complex between the analyte molecule and the metal surface [38]. The energy created from the generation of electron-hole pairs in the metal is transferred to the analyte, enabling the Raman process to occur. The chemical enhancement mechanisms are highly dependent on the electronic structure of the analyte molecule and the metal surface. It is typically observed for molecules with pi-bonding, such as aromatic compounds, as well as for molecules with lone pair electrons, such as thiols and amines. The metal surface also plays a critical role in the chemical enhancement mechanisms, with different metals exhibiting varying degrees of chemical enhancement. This complex results in a change in the molecular vibrations of the molecule, leading to an increase in the Raman scattering cross-section and the Raman signal intensity. Physical adsorption of molecules driven by Van der Waals force is weaker and only slightly modifies the structure of the molecule. A stronger Raman effect is expected in the case of chemical adsorption (chemisorption), in which a chemical bond between the molecule and substrate is formed. Although the enhancement is less significant compared to electromagnetic enhancement, chemical enhancement influences the spectral pattern of SERS [38].

Chemical enhancement is dependent on three mechanisms, as shown in Fig. 2. The first mechanism is the Raman resonance (RR) scattering, which is induced by resonance, takes place between the molecules and the incident light. In SERS, the presence of metal nanoparticles forms a complex with the molecule that can alter the Raman resonance frequency. Metal-adsorbate charge transfer can only occur when the sufficient overlap of the molecule and substrate wave functions is achieved [39,40]. The dependence of this relies on the relative positions of the Fermi level in the metal and the levels of the highest occupied/lowest unoccupied molecular orbital in the molecule. Electron transfer can occur from molecule to metal or vice versa. The last mechanism present in chemical enhancement is ground state charge transfer, which is a non-resonant electron transfer that occurs without excitation. This is attributed to chemisorption interaction which does not form a new electronic state but alters

the geometrical or electronic structure of the molecules, resulting in a slight improvement of the Raman shift and intensity of vibrational modes [41].

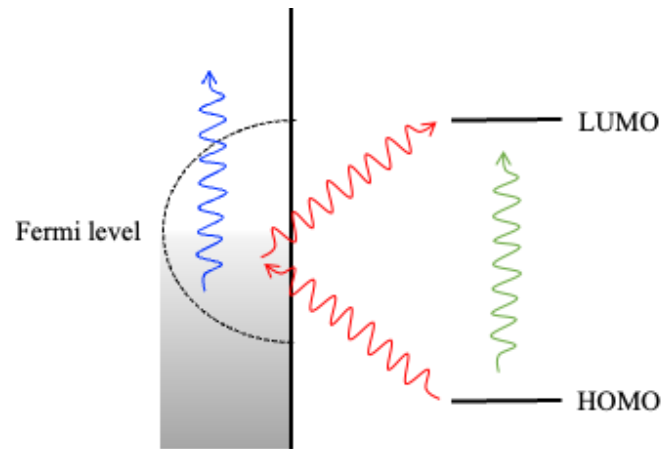


Fig.2. Mechanisms of chemical enhancement represented by a blue arrow (ground state charge transfer), a red arrow (metal-adsorbate charge transfer), and a green arrow (Raman resonance scattering)

The interplay between electromagnetic and chemical enhancement is an intricate interdependence [42]. Achieving optimal SERS enhancement necessitates a delicate balance between these two mechanisms. Factors such as the choice of metal substrate, the nature of the analytes molecules, and experimental conditions play pivotal roles in determining the extent to which each enhancement mechanism contributes. Moreover, the interplay is not uniform across the SERS substrate as different regions may exhibit varying degrees of electromagnetic and chemical enhancement. Quantitative estimation of signal enhancement can be calculated using average enhancement factor (EF) based on the following equation:

$$EF = \frac{I_{SERS}/N_{SERS}}{I_{bulk}/N_{bulk}} \quad (4)$$

I_{SERS} and I_{bulk} denote the enhanced and normal Raman intensities, respectively while N_{SERS} and N_{bulk} are the corresponding number of probe molecules contributing to the intensities. This equation provides the overall enhancement from SERS but minimal information on the individual contribution of electromagnetic and chemical enhancements [43]. One method to observe the influence of chemical enhancement is through the experimentally derived spectral output. In [44], the presence of a weak absorption peak at 1,060 nm for rhodamine 6G (R6G) adsorbed on Ag nanoparticles, is evidence of the formation of charge transfer complex between a molecule and substrate. Varied spectral shapes in SERS relative to normal Raman spectra are also an indicator of charge transfer contribution. Clear distinction between electromagnetic and chemical enhancements can be achieved by utilizing plasmon-free materials as SERS substrate, allowing the generation of SERS heavily based on charge transfer mechanism [45,46]. Liu *et al.* have recently reported groundbreaking research introducing a miniaturized and cost-effective method for creating an exceptionally sensitive and mechanically stable fiber SERS substrate [47,48]. This innovative approach involves the fabrication of $Ti_3C_2T_xMXene@graphene\ oxide/Au$ nanoclusters through wet spinning and

subsequent *in situ* reduction processes. In the reported work the use of MXene@graphene fiber provides good flexibility and improves the charge transfer enhancement (i.e., chemical mechanism) for a SERS sensor allowing additional *in situ* growth of AuNCs on its surface to create extremely sensitive hot spots (i.e., electromagnetic mechanism), enhancing the capability of SERS performance of the substrate in challenging environments. Therefore, the flexible $\text{Ti}_3\text{C}_2\text{T}_x\text{MXene@graphene oxide/Au}$ nanoclusters fiber exhibits a noteworthy low limit of detection (LOD) of 1×10^{-11} M, accompanied by a substantial enhancement factor of 2.01×10^9 . The reported work also exhibits excellent signal repeatability and temporal stability of 9.80% and 75% for R6G molecules even after 90 days of storage.

3. Optical fiber SERS sensor geometries:

The miniaturization of the technology has appeared as an growing research area which is based on the integration of optically active materials onto a micro- or nano-scale surface of optical fiber advancing the new generation of all-in-fiber miniaturized sensing configuration with several applications [49]. The technology is primarily based on advancing conventional fiber into a multi-parameter sensing device comprises with ultra-compact labs for various applications [50]. In the context of biosensing, the device unveils the precise control of light at the nanoscale, in conjunction with sophisticated chemistry techniques, to improve the light-matter interaction [51]. The light-matter interaction occurring between the incident light and target molecule may take place either inside the fiber (such as the air hole cladding of microstructured optical fiber (MOF)) or on the sensing materials deposited around the optical fiber surface or on fiber tip. When the probe is based on the material coated around the fiber it is known as lab-around-fiber allowing the light-matter interaction takes place around the fiber. The classification of this phenomenon primarily relies on the utilized mechanism to extract photons as they propagate along the core of fiber and direct them towards the surrounding medium. These devices can be categorized into two major classes among which (i) one deals with the complete or partial reduction of the diameter of fiber cladding e.g., tapered fiber, D-shaped fiber, etc., whereas (ii) second is based on the introduction of periodic changes in the RI of fiber core that allows the coupling of light from core to the cladding, like in fiber Bragg grating (FBG), titled fiber Bragg grating (TFBG), and chirped fiber Bragg grating [52]. Therefore, the lab-on-fiber technology encompasses various platforms which are categorized based on the location of the sensitive material, referred to as the lab. In this study, we are exclusively focusing on fiber probes integrated with SERS material for various applications. An appropriately configured miniaturized SERS sensing system is considered as the most significant analytical detection tool for accurate specific detection in various fields. This section covers various types of optical fiber SERS sensing configurations along with their sensing principle, advantages, and limitations.

3.1. End-coupled SERS probe:

The end-coupled SERS sensors are also known as optrode aims to exploit the advantages of alignment-free sampling using optical fibers. The optrode generally achieve this feature by employing a single fiber in order to transmit and receive both simultaneously, i.e., the excitation light and the backscattered SERS signal, thereby simplifying the sampling process.

In the optrode configuration the SERS substrate used to be considered on tip of fiber ensuring an excellent overlapping of excited and collection signals. In 2019, Kwak *et al.* reported an plasmonic optrode utilizing gold nano-islands as SERS substrate [53]. The sensing probe comprises with Au nanoislands on the fiber-tip, fabricated through iterative solid-state dewetting, which induces a strong EM fields and improve the Raman scattering of biomolecules. The SERS enhancement factors for plasmonic optrode were first measured on the top surface of optrode based on repeated dewetting condition. In the experiment, the tip of fiber was immersed for 12 h in 3mM concentration of BT in methanol. The SERS signals of BT were monitored using He-Ne laser and a spectrometer used with an inverted microscope. An excitation laser was coupled along the multimode fiber, and the SERS signals from biomolecules near the fiber-top surface were collected through the same fiber, enabling highly sensitive detection. The reported probe exhibited an enhanced SERS factor of 7.8×10^6 with a low LOD of 100 nM for crystal violet. In 2023, Li *et al.* demonstrated the first dual-mode SERS-fluorescence optrode for detection of R6G in aqueous solution with an improved performance using tapered optical fiber coated with Ag nanoparticles [54]. The fabrication of sensor consists of two steps i.e., tapering and half-coating. In first step a small segment of hydroxyl multimode fiber (MMF) was processed to form tapered waist which was later cut to obtain two separate tips, as shown in Fig. 3 (a). The automated program of splicing system allows precise control over the shape of the fiber tip, including the arc power and tensile speed. Figure 3 (b) showed the schematic of the experimental setup utilized for SERS detection. The fabricated sensor was set on a fiber holder fixed on a 3-axis stage as shown in Fig. 3 (b). The exciting laser, emitting from the Raman spectrometer, was coupled to the fiber sensor via mechanical splicing. The Raman signal was received and amplified at the partially Ag nanoparticles coated fiber tip before being transmitted back to the spectrometer. In reported work only 20% out of 80 mW of the total exciting power was used for the detection. The NA of the utilized objective lens was selected to be 0.22 to match with the MMF. The working distance was considered to be ~ 6 mm. In order to prevent the influence of surrounding light the experiment was performed in the dark environment. The spectrum of pure water was recorded in advance and subtracted from the detected spectra as the background. The minimum detectable aqueous R6G concentration using the reported optrode was achieved of 10^{-6} M, with a low LOD of 0.2×10^{-6} M while for the same concentration, the fluorescence spectra were recorded along with the LOD of 2.25×10^{-6} M. The two modes exhibited a closely aligned range of detection, with recognition and quantitation analyses reported to be achieved at comparable magnitudes.

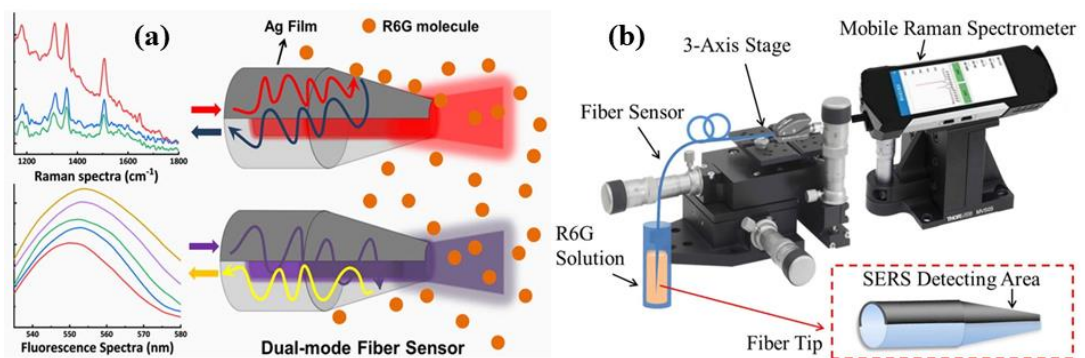


Fig.3 (a). Schematic diagram of the fabricated optrode, and (b). experimental setup used to characterize the performance of the sensor (**Reprinted/adapted from** [54])

Several techniques have been reported so far to develop an effective SERS optrode with improved performance. These techniques mainly include the alumina nanoparticles and Ag coatings on the fiber [55], immobilization with colloidal Ag particles [56], and diamond particles [57]. Au nanostructures such as nanopillars and nanorods have been deposited on the tip of fiber using the focused ion beam milling technique [58], whereas the layer of Ag nanoparticle has been deposited using photochemical modification [59]. In 1998, Viets and Hill reported a comparative study in which they observed that the optrode fabricated using metal nano-islands layer over the nanoparticle and thin film over the sandblast-roughened surfaces. From the reported work they concluded similar enhancements in the intensities of the Raman signal using both approach [57]. Furthermore, they also concluded that the sandblast approach can be considered in real applications as it provides the most robust sensing platform. In 2023, Du *et al.* reported an experimental approach of oil-water separation utilized to modify AgNPs on the end face of fiber to fabricate optocla fiber SERS substrates and therefore effectively improve the Raman signals [60]. The preparation of SERS probe requires three steps as shown in Fig. 4 (a). The first step comprises the preparation of fiber by stripping and cleaving the end face to make it perfectly flat facet. In second step require the centrifugation and functionalization of AgNPs on the tip of fiber. Before functionalization the prepared silver sol was centrifuged at 6000 rpm to obtain the desired silver solution. After centrifugation n-hexane and AgNps was mixed in into a separate cleaned petri dish which was later extracted with absolute ethanol. Finally the separated silver film was functionalized on the fiber face. The last step contains the immersion of prepared substrate in the analytes for 20 min and then dried for monitoring by dip and dry technique. Figure 4 (b) illustrates the experimental setup used for the characterizations. The setup mainly consists of laser source, spectrometer, compute and sensor attached with Raman probe. All SERS signals were collected by portable Raman system instrument and excited by 785 nm laser. The laser power is 100 % (500 mW), and the signal acquisition time is 6 s. The R6G was diluted to a concentration of 10^{-4} M with deionized water, and R6G with a concentration of 10^{-4} M was selected for detection.

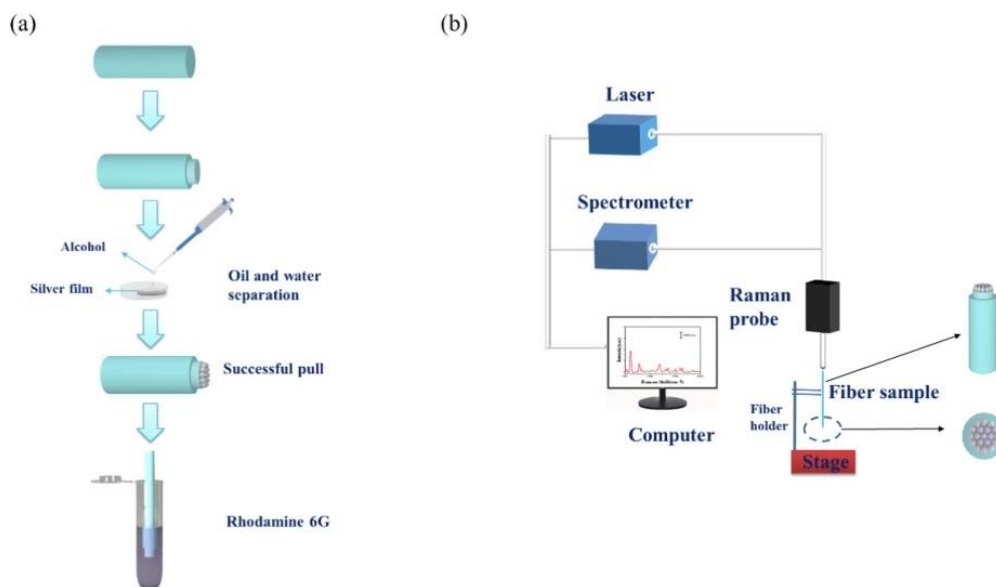


Fig. 4. (a). Flowchart of preparation of fiber SERS substrate, (b) Diagram of experimental testing device. (Reprinted/adapted from [60])

Therefore, from above discussion it can be stated that the SERS signals can be improved either by appropriate geometry of fiber tip or by selecting the correct deposition approach. The proximity of the optical fiber to the SERS-active surface maximizes the excitation and collection efficiency, resulting in a significant boost in the overall enhancement factor, thereby improving the sensitivity and reliability of SERS measurements.

3.2. Cladding-coupled SERS probe:

As discussed above, optrode are relying on the LSPR excitation due to the interaction of the evanescent field at the core-cladding interface. It has been reported previously by several researchers that the large surface area for sensing provides an improved sensitivity and low LOD [61]. Moreover, it is important to highlight that the signal photons produced within the cladding region can only recoupled with the propagating modes of the fiber via evanescent field mechanism. The mechanism is a relatively inefficient process, which allow a typical capture efficiency of less than 1% for the light sources which are concentrated in the thin sensing layer at core-cladding interface [62]. In 1995, Stokes *et al.* reported the first cladding coupled SERS sensor by utilizing a thin silver layer coated over nanoparticle on a 1 cm length of the exposed core of fiber [63]. Later in 2000, the same group reported another type of cladding coupled sensor utilizing alumina nanoparticles and a thin silver coatings on the tip of optical fiber [43]. The reported SERS sensor was demonstrated for *in situ* monitoring of cresyl fast violet and brilliant cresyl blue in aqueous solution. A good calibration curve was obtained for cresyl fast violet in groundwater with a low LOD of 50 ppb cresyl fast violet.

In 2004, Xu *et al.* reported a cylindrical waveguide fabricated using a silica capillary whose inner wall was functionalized with silver nanoparticles which enhances the Raman signals [64]. In the reported work author utilized 3 cm long silica capillary tube of the inner and outer diameter of 350 and 450 μm , respectively. Before coating of silver nanoparticles the inner was of the fiber was functionalized to achieve hydroxyl surface using piranha solution and washed

multiple time using ultrapure water. After functionalization the treated capillary tube was placed in solution of the poly(dially-dimethylammonium) chloride for one hour resulting the formation positive charges on the inner wall. After all this modification the capillary tube was immersed in silver nanoparticle solution for 12h to achieve SERS substrate. Another capillary tube with larger diameter ($\sim 0.9\text{--}1.1\text{ mm}$) was placed at an angle to form a U-type shape fixed on a microscope slide, allowing one to hold the fabricated SERS silica capillary tube as well as supply a measurand sample into it when it is volatilized. The schematic diagram of the fabricated device is shown in Fig. 5. To characterize the fabricated device an optical microscope was attached to Raman spectrometer in order to observe the cross section of the sensor. The excitation input was provided by the 514.5 nm line of an air-cooled argon ion laser. The excitation power at the wall of SERS sensor was kept lower than a few milliwatts and a 20x objective lens was utilized to focus the laser beam onto a spot of approximately 1 mm in diameter. The SERS signals were collected in the reverse direction corresponding to the laser direction and measured with a Renishaw model 1000 confocal microscopy Raman spectrometer. The incident laser beam propagates through the SERS active capillary based on total internal reflection phenomenon and penetrates a small distance into the sample solution by the evanescent wave field. The sensor exhibited a low LOD of 10^{-9} mol/L when the capillary was filled with methanol.

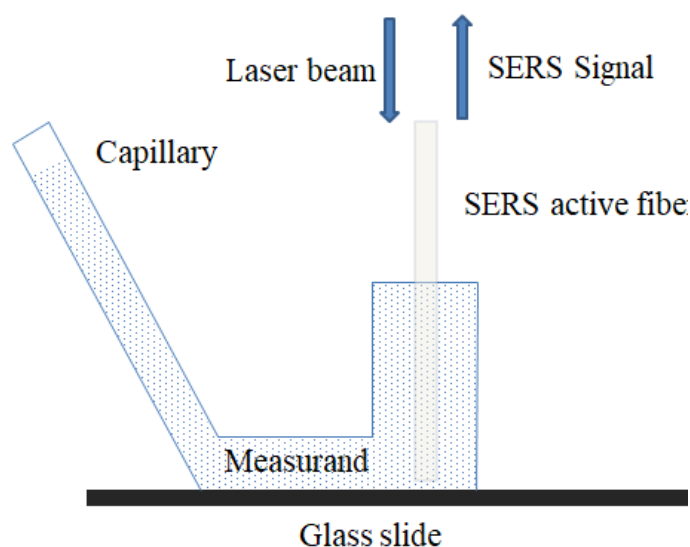


Fig.5. Schematic diagram of U-type capillary system for the SERS detection with the silver nanoparticle functionalized capillary tube.

In 2019, Li *et al.* reported the potential of double-cladded fiber in the development of a SERS probe [65]. To fabricate the sensor the fiber splicer was utilized to perform the splicing of multimode fiber and double-cladded fiber. After splicing the double-cladded fiber was functionalized using poly (dially-dimethylammonium) chloride. After functionalization the probe was immersed in gold colloidal solution to and deposited gold nanoparticle on the outer surface of the double-cladded fiber using self-assembled method. The SERS active substrate was fixed in a microfluidic chip containing a polydimethylsiloxane (PDMS) cover and a slide. The measurand was injected through the microfluidic channel, which flows through the sensing region and finally exits through the outlet port. To characterize the sensor a laser source with a

center wavelength of 785 nm was launched via a splitter module into the SERS active probe. The splitter module eliminates the fiber Raman background in the excitation light from port 1 using a bandpass filter and transmits only the Raman scattered light from port 2 to port 3 through a long-pass filter. Due to the depressed cladding of double-cladded fiber, the field distribution was observed to be more accessible to the outer surface compared to a non-depressed coreless fiber, which leads to the improved excitation efficiency to generate Raman scattered light. The impact of the dispersed double-cladding fiber on the sensing performance of the fabricated probe was investigated using silver nanoparticles on top of it. The Raman spectra for R6G was measured using the depressed double-cladded fiber-based optrode embedded in the microfluidic chip.

In some cases, the author utilized a D-shaped fiber, which generally fabricated by placing the fiber in a V-groove and polished from one end to precisely reduce the diameter to obtain D-shaped and strengthen the evanescent field interaction [66]. In 2005, Zhang *et al.* reported D-shaped SERS sensor to detect R6G [15]. The light was reported to be coupled from polished surface into the deposited silver nanostructured films, which not only increase the active surface volume ration but also improved the enhancement factor. Initial modeling of the configuration showed the 70% of the light are coupled into the SERS layer. For the D-shaped fiber, its SERS configuration yields an 80000 μm^2 active surface compared to a convectional end-polished fiber which provides only $\sim 50 \mu\text{m}^2$.

The emerging advancement of microstructured optical fiber (MOF) has been recognized as a key development in cladding coupled SERS substrates [67]. In 2008, Guo *et al.* reported a PCF-based SERS sensor using silver nanoparticle colloid for the monitoring the concentration of 4-mercaptobenzoic acid molecules in aqueous solution [68]. The initial idea was filling Ag nanoparticles inside the air holes. The SERS sensing was demonstrated for 4-mercaptobenzoic acid molecules which exhibited a 7 orders of magnitude enhancement. Similarly in 2022, Sun *et al.* reported a solid-core PCF SERS sensor by selectively filling its channel with Ag nanoparticles [69]. A schematic diagram of the preparation of avoided-crossing-based SERS-active suspended core PCFs is shown in Figure 6. Initially, the sodium hydroxide (NaOH) solution was flushed continuously through the fiber for 10 min under the constant pressure of nitrogen gas in order to hydroxylate the inner wall of the suspended core PCF. Later the air holes were washed with the deionized water and dried with the nitrogen gas. Subsequently, the AgNPs were grown on the inner wall of the suspended core PCF following a silver mirror reaction, which was performed by reducing silver ammonia solution with glucose. The reported performance of the device was numerically optimized and experimentally validated. Numerical analysis exhibited that the intensity in the Ag filled channels was significantly improved from 2.8 % to 42 %. The sensor exhibited a good sensitivity and reproducibility with maximum deviation of 4.8 for crystal violet solution along with a low LOD of 10^{-12} M with an enhancement factor of 10^{10} .

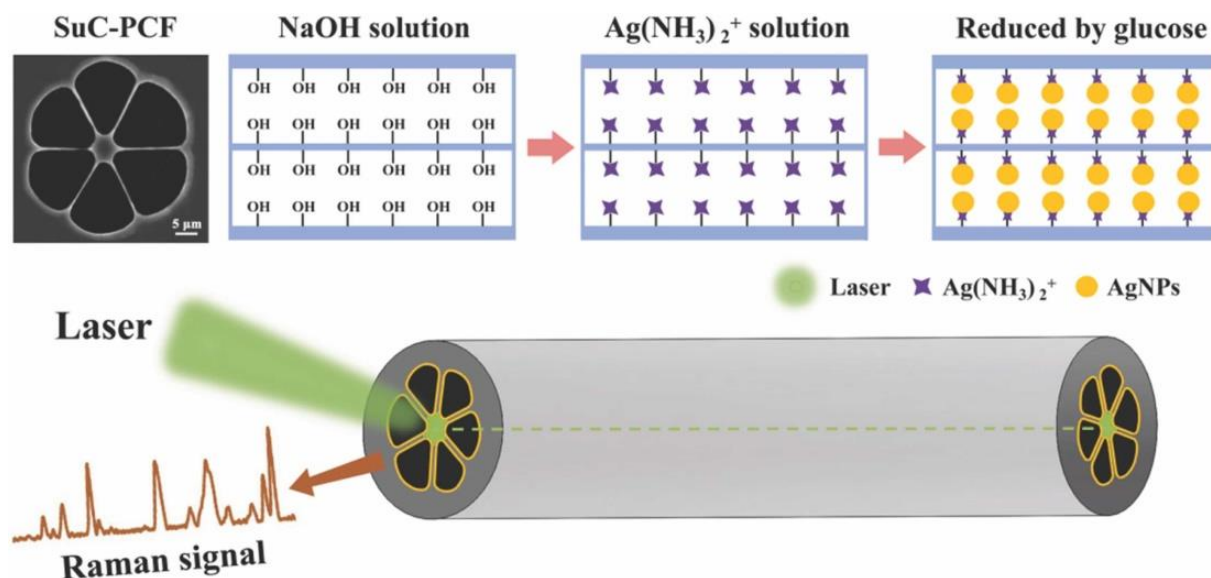


Fig.6. A schematic representation of surface functionalized and AgNPs coated cladding coupled SERS substrate (**Reprinted/adapted from [69]**)

The cladded-coupled SERS are still in its nascent stage giving a reason for confusion whether the increasing overlap between the SERS active substrate and optical field resulting an overall improvement in detection accuracy.

3.3. Core-Coupled SERS:

The MOF design comprises single or multiple arrangements of air holes, which gain huge attention in SERS-based sensors. In the previously discussed section, the author selectively filled the metallic nanoparticles inside of these air holes to make them SERS active. In a MOF the light propagation takes place via photonic band-gap in which a comprehensive examination of the sensing layer and the surrounding are investigated for sensing applications. One of the drawback of such MOF is the restriction of backscattered Raman signal for a given excitation wavelength due to its narrow transmission window. Considering the limitation in 2008, Han *et al.* reported an liquid-core (LC) photonics crystal fiber (PCF) for solution detection using normal and SERS [70]. To fabricate the sensor the hollow core photonic crystal fiber with hollow core diameter of 30 μm along with the band gap centered at wavelength 1550 nm was utilized. Filling of solution phase into the core of the hollow core PCF with cladding air channels sealed at the distal ends was conducted via liquid flow in the microfluidic hollow air core driven by a pressure differential. In particular, one end of the hollow core fiber was submerged in the required solution placed in a specially crafted pressure cell, while the opposite end of the fiber was remained exposed to the surrounding air. With chamber pressure 200 psi (nitrogen), the process takes around 5 min for complete filling of liquid in the hollow core, leading in LC-PCF with 0.1 μl liquid phase in the core. The light guided through this core due to the index contrast between the low index air cladding and high index liquid. In the reported work the normal Raman spectra for ethanol, water, and 1 vol% ethanol in water were monitored. The sensor exhibited a high sensitivity and reproducible performance for 1.7×10^{-7} M thiocyanate anions in water. In the same year, Shi *et al.* evidently showed that the device performance can be further improved by considering two different types of Ag nanoparticles

to the inner wall of a hollow-core fiber [71]. Both cladding-coupled and core-coupled sensors have drawn a huge interest in the field of distributed chemical monitoring. These sensors can accurately perform a target specific detection along the sensor's length by utilizing time-resolved backscatter signals from pulsed sources.

4. Application of optical fiber SERS sensors:

The versatility of optical fiber SERS sensors extends across several applicative domains, showcasing their potential transformative impact on the market. In chemical sensing, these sensors excel at detecting and analyzing trace amounts of substances with remarkable precision and accuracy, providing invaluable insights for quality control and process optimization. In biosensing, optical fiber SERS sensors serve as powerful tools for identifying and quantifying biomolecules, revolutionizing medical diagnostics, and contributing to advancements in biomedical research. In drug monitoring, the high sensitivity of SERS technology allows for the detection of pharmaceutical compounds at low concentrations, offering a potential breakthrough in personalized medicine and therapy monitoring and treatments. Agriculture also benefits from these sensors by enabling real-time monitoring of soil composition, nutrient levels, and pesticide residues, thereby promoting sustainable and efficient farming practices. The ability to adapt of optical fiber SERS sensors across these diverse settings underscores their significance in advancing scientific research, industry practices, and healthcare solutions. Detailed discussions over these applications are given in the following subsections.

4.1. SERS in Chemical Sensing:

Optical fiber chemical sensors based on SERS phenomena have emerged as a promising approach for real-time and in-situ detection of various analytes in numerous applications, including environmental monitoring, biomedical diagnostics, and food safety [72]. The underlying principle of SERS-based optical fiber chemical sensors is to functionalize the optical fiber's surface with metallic nanoparticles, such as gold or silver that can amplify the Raman signal of the analytes immobilized onto the nanoparticles' surface [73]. A spectrometer or portable Raman device can be used to measure the strength of the Raman signal in order to identify the analytes. The use of optical fibers in SERS-based chemical sensors offers several advantages, such as flexibility, remote sensing capabilities, and ability to detect analytes in harsh or remote environments. Moreover, the integration of SERS-based optical fiber sensors with microfluidic systems allows for the development of highly sensitive and selective sensors for rapid and accurate detection of a wide range of analytes. Sensors like these can be adapted to detect particular molecules or to work as multiplexed sensors to detect several analytes at once.

The exploration of suitable optical fiber SERS probes for extremely sensitive and field detections is a topic of immense scientific interest. Currently, two significant optical designs for this technique have been investigated. In the initial design, fiber optics are employed as a single waveguide to transmit the light and gather the resulting Raman scattering signal emitted from a distinct SERS-active substrate [74]. This particular design is commonly known as extrinsic fiber optics SERS sensors [19]. The second approach referred to as intrinsic fiber optics SERS sensors, on the other hand, entails fusing metallic SERS-active nanostructures with the fiber optic, generally at its end. As a result, the fiber optic probe functions as both a

waveguide and a platform that is SERS-active [38, 56–61]. Kneipp *et al.* successfully demonstrated the possibility of obtaining SERS spectra of individual molecules in highly diluted solutions by utilizing colloidal silver nanoparticles [81,82]. Similarly, Andrade *et al.* reported silver nanoparticles-modified fiber head for SERS remote sensing [80]. Cao *et al.* proposed another sensitive SERS probe by using the silver nanoplates coated on cone-shaped fiber using hydrothermal technique [83]. The performance of the proposed sensor was examined for 4-aminothiophenol (4-ATP) molecule in terms of sensitivity and repeatability. In 2015 same group reported more sensitive SERS optrode coated with silver nanopolyhedra through an autoclave reaction process [84]. An innovative approach proposed for a micro-coffee-ring-patterned (MCRP) fiber SERS probe, aiming to achieve remarkable sensitivity and reproducibility in SERS detection by Cao *et al.* in 2019 [85]. MMF integrated with gold nanoislands were used for the investigation as a means to create a spatially resolved SERS endoscope [86]. We can clearly observe from these studies that the Raman spectroscopy has expanded its applications beyond traditional laboratory settings, particularly with the emergence of portable Raman spectrometers with measuring heads linked to the main device through optical fiber connections. The utilization of fiber-optic links enables the acquisition of Raman spectra from samples located remotely or in hazardous environments. Furthermore, by integrating SERS-based optical fiber chemical sensors with other analytical techniques like chromatography and mass spectrometry, their capabilities for detecting and identifying trace amounts of analytes in complex samples have been significantly enhanced. In summary, SERS-based optical fiber chemical sensors exhibit tremendous potential for future research and development due to their exceptional sensitivity, selectivity, and versatility in real-time and in-situ detection of a broad range of analytical substances [63,87,88]. In this section a detailed literature survey has been carried out on various types of SERS based optical fiber chemical sensors.

In 2010, Andrade *et al.* reported the design and optimization of silver nanoparticles-modified fiber head for SERS remote sensing using a "layer-by-layer" deposition of Ag nanoparticles (Ag-NPs) as shown in Fig. 7 [80]. The process involves modifying an optical fiber tip (OFT) by removing the polymer protection layer from the tip of fiber. The tip was then cleaved using a ceramic cutter to achieve a flat surface. The OFT was cleaned in piranha solution, washed with deionized water, and dried under N₂ gas flow. It was later soaked in a 10 mM APTMS ethanolic solution for 24 hours. After modification with APTMS, the OFT was washed, dried, and soaked in an Ag-NPs suspension for an additional 24 hours. This process was repeated for multiple layers of Ag-NPs, with intermediate steps involving APTMS sol-gel solution. After the last layer of Ag-NPs is deposited, the Ag-NPs-MOFT was heated in N₂ atmosphere to approximately 110 °C for 15 minutes to induce cross-linking among the APTMS sol-gel layers and enhance the stability of the modifier layers of Ag-NPs. The SERS performance was observed to be optimized at 5 "layers" of Ag-NPs for 200 nM of the R6G dye. From the reported result, it was expected that the fabricated optrode can successfully detect various dye molecules of various shapes and charges, including neutral species, anions and cations at the concentration of micro-molar level.

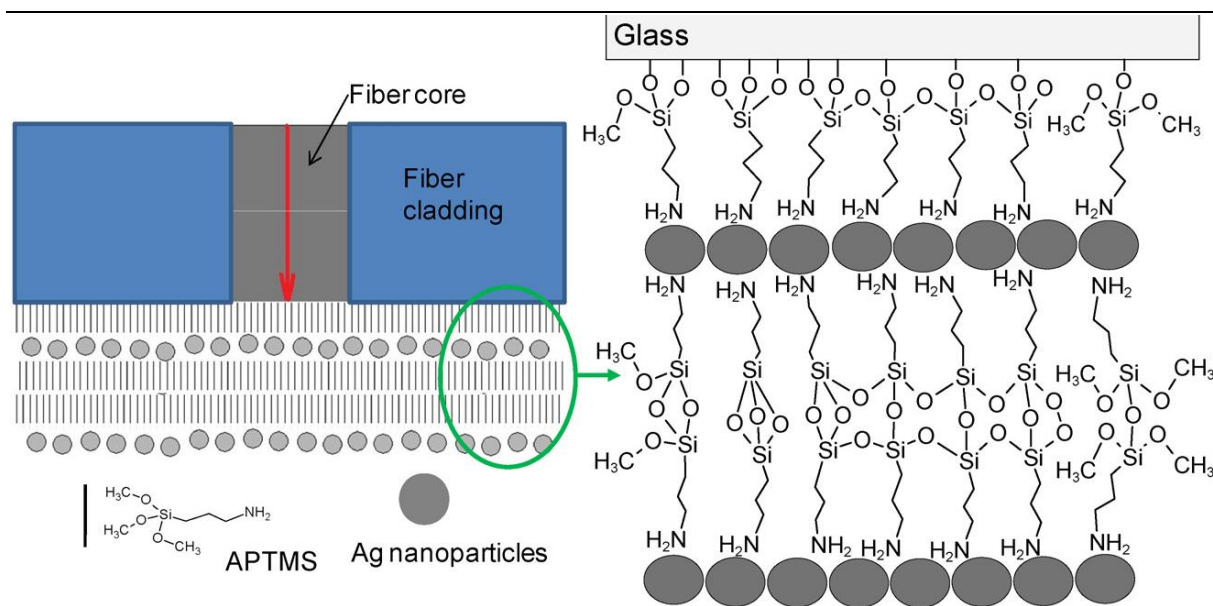


Fig. 7: Multilayer Ag-NPs self-assembly on the tip of the optical fiber. (Reprinted/adapted from [80]).

Fan *et al.* introduced a novel technique that involves integrating optical fiber optrodes as SERS-detecting components within microfluidic chips [89]. This technique offers numerous features, including the capability for on-chip detection of highly localized, sensitive and multiplexed SERS signals. Furthermore, this optical infrastructure may be physically segregated from a chip, facilitating flexibility in system design. The adjustable nature of the optrode with chip allows for the utilization of either portable spectrometers or high-performance microscopes, depending on the specific requirements. Additionally, the fiber integration into the chip is simple, permitting simple swapping of chips and sensors as required for various applications. In 2012, Yang *et al.* proposed a ultrasensitive SERS optrode patterned with a nanopillars array coated with silver using a lithography technique [71]. The optrode exhibited an enhancement factor of 1.2×10^7 for trans-1,2-bis(4-pyridyl)-ethylene (BPE) monolayer. The reported optrode was further investigated for *in situ* remote detection of toluene vapor. Figure 8 exhibits the steps of fabrication of the device in which Fig. 8 (a), (b), (c), and (d) exhibit the spin coating process, photograph of the fiber ferrule, SEM image of the fiber ferrule facet, and the observed SERS spectrum of the fabricated optical fiber sensing device for front end detection and the remote end detection of the toluene vapor, respectively.

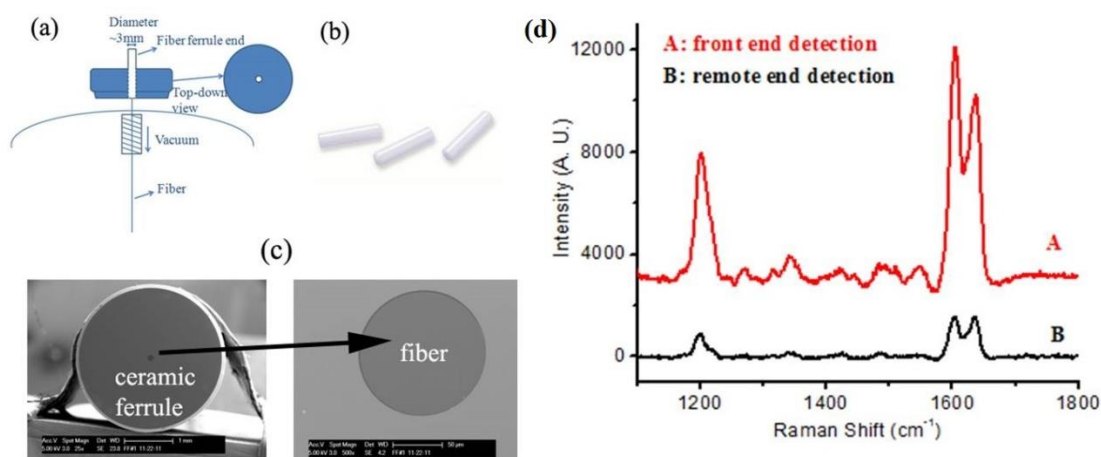


Fig. 8: (a) Spin coating procedure; (b) fiber ferrule photograph; (c) fiber ferrule facet SEM image, and (d) SERS spectra of the proposed fiber SERS sensor probe **(Reprinted/adapted from [90]).**

Another sensitive fiber SERS probe was reported by Cao *et al.* using silver nanoplates coated on cone-shaped fiber using hydrothermal technique [83]. The performance of the proposed sensor was examined for 4-aminothiophenol (4-ATP) molecule in terms of sensitivity and repeatability. Figure 9(a) depicts the experimental setup used for characterization in which a 785 nm wavelength laser source is used for the excitation and spectrometer is used to collect the reflected light from the sensor while and Figure 9(b) shows the SERS spectrum of 4-ATP molecule using 8 different fiber probes. In 2015, Cao and Wang reported SERS optrode coated with silver nanopolyhedra through an autoclave reaction process [84]. The SERS detection findings of the optrode reveal that for 4-ATP aqueous solution, the device exhibited a low LOD of 10^{-9} M.

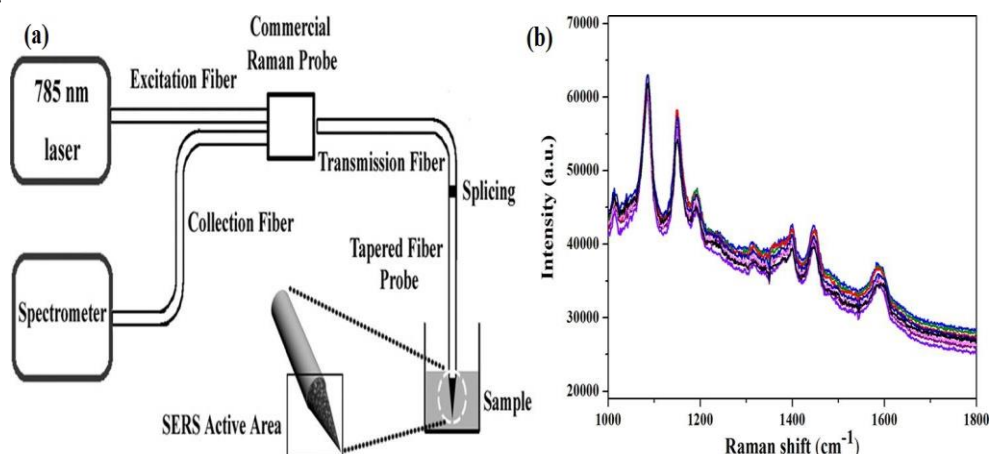


Fig. 9: (a) Experimental setup for the SERS experiment, and (b) SERS spectra of eight different fabricated SERS tapered fiber probes **(Reprinted/adapted from [83]).**

The combination of plasmonic nanostructures with optical fiber-Raman devices presents intriguing possibilities for remote investigation of biological and liquid samples. In such cases, fiber probe must demonstrate both stable SERS signals and exceptional sensitivity towards the target species. Addressing this requirement, a straightforward yet highly effective method was

introduced, involving the implantation of adjustable size and different shape of the metallic nanostructures onto the surface of tapered fiber. Figure 10 illustrates the experimental setup employed in this study [91]. The experimental setup comprises a 785 nm wavelength laser source is used for the excitation of the Raman probe and a detector connected through the computer is used for the detecting the reflected signals from the fiber probe which is then studied.

Tapered fiber probes modified with (3-aminopropyl)trimethoxysilane or carboxyethyl silanetriol sodium enable the uniform and stable assembly of negatively or positively charged noble metal nanostructures (e.g., Au, Ag) exhibiting diverse morphologies (e.g., nanorods, nanospheres, core-shell nanorods, nanocubes). By utilizing para-aminothiophenol and methyl-parathion as probe molecules, the relative standard deviation (RSD) of the SERS signals in the analyte solution can be reduced to an impressive 2%.

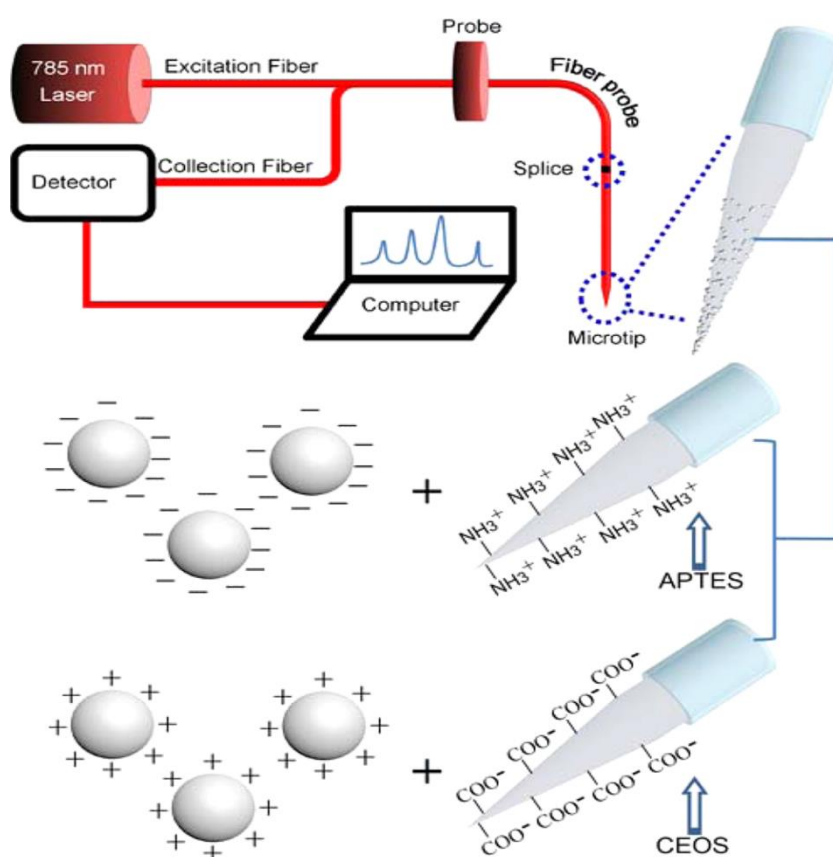


Fig. 10. Fiber Raman experimental setup and the electrostatic attraction dominated assembly of charged noble metal nanoparticles onto reversely charged tapered fiber probe (Reprinted/adapted from [91]).

Breath gas analysis is an innovative and potent technology for the noninvasive early detection of metabolic abnormalities and some other kind of illnesses. Methane and molecular hydrogen serve as indicators for colonic colorectal production due to conditions such as oligosaccharide malabsorption (e.g., fructose or lactose intolerance) and small intestine bacterial overgrowth. Recent research has connected obesity by analyzing the present gases in exhaled human breath. In a complicated gas mixture made up of H_2 , N_2 , O_2 , CH_4 and CO_2 , Hanf *et al.* described the use of fiber-enhanced Raman spectroscopy for the detection of methane

and molecular hydrogen [91]. In Figure 11(a), the Raman spectrum of hydrogen gas measurement by using the proposed hollow-core fiber presented, while Figure 11(b) depicts SEM image of the SERS active hollow-core fiber. This hollow core fiber Raman sensor for hydrogen sensing offers numerous advantages over other hydrogen sensors: (i) it can be safely used in volatile atmospheres due to the lack of electrical connections and the lack of sparks it produces, unlike electrical sensors; (ii) it doesn't exhibit cross-sensitivity to mix gaseous environment; and (iii) it enables remote sensing capabilities. Moreover, the sensor's ability to simultaneously monitor H_2 and CH_4 opens up a vast range of applications including hydrogen-based energy and biogas production systems.

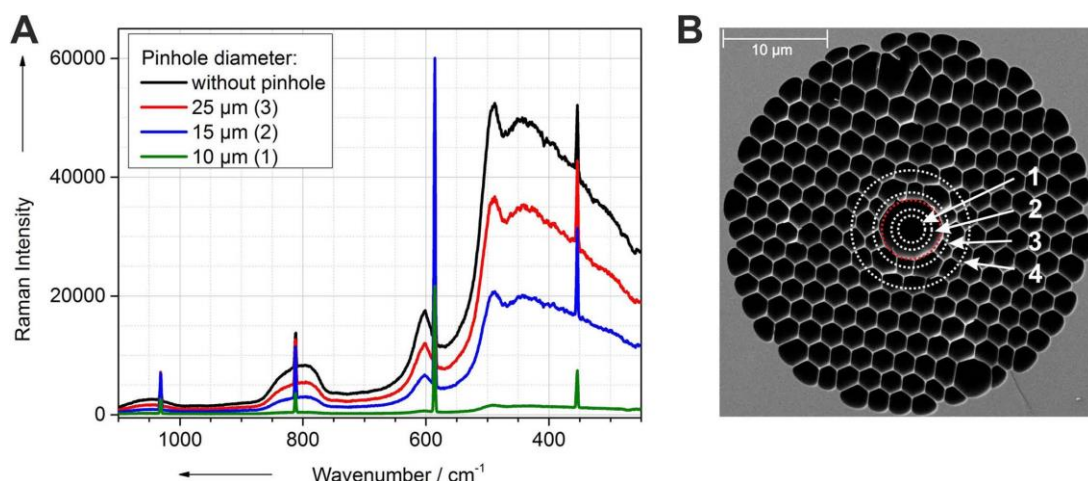


Fig. 11: (a) The rotational Raman spectra at different diameters, and (b) SEM image of fiber end-face. (Reprinted/adapted from [91]).

In 2016, a highly improved SERS optical fiber sensor utilizing by the combination of GO/AgNPs/rGO to form a sandwich structure was introduced. The study focused on employing R6G to examine the antioxidation capability of developed sensing device. Through the optimization of photochemical deposition time, it was discovered that the highest SERS enhancement occurred at duration of 3 minutes for the AgNPs film. Remarkably, after 30 days of exposure to ambient conditions at 613 cm^{-1} , the relative intensity of R6G decreased from 229% to $79 \pm 8.61\%$, in comparison to the $5 \pm 2\%$ observed on the GO/AgNPs film. This decrease in intensity could be pertaining to the rGO film's protective action. This research might lead to the development of an low cost, long-term sustainable and very efficient SERS substrate on the end face of optical fiber [92]. Researchers explored various types of optical fibers which are specifically used for the SERS-based chemical sensing applications. The first-ever single ring hollow core optical fibers (SRHCOFs) were fabricated using a billet extrusion preform and employed as a SERS-based chemical sensor. These SRHCOFs were manufactured from lead-silicate glass (F2, Schott) by applying increasing equal pressurization values to all preform holes, leading to preferential inflation of the slightly larger outer holes. The objective of this study was to utilize these fibers for guiding the visible portion of the spectrum and performing Raman spectroscopy of methanol [93]. Figure 12(a) depicts a close-up view of the

fiber with different focusing position utilized in Raman sensing, while the Raman spectrum obtained from this fabricated hollow core fiber is presented in Figure 12(b).

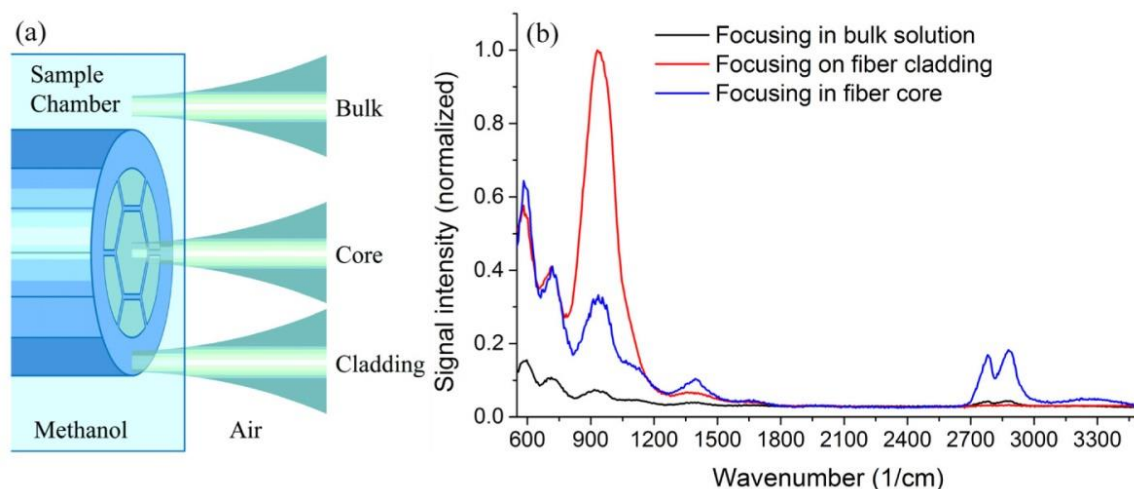


Fig. 12: (a) Different focusing locations of the fiber and, (b) Raman spectrum of proposed sensor. (**Reprinted/adapted from** [93]).

Cao *et al.* demonstrated a unique approach for fabricating high-performance optical fiber SERS probes capable of distant sensing by thiol functionalizing tapered silica fiber and then nucleating and developing AgNPs in situ [94]. Figure 13(a) and (b) display the optical micrograph and SEM images of the tapered fiber probes, respectively. Using an adaptable commercialized Raman spectrometer, the fabricated fiber probes demonstrated efficient identification of the analyte 4-ATP, achieving an impressive LOD of 2.15×10^{-11} M. Additionally, these fiber probes exhibited good repeatability, with a RSD of 7.6%, and maintained excellent signal stability at room temperature over a span of one month. The SERS spectrum of fiber probe silanized with 3-mercaptopropyltrimethoxysilane (curve 1) and -mercaptopropyltriethoxysilane (curve 2) at a concentration of 10^{-7} M for 4-aminothiophenol depicted in Figure 13(c). Furthermore, this innovative technique offers valuable insights regarding the manufacturing of fiber SERS probes, with considerable benefits for the purposes of sensitivity, stability and reproducibility showing its great practical applications.

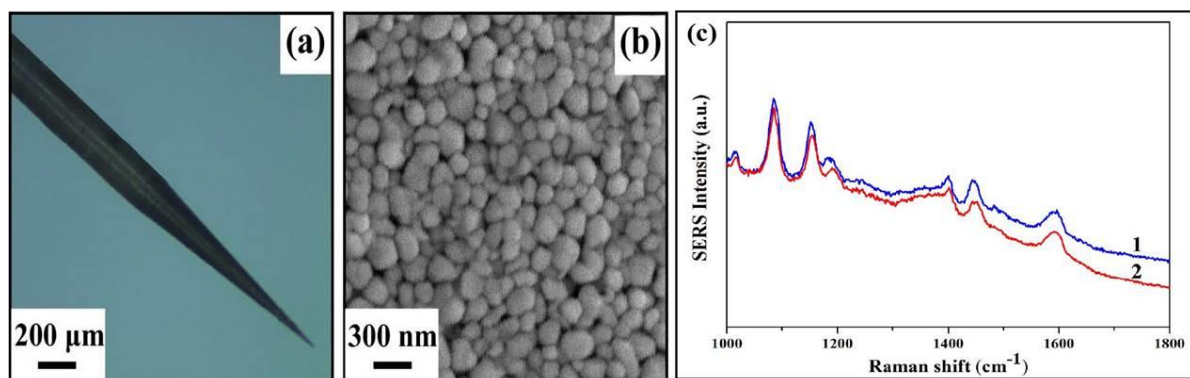


Fig. 13: (a) Microscope image of optrode (b) SEM image of 3-mercaptopropyltrimethoxysilane silanized optrode anchored with [AgNPs](#). (c) SERS spectrum

of 3-mercaptopropyltrimethoxysilane silanized fiber probe at a 10^{-7} M concentration
(Reprinted/adapted from [94]).

In 2019, Liu *et al.* introduced an innovative approach by proposing a micro-coffee-ring-patterned (MCRP) fiber SERS probe, aiming to achieve remarkable sensitivity and reproducibility in SERS detection. By using the laser-induced dynamic dip-coating method, the MCRP on the fiber facets were created [85]. Figure 14 (a) depicts the scanning electron microscope image of the fabricated MCRP SERS fiber probe and (b) shows the enlarge view of the SEM image of the fabricated MCRP SERS fiber probe used for the sensing. The optimized SERS probes exhibit great detection sensitivity (10^{-8} M in methyl parathion and thiram aqueous solutions) and repeatability (less than 6% RSD for Raman peak intensity). The exceptional sensitivity of the MCRP SERS fiber probes can be attributed to the abundant presence of hotspots generated by the micro-coffee rings. Additionally, the remarkable reproducibility is a result of the incorporation of SERS fiber probes and reliable fiber probes production. Importantly, the abilities of these sensors to identify trace SERS in intricate fluid systems was effectively proven. This included the detection of thiram in lake water (at a concentration of 10^{-7} M), thiram in orange juice (at 10^{-7} M), melamine in liquid milk (at 10^{-6} M), and tetracycline in liquid milk (at 10^{-6} M). SERS spectrum of the fabricated MCRP fiber optrode sensing device for methyl parathion and thiram aqueous solutions detection and seven different probe with different dip coating cycle is used for the measurement as shown in figure 14(c). These results highlight the capability of MCRP SERS fiber probes for SERS detection in complex liquid environments.

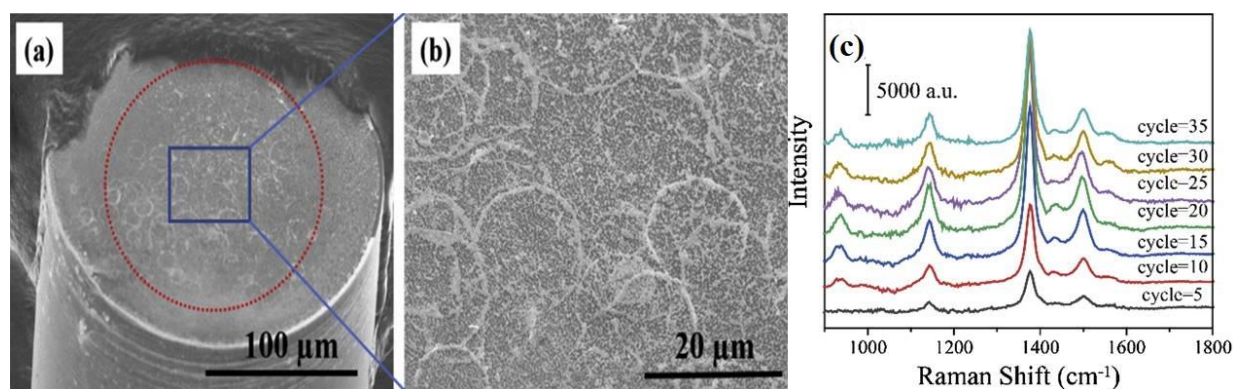


Fig. 14: (a, b) SEM images MCRP optrode, (c) SERS spectrum of MCRP optrode with various dip-coating cycles (Reprinted/adapted from [85]).

In their ground-breaking study, Long *et al.* introduced a novel concept of a restricted Gaussian distributed electromagnetic field for an SERS fiber probe, incorporating two key influencing variables: the LSPR of Ag and the waveguide propagation of the optical fiber [95]. A new SnCl_2 sensitization assisted solvothermal approach was used to create a very sensitive and repeatable SERS fiber probes. Figure 15 depicts the experimental setup for the SERS sensing and silver nanoparticles (AgNPs) coated optical fiber facet. Typically, the excitation light is directed towards the central region of the fiber core, travels through the SERS fiber probe, and engages with silver nanoparticles located at the distal end. Subsequently, the Raman

scattering light is conveyed in reverse through a singular optical fiber. There is evidence of LSPR-induced electromagnetic amplification. Silver particles have lower diameters and narrower interparticle gaps after a sensitization operation, which greatly influences the LSPR and electromagnetic amplification of the probe.

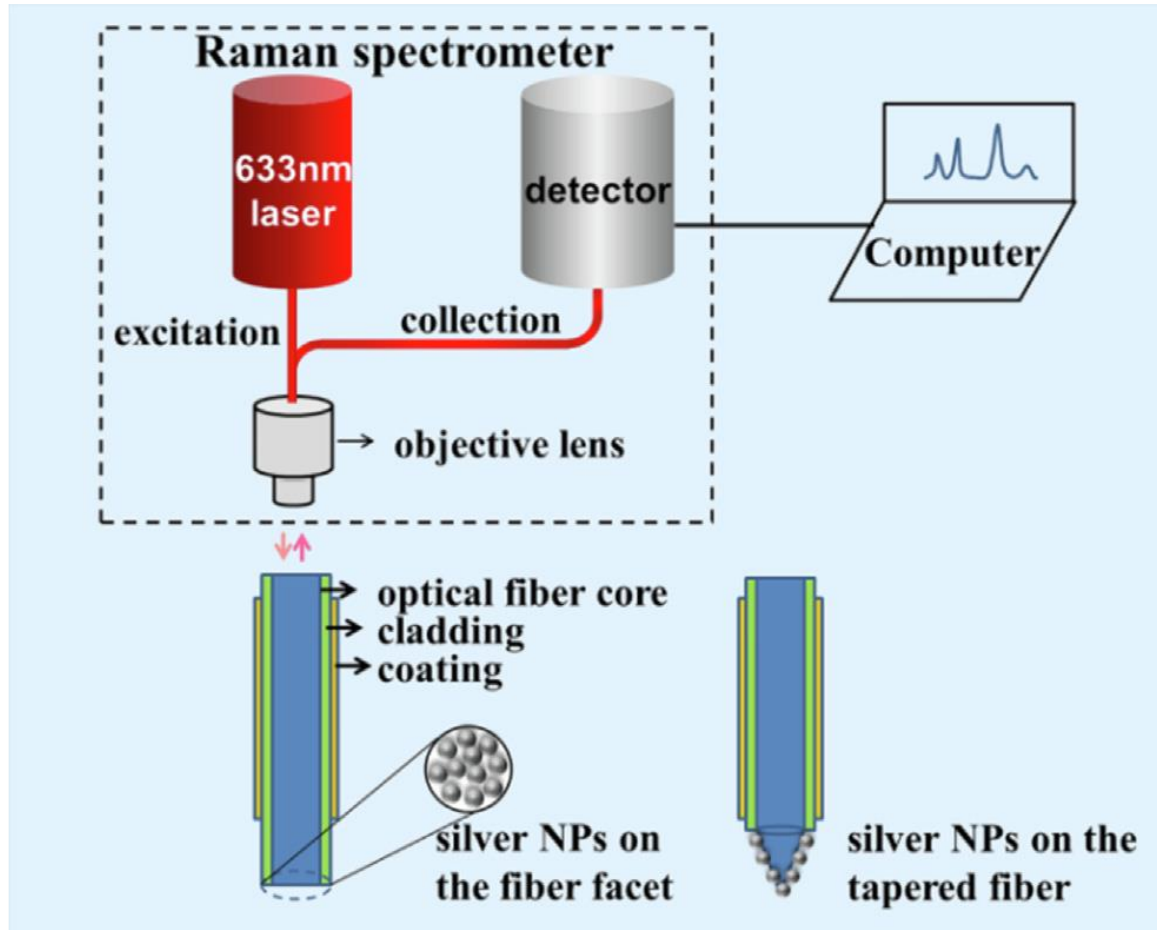


Fig. 15: Experimental SERS setup for SERS optical fiber probe and two different configurations of optical fiber probes coated with AgNPs (**Reprinted/adapted from [95]**).

Collard *et al.* proposed a novel approach in their study, wherein they leverage the information stored in multimode optical fiber modal propagation to provide reconfigurable oversight of spatiotemporal patterns of plasmonic resonances [86]. In the reported work, the authors utilized holography, specifically, to regulate the performance of SPR and LSPR for two different types of nanostructures i.e., periodic arrays and nanoislands. By dynamically modifying these structures, they were able to modify the distribution patterns of radiative angles and intensity. Due to their precise plasmonic resonances, periodic nanostructures are recognized for having excellent optical transmission. On the other hand, NIs has demonstrated substantial enhancement factors for SERS. The integration of gold nanoislands with a MMF is investigated as a means to create a spatially resolved SERS endoscope. The layer of nanoislands on the fiber facet facilitates strong amplification of the local field, serving as a highly active SERS substrate. Figure 16(a) showcase the plasmonic MMF design, with an inset

depicting the focused spot generated through the NIs fiber. Additionally, SEM image of NIs fiber facet is presented in figure 16(b), with scale bars indicating measurements of 50, 2 μm , and 500 nm (top to bottom) respectively. Figure 16(c) displays the transmission spectrum of the NIs fiber, where the black curve represents light collected from the entire facet and the blue curve represents the average of five different collection spots within a micrometer-sized sub-region. Figure 16(d) shows the intensity of a 30×30 array of focused spots produced via the fiber. Furthermore, Figure 16(e) depicts a histogram presenting the distribution of waist sizes for the focused spots. Figures 16(f) to (h) illustrate SERS transmission spectrum of BT molecules, with the graphs on the right displaying the spectral data while the left portion exhibits a transmission image showing the subset of activated NIs on the fiber facet. The power used for these measurements was fixed at 1 mW at the proximal facet.

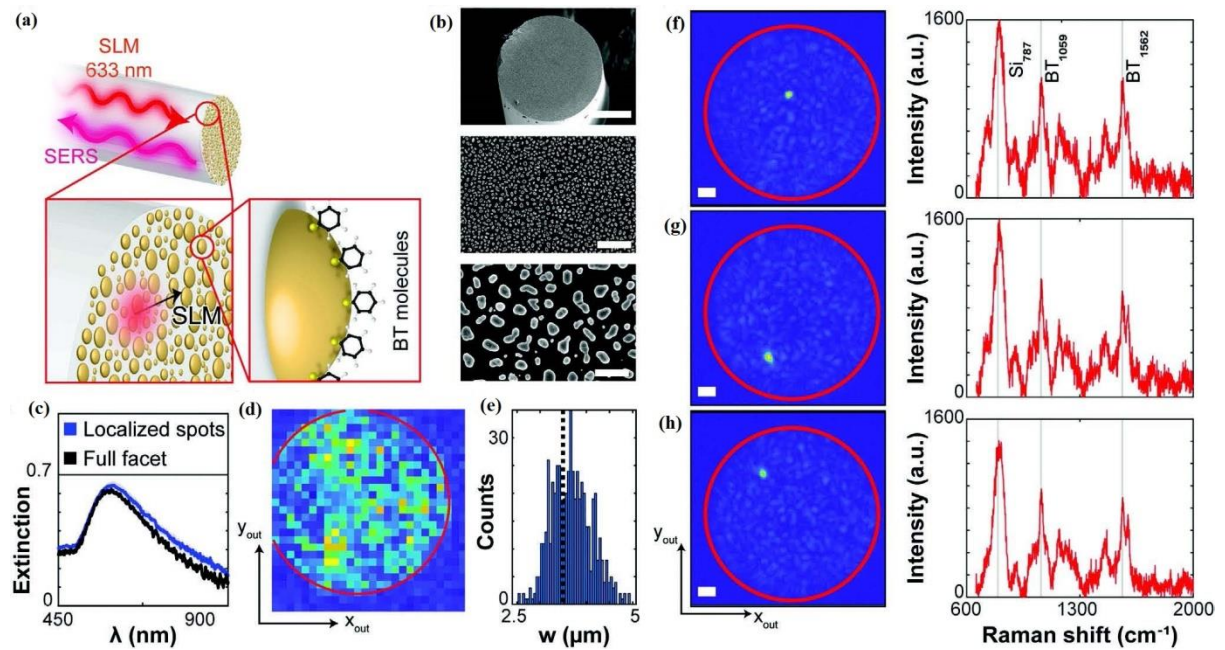


Fig. 16: Spatially resolved SERS via plasmonic MMF. (a) schematic of SERS coated MMF, (b) SEM image of nanoisland on end facet of fiber, (c) transmission spectrum of a nanoisland coated fiber, (d) intensity graph obtained from focused spots, (e) histogram plot of the focused spots, (f-h) SERS spectrum (**Reprinted/adapted from [86]**).

The amalgamation of optical fiber based neural probes with plasmonic nanostructures presents a ground breaking avenue for studying brain activity through label-free detection of chemical fingerprints using SERS. While preserving the requisite sensitivity to identify biomolecular signals in a physiological context, the creation of neuroplasmonic probes which can interact with deep brain regions with less invasiveness presents a substantial challenge. In their study, the authors propose a SERS-active brain probe consisting of a TF coated with gold NIs, which demonstrates the capability to detect neurotransmitters at micromolar levels [96]. A novel and nonplanar repeated dewetting process was developed to fabricate AuNIs having sub-10 nm gaps, ensuring their uniform distribution across the highly curved surface of the TF on a broad scale (square millimeter range in surface area). Experimental and statistical evidence

demonstrate the remarkable broadband near-field enhancement provided by the densely packed NIs layer, enabling SERS at near-infrared wavelengths. This breakthrough achieves an impressive LOD in aqueous solutions, reaching 10^{-7} M for R6G and 10^{-5} M for serotonin and dopamine. In Figure 17(a), the configuration of the NIs-TF is illustrated; showcasing measurements conducted using BT molecule functionalization, R6G, and aqueous solutions of serotonin and dopamine. Figure 17 (b) present the SERS spectrum of the BT molecule functionalized npRDW (red curve), npSDW (green curve), 10 nm thin gold film coated (black curve), and bare tapered fibers (gray curve) while 17(c) exhibit the npRDW tapered fiber measurement of R6G aqueous solutions with different concentration varying from 10^{-10} to 10^{-4} M. The inset shows the concentration dependence of the area under 1356 (blue points) and 1504 cm^{-1} (red points) after locally subtracting the background. In figure 17(d), SERS spectrum at different concentration of npRDW TF detection of serotonin aqueous solution varying from 10^{-10} to 10^{-4} M is shown, and 17(e) depicts the SERS spectra of the npRDW TF detection of dopamine aqueous solution for varying concentration, and (f) SERS spectrum of dopamine in (e) with silica background subtracted is presented. For the BT molecule, the SERS signal dominates the overall spectrum, while the silica Raman signal recedes into the background. In cases of neurotransmitters and R6G, the chemical fingerprints coincides with the silica Raman background, resulting in diminished relative intensities of the molecular SERS signals. Notably, R6G SERS displays slightly higher relative strength compared to the other two neurotransmitters due to its lower LOD. The relative intensities of dopamine and serotonin SERS are equal, indicating the same LOD for both neurotransmitters.

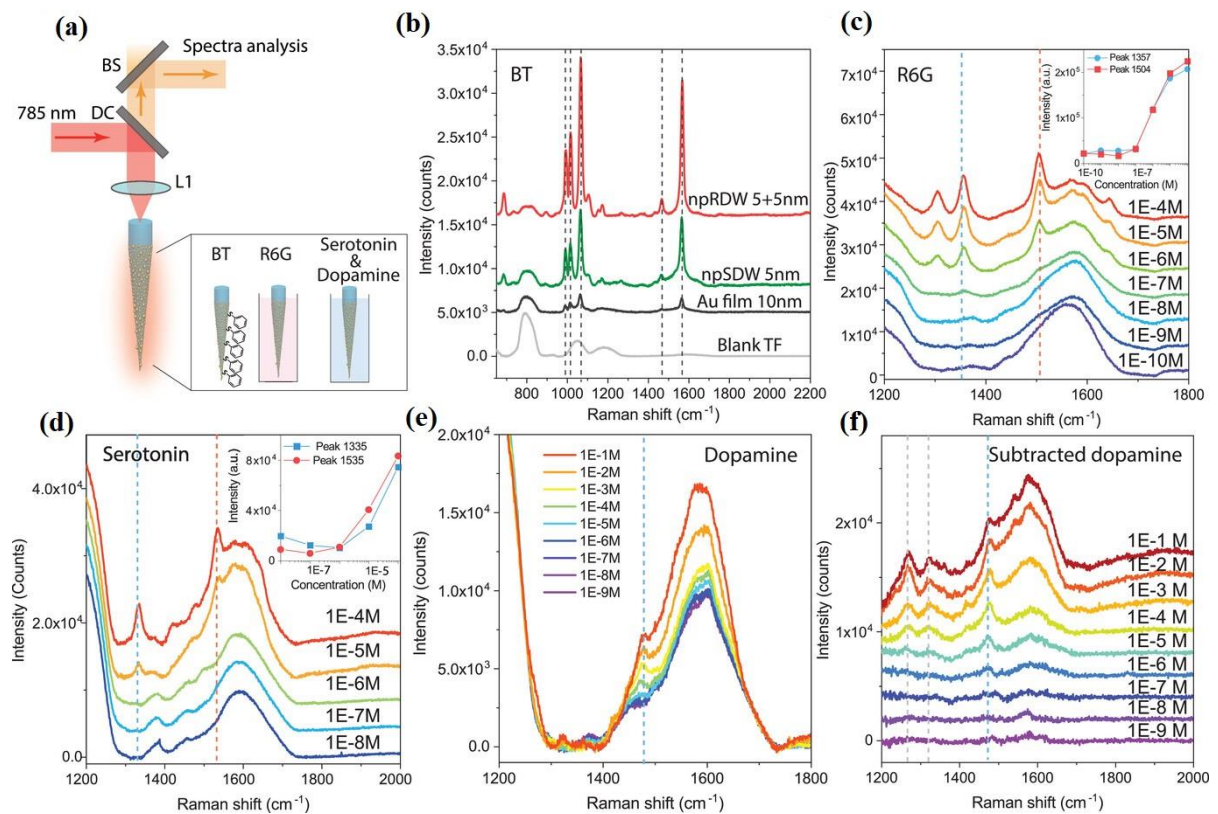


Fig. 17: (a) Experimental setup for the Raman measurement for the different aqueous solutions, (b) SERS spectrum of npRDW, npSDW, 10 nm thin gold film coated, and bare

tapered fibers, (c) npRDW tapered fiber measurement of R6G aqueous solutions, (d) npRDW TF detection of serotonin aqueous solution, (e) npRDW TF detection of dopamine aqueous solution, and (f) SERS spectrum of dopamine in (e) with silica background subtracted. (Reprinted/adapted from [96]).

To summarize, the evolution of SERS-based optical fiber chemical sensors is an attractive field of study with intriguing applications. These sensors have unique benefits such as distant sensing and the ability to interface with existing fiber-optic communication networks. These sensors can detect and identify tiny levels of numerous chemical and biological contaminants in real-time and in-situ by leveraging the excellent selectivity and sensitivity of SERS. As technology continues to progress, SERS-based optical fiber chemical sensors are anticipated to assume a progressively crucial role in various sectors. These sensors offer a practical solution for addressing critical challenges and expanding our understanding of the environment across multiple domains. Table 1 summarizes the reported optical fiber SERS based chemical sensors.

Table 1. Comparative table showing various SERS-based optical fiber chemical sensors

Ref.	Type of probe	Target analytes	SERS substrate	Operating range	LOD
[83]	Multimode fiber tip	4-aminothiophenol	AgNPs	10^{-7} M	N.A.
[97]	Suspended core PCF	4-Aminothiophenol, Haptoglobin in ovarian cyst fluid	AuNPs	NA	N.A.
[84]	Multimode fiber	4-aminothiophenol	Ag nanopolyhedra	10^{-6} M to 10^{-9} M	10^{-9}
[98]	Silica-based fiber tip	4-aminothiophenol	AgNP	10^{-5} M to 10^{-9} M	10^{-9}
[99]	Tapered multimode optical fiber tip	Rhodamine 6G	AuNPs	10^{-5} mol/L to 10^{-8} mol/L	10^{-8}
[100]	Fiber tip	Metal (Cd^{2+}) ions	AgNP	0, 10 μM , 20 μM , 80 μM and 200 μM	N.A.
[94]	Multimode fiber tip	4-aminothiophenol	AgNPs	10^{-2} M to 10^{-6} M	2.15×10^{-11}
[89]	Multimode fiber tip	Nile blue A Rhodamine 6G Oxazine 170 Cardiogreen	AgNP	5 μM 10 μM 5 μM 10 μM	N.A.

[101]	Multimode fiber	Glycerol solution	AgNP	0 to 30% (v/v)	4 mM
[102]	Fiber tip	4- aminothiophenol	AuNP	0.2 M	-

4.2. **SERS in Biosensing**

Optical biosensors are a class of biosensors, different from electrochemical ones, that have attracted the attention of the scientific community over the last years and still have a growing consideration in cutting-edge applications, ranging from clinical diagnostics and personalized medicine to monitoring of environmental parameters and conditions [103]. Those based on optical fibers enable fascinating and peculiar light management at unprecedented and outstanding levels, together with other inherent features, that other optical technology platforms can hardly attain [89,90]. Regardless of the optical fiber configuration used that underpins different types of surface waves (evanescent waves, Bloch waves, surface plasmon polaritons, waves related to lossy/leaky mode or derived from guided mode, etc.), the interaction of light traveling within the fiber with the surrounding environment by the evanescent field allows assessing any change in RI occurring in the region surrounding the fiber [91]. More specifically in biosensing, any binding event that occurs between a biological recognition element (BRE) grafted onto the sensing region of the fiber and the target analyte brings about a change in surface RI, which can be measured using optical methodologies. For the sake of clarity, the change in surface RI is related to the biomolecular overlay surrounding the fiber and can entail a change in the effective RI of the surrounding medium and/or in the thickness of the overlay [92]. Fulfilling a specific coupling condition of fiber modes, these technology platforms feature an optical resonance (attenuation dip or absorption peak) in their transmission or reflection spectrum whose characteristics vary as a function of the surface RI. In addition, micro/nano optical fiber sensing platforms, together with NPs, nanofilms, or nanostructures, enable tailoring the light-matter interaction with remarkable resolution, precision, and accuracy, therefore envisaging advanced technology platforms with ultra-high performances [108,109].

Among the various spectroscopic optical techniques, SERS which boasts million-fold enhancement in the Raman signals by using suitable SERS substrates is one of the most promising, sensitive, and powerful techniques for developing an optical biosensor. SERS-based biosensors possess the following advantages in comparison to other optical techniques [110]:

- the capability of reflecting the fingerprint information of biomolecules;
- ultra-high sensitivity down to the single molecule level;
- narrow peak bandwidth with good resistance to photobleaching and photodegradation compared with fluorescence;
- many choices of substrates with different sizes and shapes for signal enhancement depending on the application;
- the capacity of detecting multiple analytes at the same time using different Raman reporters;

f. larger light penetration depth facilitating both *in vitro* and *in vivo* diagnosis and imaging.

As sketched in Figure 18, there are mainly two schemes for the design and development of SERS-based biosensors [111]: direct (or label-free) detection and indirect detection needing SERS reporters, similar to a labelled-based approach. In the former (Figure 18(a)), direct detection enables to obtain the fingerprint information of biomolecules since the intrinsic molecular vibrations are monitored without the need for any label. The confinement of biomolecules near the electromagnetic (EM) field of the enhancing substrates allows biosensing via SERS. However, surface-bound affinity agents are required for biomolecules that are unable to stay in this area or in case of a small concentration of the analyte [112]. The main shortcoming of direct biosensing with SERS stems from the detection mechanism itself. The signals from some biomolecules are very weak and complex and tend to be hidden by signals coming from interfering molecules present in the biological matrix. This last is mostly true when the analyte under investigation is spiked in real biofluids (like serum, blood-plasma, etc.) [98]. Conversely, indirect SERS biosensing relies on specific SERS signals coming from SERS reporters (like labeled biomolecules) that are grafted on the enhancing substrate via chemically-attached metallic NPs. Therefore, this type of biosensing is built up by three main components: Raman reporters that inherently possess high Raman scattering cross-section to provide the featured peaks as readout, metallic NPs or nanostructures with strong EM fields to improve the Raman signal, and ligands grafted via the nanostructures to detect the specific target analyte. In this case, the SERS signal can be observed and recorded only when the analyte is bound to:

1. The BRE in response to a binding event as in Figure 18(b);
2. The SERS reporters are directly in response to environmental property changes, such as the pH value, ionic concentration, or temperature, which indicate a change in the biological environment as in Figure 18(c).

Indirect SERS biosensing disregards the advantage of giving the direct molecular fingerprint but enables the possibility of qualitative and quantitative detection of biomolecules due to the inherent features and stable signals of SERS reporters, which can specifically be envisioned during the design and development of the biosensors.

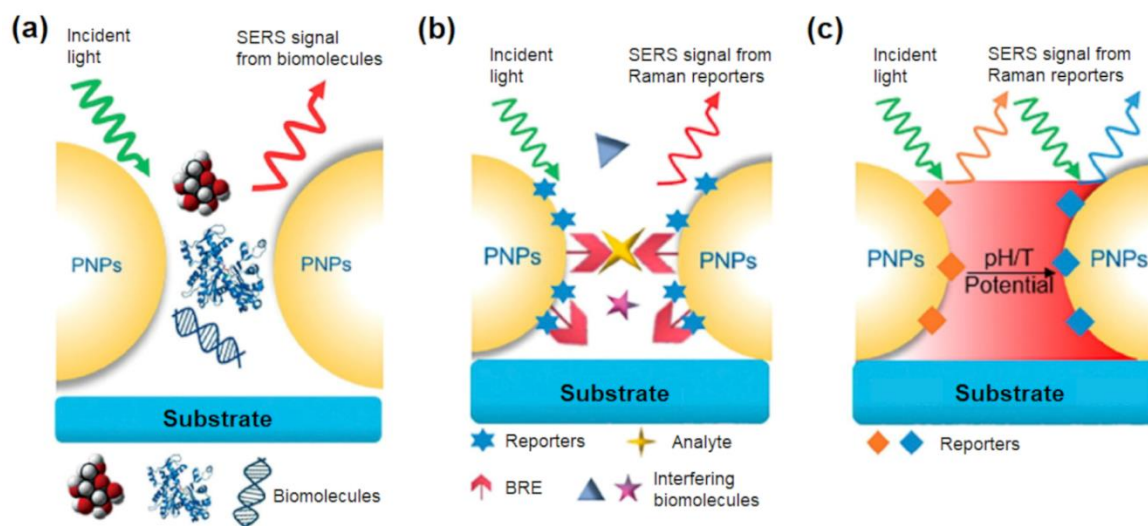


Fig.18. Sketch of SERS-based biosensors. (a) Direct SERS detection in which the inherent SERS signal of biomolecules is captured from the substrate without any additional label. (b) Indirect SERS detection in which the SERS signal is retrieved from Raman reporters as an indirect response to a binding event between the BRE and the investigated analyte. (c) Indirect SERS detection in which the SERS signal is retrieved from Raman reporters as indirect response to variations in the environmental features. Reprinted/adapted from [110]. PNPs: plasmonic NPs.

The use of optical fibers as enhancing substrate with different sensing configurations and fiber types is spreading in recent years. There are several advantages for using optical fibers as SERS enhancing substrate in comparison to chip-based or paper-based devices, such as commercially-available manufacturing, highly automatized operation, μL -level volume of samples and reagents, high sensitivity and low LOD [99]. In addition, given the fiber peculiarities, it is possible to realize both label-free direct SERS and indirect SERS platforms that make SERS a powerful tool in biological and biomedical sensing, especially for the detection of biomolecules such as proteins, DNA and microRNA, and for monitoring biological features of molecules. There have been several applications of optical fibers in Raman spectroscopy, but just a few of them exploit SERS for the development of a compact biosensor. More specifically, it is possible to distinguish two cases:

- i. Unidirectional SERS probe where optical fibers are used as unidirectional light propagation medium, to inject and collect the light related to a SERS signal (Figure 19(a)), to collect the light from an external illuminating source (Figure 19(b)) or to guide the light from the enhancing substrate to an external Raman detector (Figure 19(c));
- ii. Bidirectional SERS probe where optical fibers are used as bidirectional light propagation medium to develop complete and compact SERS biosensors, and hence optical fibers are not just used to inject or collect the light, but also to host the enhancing substrate suitably functionalized to immobilize a BRE (Figures 19(d)-(e)).

In the former, the enhancing substrate can be located externally from the optical fiber as in Figure 19(a), or can be embedded within the optical fiber exploiting its own structure as in Figure 19(b), or, eventually, on the optical fiber as in Figure 19(c). In the latter, different types of metallic nanostructures are realized at the fiber end that is cleaved or made as a tip. In both

cases, the light traveling through the fiber interacts with the nanostructures that represent the SERS-active surface, which generates the SERS signal that in turn is collected back from the fiber, which directly carries on the SERS signal (Figures 19(d)-(e)).

Bidirectional SERS probes can be developed using a fiber bundle or a single optical fiber. This configuration enables *in situ* and, eventually, *in vivo* measurements of multiple analytes by dipping the probe in the desired solution or by inserting the probe into a tissue, organ, or part of the body, and then measuring the reflected spectra. In addition, this approach allows embedding the SERS fiber probe into a microfluidic system or chip toward the development of a portable and compact device.

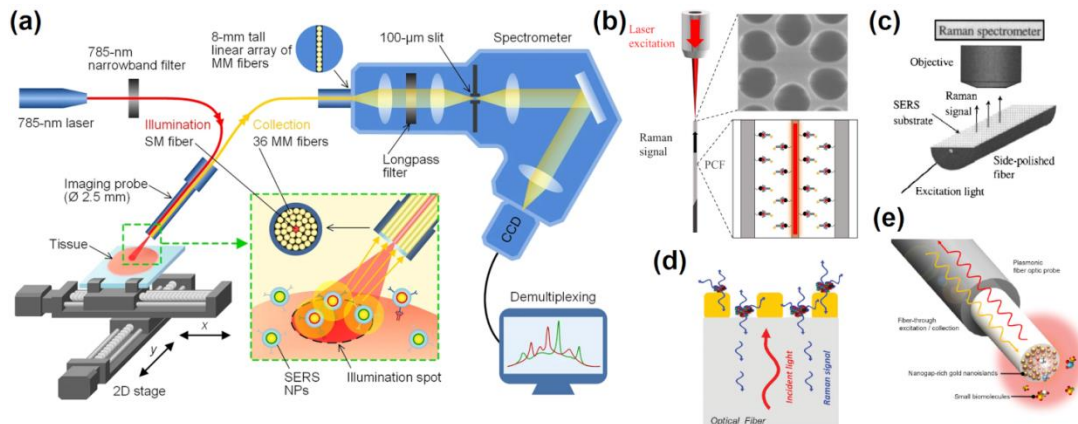


Fig.19. Sketch of optical fiber-based SERS biosensors. (a) Unidirectional SERS biosensor where optical fibers are separately used to inject and to collect the light carrying on the SERS signal (Reprinted/adapted from [115]). (b) Unidirectional SERS biosensor where an optical fiber collects the SERS signal when an external illuminating laser source is used (Reprinted/adapted from [116]). (c) Unidirectional SERS biosensor where an optical fiber brings the light to the enhancing substrate and the SERS signal is collected from a Raman detector (Reprinted/adapted from [15]). (d)-(e) Bidirectional SERS biosensors where the optical fibers act as light carrying source and detector of the Raman signal (Reprinted/adapted from [49] and [53]).

Till now, the mentioned optical fiber-based SERS biosensors are built on the integration of the fiber tip or cleaved end surface with metallic nanostructures of different shapes or patterned layers. In all these cases, the light-matter interaction is underpinned by the strong EM field enhancement due to the excitation of optical (mostly plasmonic) resonances. A separate footnote must be dedicated to photonic crystal fibers (PCFs) or microstructured optical fibers (MOFs). These configurations that come out later than single-mode (SMF) or multi-mode (MMF) fibers allow in principle to develop both unidirectional and bidirectional SERS probes [101]. PCFs and MOFs enable efficient light control and trapping on sub-wavelength scales. Given the inherent structure, it is not easy at all to effectively functionalize the sensing surface, and becomes more complicated to work with biofluids in a real application scenario. Conversely, the low loss feature of most dielectric or semiconductor materials at VIS-NIR wavelengths permits to generate of a resonant effect with high Q -factors, which in principle might enhance the SERS signal. Therefore, despite they are potentially very promising platforms for label-free biosensing, there is a very limited number of such devices developed for SERS biosensing in the literature.

Here, the most relevant examples of SERS-based optical fiber biosensors are presented, and applications such as *in vitro* bioanalysis, determination of the *ex vivo* biofluids or cellular systems, detection of biomolecules such as proteins and nucleic acids, as well as monitoring of cellular pH, temperature and ionic environment, are briefly described. The first example of a bidirectional optical fiber-based SERS device was reported by *C. Viets and W. Hill* in 1998 [57], where different techniques were studied for the fabrication of precisely roughened metal layer on the tip of the fibers. Two years later, a work from David L. Stokes and Tuan Vo-Dinh [55] came out, where a novel single mode fiber was developed to generate the SERS effect by incorporating alumina nanoparticle and Ag coatings on the tip of fiber. However, in both cases, the Authors tested the device using liquid solutions of chemical compounds, and hence any biosensing device was developed indeed.

The first real example of an optical fiber-based SERS biosensor was described by Scafid di *et al.* in 2009 [117]. The fiber tip was covered with silver island film (AgIF) to excite the plasmonic effect and, subsequently, the nanoprobe s were functionalized using *para*-mercaptobenzoic acid (pMBA). The device's effectiveness was tested by means of the monitoring of intracellular pH in HMEC-15/hTERT immortalized “normal” human mammary epithelial cells and PC-3 human prostate cancer cells. A sensitive and selective means to monitor cellular microenvironments at the single cell level was pinpointed by assessing the change in the physiological pH from pH 6.0 to pH 7.5 due to the cellular degree of protonation/deprotonation. This enabled for the very first time to envisage a kind of cell manipulation using optical fibers.

Following the previous work, Wang *et al.* in 2019 developed a SERS-active fiber tip for intra and extra cellular pH sensing and microenvironment analysis in living cells [118]. The Authors built a single cell analysis platform by using Ag NPs decorated optical fiber tip with a diameter of less than 500 nm and with embedded micro-functionalities for sensing, cell manipulation, and *in-situ* spectroscopy and imaging, especially for exploring the subcellular microenvironment (Figure 20(a)). In view of the fiber flexibility and other peculiarities, Ag NPs and pH sensitive Raman reporters were both modified on the fiber tip surface by the one-step laser-induced Ag deposition method using 4-mercaptopyridine as a probe molecule. The Raman spectra of intracellular (pH_i) and extracellular (pH_e) pH of human non-cancer and cancer cell lines, such as liver cell line (LO2) and hepatoma cell line (HepG2), were recorded in terms of normalized intensity (Figure 20(b)). Figure 20(c) shows an SEM image of the locations (red, intracellular; yellow, extracellular) where the pH measurements were carried out with the fiber tip. The related histograms are shown in Figure 20(d) with an exposure time of 10 s.

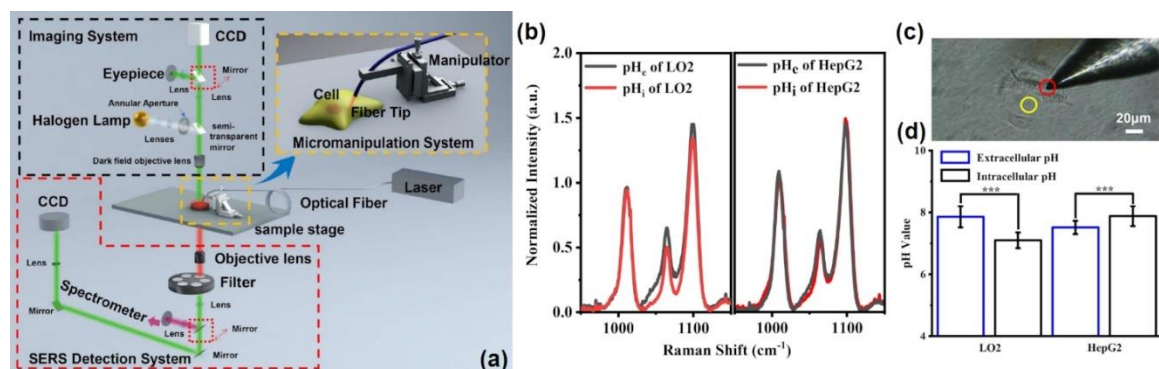


Fig.20. (a) Sketch of the multi-functional micro-manipulation system for imaging and SERS detection. **(b)** Extracellular and intracellular pH of LO2 and HepG2 cell line. **(c)** Locations of the pH measurements for intracellular (red circle) and extracellular (yellow circle) pH sensing. **(d)** Histogram of pH value from LO2 and HepG2 cell line with an exposure time of 10 s. (**Reprinted/adapted from** [118]).

Afterward, in 2011, Yang *et al.* reported an effective example of the development of a bidirectional SERS probe based on optical fibers (Figure 21(a)) [119]. The Authors described the detection of the proteins lysozyme and cytochrome c, as well as the live bacterial cells of *Shewanella oneidensis* MR-1 in aqueous solutions, by using two different configurations of bidirectional optical fiber-based SERS biosensors and cetyltrimethylammonium bromide (CTAB)-capped/citrate-reduced Ag NPs. SEM and TEM images of Ag NPs are shown in Figures 21(d) and 21(e), respectively. The former fiber configuration was a tip-coated MMF (Figure 21(b)) with a double-substrate sandwiched structure and a LOD of 0.2 μg/mL was achieved in protein detections. The latter one was a liquid core PCF (Figure 21(c)) with better confinement of light inside the fiber core, and hence a LOD of 10⁶ cells/mL was attained for the bacteria detection.

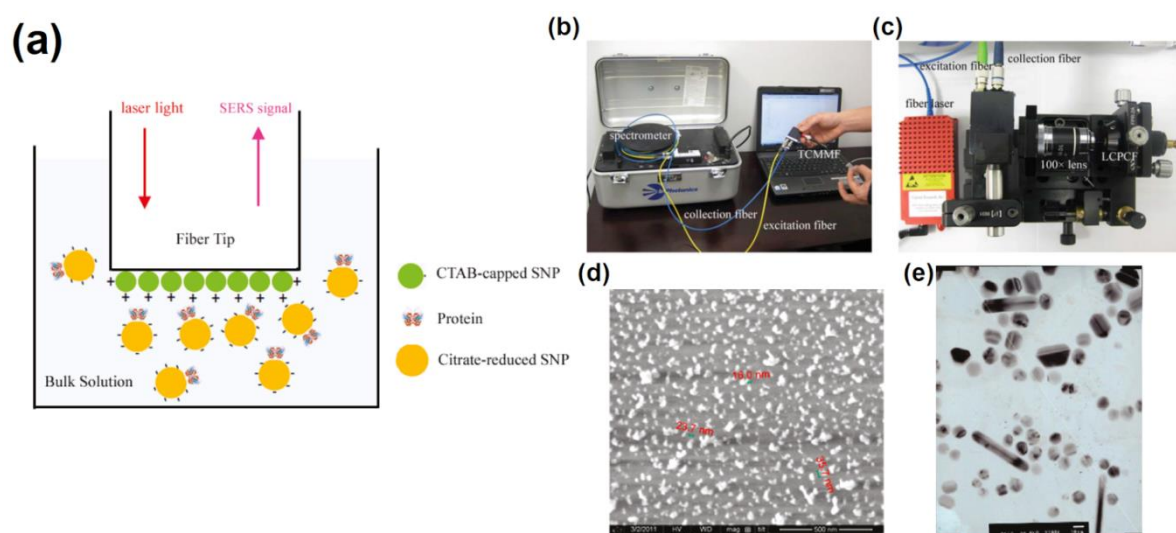


Fig.21. (a) Sketch of the tip-coated MMF SERS probe used for the detection of proteins in the aqueous environment **(b)** Experimental setup of the tip-coated MMF portable SERS system and **(c)** of the liquid core PCF portable SERS system. **(d)** SEM image of the

cetyltrimethylammonium bromide (CTAB)-capped Ag NPs coated on the fiber end. **(e)** TEM image of the citrate-reduced Ag NPs. **(Reprinted/adapted from [119] and [120]).**

Another interesting example of the detection of multiple cancer biomarkers using the combination of SERS and hollow core PCFs was reported by *U.S. Dinish et al.* in 2014 [22]. Axially aligned air channels of hollow core PCF provided an excellent platform for optical biosensing using bidirectional SERS, as shown in the SEM image of Figure 22(a). The central inner core was functionalized using poly-L-lysine (PLL), while three SERS nanotags were prepared from Raman reporter molecules: Cyanine 5 (Cy5), malachite green isothiocyanate (MGITC) and naphthalene thiol (NT). These three reporters were selected for the multiplexed detection of cancer biomarkers using antibody-conjugated SERS-active nanoparticles. A sketch of the proposed biosensing system is detailed in Figure 22(b). The Authors initially performed the detection of epidermal growth factor receptor (EGFR) biomarker in oral squamous carcinoma cell lysate using the three different SERS nanotags [121]. In this case, the lowest detected concentration (LDC) was 100 pg/mL which represented a big progress in performance at that time. Subsequently, the simultaneous detection of hepatocellular carcinoma (HCC) biomarkers-alpha fetoprotein (AFP) and alpha-1-antitrypsin (A1AT) secreted in the supernatant from Hep3b cancer cell line was carried out using the same fiber structure. Despite any complete assessment of the performance was carried out in terms of LOD or specificity, this work represented a milestone as it was the first example where multiple biomarkers were detected using an optical fiber biosensing system.

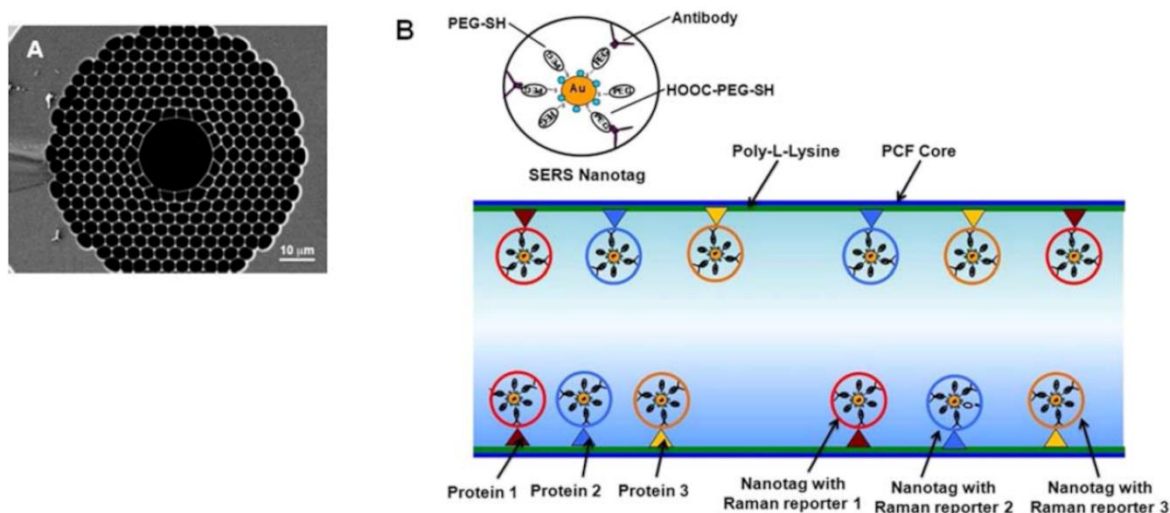


Fig.22. (a) SEM of the cross-section of hollow core PCF. **(b)** Sketch of the binding of SERS nanotags with immobilized biomarkers inside the core of hollow core PCF for multiplex detection of target analytes. **(Reprinted/adapted from [22]).**

Another example of labeled PCF-based SERS biosensor was reported by *Gong et al.* in 2016 [122]. In this case, a side channel PCF was used as SERS enhancing substrate that enabled to accurately monitor in-cellular modifications of lipid peroxidation-derived protein. The sketch of the drawing process of the home-made side channel PCF is shown in Figure 23(a), while its preparation for SERS detection is depicted in Figure 23(b). The proposed bidirectional

SERS probe incorporated linoleamide alkyne (LAA), which was oxidized and, subsequently, modified proteins in cells with an alkyne functional group that induced the lipid peroxidation by means of the interaction with cumene hydroperoxide (CH) at different concentrations (5-150 μM). By injecting the side channel of PCF with a mixture of Au NPs and LAA treated cells and, subsequently, measuring the interference-free alkyne Raman peak from these proteins in cells, a strong SERS signal was achieved (Figure 23(c)). With a LOD of 5 μM calculated from the dose-response curve (Figure 23(d)), the platform provided a method for the rapid monitoring of lipid peroxidation derived protein modification in cells.

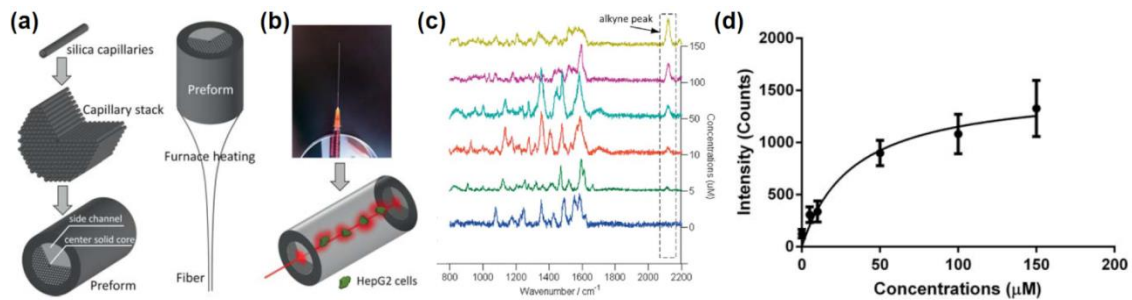


Fig.23. (a) Sketch of drawing procedure to manufacture of side channel PCF sensor. (b) Preparation of side channel PCF-based sensor and schematic of the SERS detection process. (c) Raman spectra of cells treated with different concentrations of cumene hydroperoxide. (d) Dose-response curve as a function of Raman signal Intensity of the alkyne peak at 2113 cm^{-1} . (Reprinted/adapted from [122]).

Still using hollow core PCFs, Khetani *et al.* in 2015 demonstrated that the optimal volume and size of Ag NPs enabled to maximization of the Raman signal enhancement (Figure 24(a)) [123]. By integrating hollow core PCF with nanoparticles, a portable label-free biosensing system was proposed to detect malignant cells, such as HL60 acute myeloid leukemia, in the range of 310-25000 cells/mL. The main advantage of the proposed system was the possibility of rapid analysis and diagnosis. In addition, the system was endowed with a very low LOD of 300 cells/mL and also allowed to distinguish between apoptotic, live, and necrosis cells at different stages given the different features in Raman spectra (Figure 24(b)) and thanks to the support of multivariate data analysis, such as principal component analysis (PCA) and partial least squares (PLS).

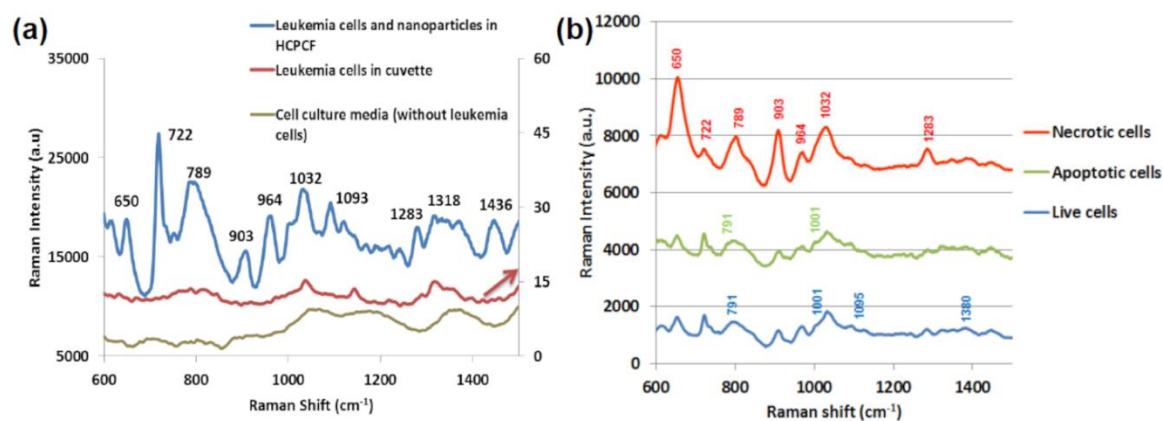


Fig.24. (a) Raman signal enhancement of HL60 leukemia cells in hollow-core PCF using Ag nanoparticles. **(b)** Raman spectra of leukemia cells at different stages with distinguishing Raman peaks in live, apoptotic, and necrotic cells. (Reprinted/adapted from [123]).

Regarding the detection of dopamine, a neuromodulatory molecule that plays several important roles in cells, there are several examples in the literature where optical fibers were used as SERS-active enhancing substrates. In the first example in 2016, Raj *et al.* developed an SPR-based optical fiber sensing system for the detection of dopamine using green synthesized Ag NPs as SERS sensing material [124]. Easy green synthesis of stable Ag NPs extracted from flowers of *Acmella oleracea* and dispersed in polyvinyl alcohol (PVA) matrix was envisaged as a novel approach in NP synthesis and then applied to an optical fiber substrate for SERS sensing. The response time of the device was 6 min in a range from 30.6 ng/mL to 12.3 μ g/mL and the LOD was roughly 30.6 ng/mL. Very recently, a big leap in performance was attained by Tran *et al.* in 2022 [125]. Integrating noble-metal and organic-inorganic hybrid crystalline porous materials, it enabled the enhancement of the Raman signal. Specifically, the Authors combined Au NPs with metal-organic frameworks (isoreticular metal-organic framework-3, IRMOF-3) developing hybrid composites. The incorporation of hot electrons produced on the surface of Au NPs with IRMOF-3 and their utilization of the porous structure significantly enhanced the LSPR effect, leading to effective capture of the target analyte. The fiber-based biosensor was embedded into a microfluidic system as shown in Figure 25(a). When dopamine is injected through microfluidics, the strong target specific affinity among the modified surface out-layer of optical fiber sensor and the measurand molecule resulted in a change in the optical power transmission signal. The device attained a very low LOD of roughly 0.2 ag/mL in a wide linear range from 1.5 ag/mL to 15.3 pg/mL (Figure 25(b)).

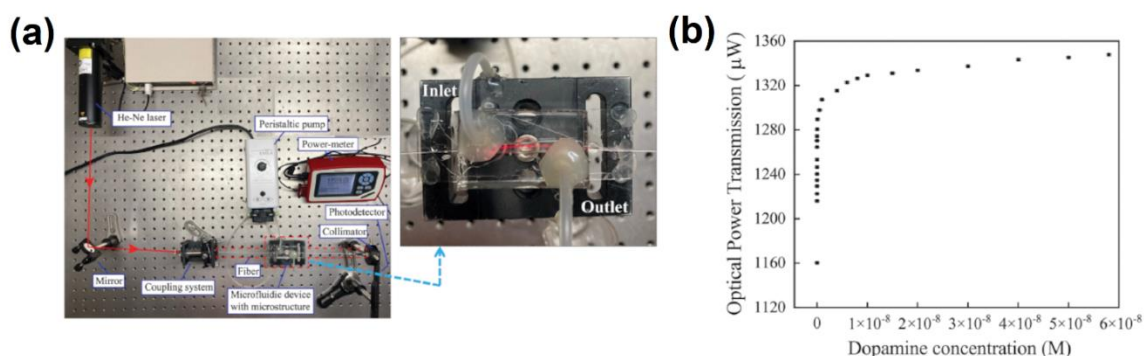


Fig.25. (a) The experimental setup consisting of the optical fiber biosensing system and PSMS microfluidics. **(b)** Dose-response curve as a function of the dopamine concentrations from 0 (blank sample) to 92 pg/mL. (**Reprinted/adapted from** [125]).

Thanks to the big steps forward of the technological tools and of the novel nanomaterials, Kwak *et al.* in 2019 monolithically manufactured nanogap-rich Au nanoislands on the tip of an MMF using repeated solid-state dewetting of thermally evaporated Au thin film, which enabled bidirectional SERS sensing [53]. The sketch of the device is shown in Figure 26(a). Single or repeated solid-state dewetting of thin Au film generated nanogap-rich Au nanoislands with highly dense and strongly coupled EM fields, such as plasmonic hotspots, and hence underpinned strong light excitation, as well as highly sensitive SERS detection of biomolecules compared to the single dewetting (Figure 26(b)). As a proof of concept, label-free SERS detection of folic acid (FA) in the concentration range of 0.44-440 μg/mL (1 μM – 1 mM) was carried out as detailed in the collected Raman spectra of Figure 26(c).

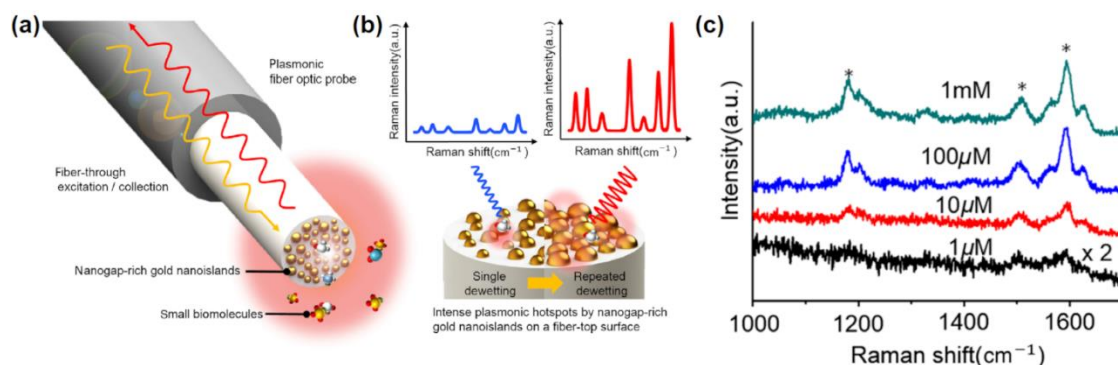


Fig.26. (a) A schematic illustration of the plasmonic bidirectional SERS-based probe, where both the laser excitation and the collection of SERS signals are transmitted through an MMF. **(b)** Plasmonic Au nanoislands are manufactured on the fiber tip surface using a single or repeated solid-state dewetting of thin Au film that improves the Raman signal. **(c)** Raman spectra as a function of different concentrations of folic acid. (**Reprinted/adapted from** [53]).

By combining low-cost polymer casting of polydimethylsiloxane (PDMS) with assembled Au NPs of varied sizes and shapes, a cap-shaped bidirectional SERS biosensing platform was developed for reversible coupling with a customized bundle of MMFs [126]. The schematic illustration of the mold piece micromachined to manufacture the elastomeric caps by means of polymer casting is shown in Figure 27(a). The acquisition of Raman spectra involved coupling

the caps with the bundle of MMF (Figure 27(b)) and using backside illumination in a reflection configuration (Figure 27(c)). The highest enhancement of the Raman signal was obtained when NP-decorated substrates were resonantly coupled with the plasmonic excitation at the irradiation wavelength in the UV-vis spectral range. The feasibility and effectiveness of the proposed device were assessed working at μM concentrations (roughly a few $\mu\text{g/mL}$) by detecting liquid biosamples of immunoglobulin G (IgG) and amyloid- β ($\text{A}\beta$) neurotoxic biomarkers, as shown in Figure 27(d) and Figure 27(e), respectively, and using specific antibodies as BRE.

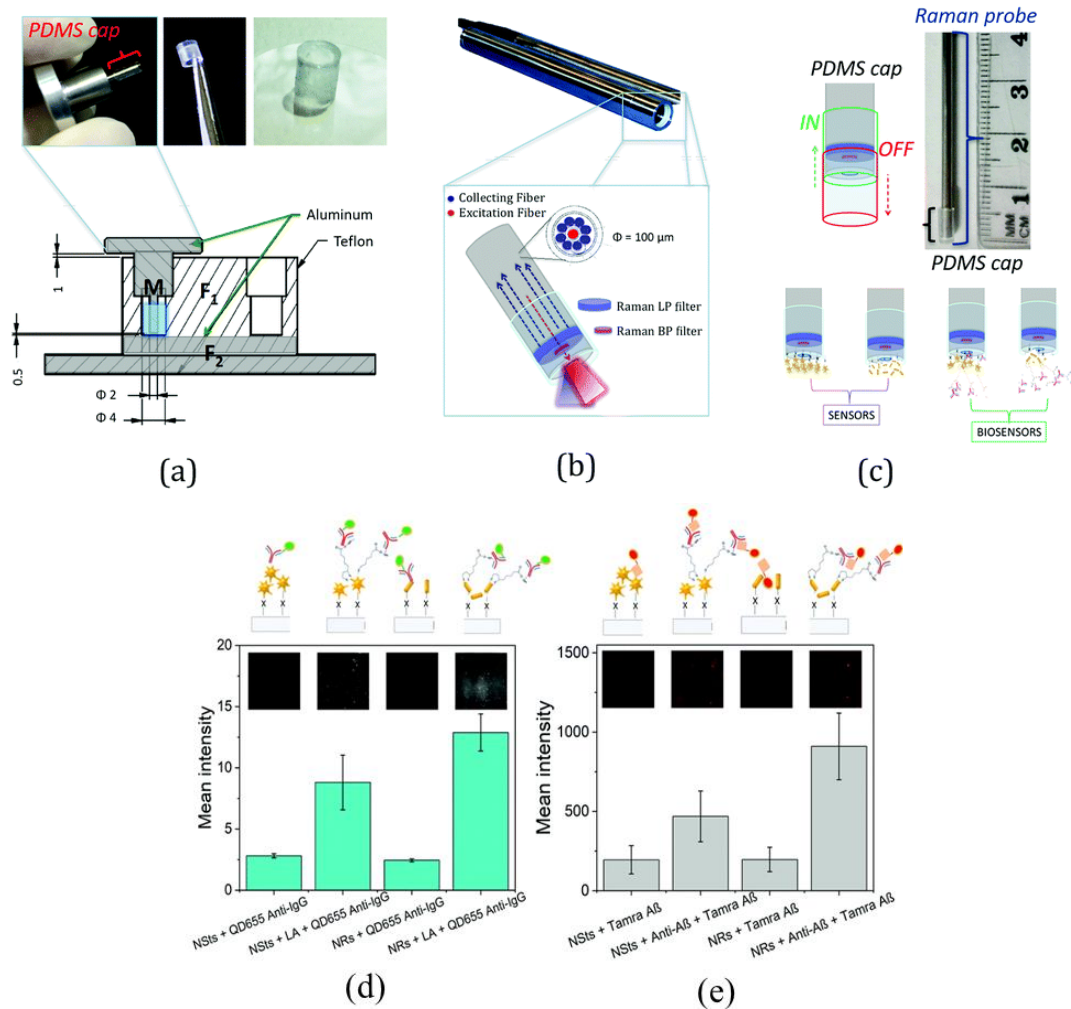


Fig.27. (a) Sketch of the mold micromachined to manufacture the elastomeric caps by means of polymer casting. (b) Sketch of the elastomeric PDMS cap to be applied from the distal end of the bundle of fibers-based Raman probe. (c) Sketch of SERS-based optical fiber biosensors in the reflective configuration. (d) Mean fluorescence intensity values of NPs- only and LA-NP-decorated substrates incubated with QD655-labeled anti-IgG. (e) Mean fluorescence intensity values of NPs- only and anti-A β -NPs decorated substrates incubated with Tamra-labeled A β . (Reprinted/adapted from [126]).

Finally, dealing with the unidirectional SERS probe, it is worth mentioning the work of Wang *et al.* in 2016 that reported the use of optical fibers to quantitatively phenotype the surface molecules of freshly excised tissues and hence to determine the presence of disease [115]. In fact, there is still a concrete need to image excised tissues during tumor-

resection procedures in order to identify residual tumors at the margins, and hence to attain their complete removal. As shown in Figure 19(a), an SMF was used as a guiding light source, while a bundle of MMFs collected the Raman signal from the tissue where SERS NPs made of Au core, Raman reporter, and silica shell, and functionalized with monoclonal antibodies were used to target specific biomarkers, such as EGFR and human epidermal growth factor receptor 2 (HER2). A range of concentrations lying in 1–400 pM was tested and validation experiments with human tumor cell lines, fresh human tumor xenografts in mice, and fresh human breast specimens demonstrated a good agreement with flow cytometry and immunohistochemistry, gold standard techniques in the field.

When developing a SERS-based optical fiber biosensor, two features mostly count for achieving high performances: the sensing mechanism often related to the type of fiber used as enhancing substrate and the nanomaterial or a combination of different nanomaterials used to generate and amplify the Raman signal. That is true in the case of bidirectional SERS probes, which represent the more interesting and promising approach to developing portable, compact, and high-performance SERS-based optical fiber biosensors.

Among the different types of fibers used to develop SERS-active substrates, it is worth distinguishing between sensing devices developed onto the tip of the fiber [53,78,117–119,126], around the outer surface of the fiber [15,124,125,127] or inside the channels/holes of MOF and PCF [77,121–123,128]. In all cases, the sensing mechanism relies on the interaction of the fiber more or modes with the medium surrounding the fiber, while the EM field is strongly enhanced by the coupling between the light traveling into the fiber and the SERS-active nanomaterial that occurs at specific wavelengths. Therefore, the enhancement of the Raman signal depends on the penetration depth of the fiber mode evanescent field that matches with the EM signature of the SERS-active nanomaterial grafted onto the fiber substrate. Regarding the SERS-active nanomaterial, Au/Ag NPs have been the first examples that come out in the literature given the easier technology and methods to develop them in a custom manner. Obviously, plasmonic structures remain the basic element to develop SERS-based devices, but the integration with hybrid nanostructures, such as metal-organic frameworks [125], or the realization of novel nanostructures, such as nanogap-rich Au nanoislands [53] or Ag nanorods [127], allows the improvement in the performance of such SERS-based optical fiber biosensing platforms, especially when low molecular weight molecules have to be detected with a weak inherent Raman signal.

Table 2 summarizes the most promising and recent examples in the literature dealing with SERS-based optical fiber biosensors. Despite in some cases, it is not possible to retrieve some performance indicators (LOD among all), it is clear however that the most fascinating manner to attain high performance might be an integration of plasmonic materials with other types of materials (non-metals or hybrids) that enhances the EM field, and hence the Raman signal [125].

Table 2. Comparative table showing various SERS-based optical fiber biosensors

Refs.	Type of probe	Target analytes	SERS substrate	Operating range	LOD
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[117]	Tip-coated MMF	Intracellular pH in tumor tissue	AgIF	6.0-7.5 pH	N/A
[118]	Tip-coated MMF	Intracellular and extracellular pH in cancer cells	Au NPs	5.0-9.0 pH	N/A
[119]	Tip-coated MMF	Lysozyme and cytochrome c proteins	Ag NPs	0.2-2 $\mu\text{g/mL}$	0.2 $\mu\text{g/mL}$
[119]	Liquid core PCF	<i>Shewanella oneidensis</i> MR-1 bacteria	Ag NPs	10^6 - 10^{10} cells/mL	10^6 cells/mL
[121]	Hollow core PCF	EGFR	Evanescent field of fiber mode	0.1-1000 ng/mL	100 pg/mL (LDC)
[122]	Side channel PCF	CH in cells (lipid peroxidation)	Au NPs	0.7-23 $\mu\text{g/mL}$	0.7 $\mu\text{g/mL}$
[123]	Hollow core PCF	HL60 acute myeloid leukemia cells	Ag NPs	310-25000 cells/mL	300 cells/mL
[124]	Multimode plastic clad silica fiber	Dopamine	Green synthesized Ag NPs	0.03-12.3 $\mu\text{g/mL}$	30.6 ng/mL
[125]	MMF	Dopamine	Au NPs/IRMOF-3 hybrids	1.5×10^{-6} – 15.3 pg/mL	0.2 ag/mL
[53]	Tip-coated MMF	Folic acid	Au nanoislands	0.44-440 $\mu\text{g/mL}$	N/A
[126]	Bundle of tip-coated MMFs	IgG and A β_{42}	Au NPs embedded in PDMS caps	in $\mu\text{g/mL}$ range	N/A
[115]	SMF & MMF	EGFR & HER2	Au/SiO ₂ NPs	0.1-100 ng/mL	N/A

Once repeatability in results, reproducibility in device manufacturing, and easier integration with optoelectronic compounds and systems are finally addressed, optical fiber-based SERS biosensors might surely represent a real competitor against the well-established lab-on-chip biosensors. More specifically, a trade-off between the minimum metal absorption and the maximum SERS signal enhancement is the main working principle. An arbitrary pattern of NPs or nanostructures is usually not advised to get a maximum SERS signal, since the size and shapes of nanostructures pinpoint the strength and directionality of their enhanced EM fields. The not-optimized coupling of light by means of the nanostructures results in the excitation of lossy, non-radiative surface plasmon modes, as well as an inefficient scattering of the SERS signal. As a consequence, the future challenge in the field of optical fiber-based

SERS devices will be how to decrease coupling losses and improve the intensity of SERS signals in parallel. This gap would be narrowed by novel nanomaterials with lower absorption at specific operating wavelengths, by new technological tools able to realize a defined pattern of nanostructures in a precise and repeatable manner (for instance, micro-/nano-lithography enables the development of SERS-active substrates with specific shapes and spacing of the nanostructures) or by novel fiber configurations and types that allow an improvement in collecting the SERS signal. However, the advantage of simple integration with medical needles and catheters, together with a small cross-section and large aspect ratio, endow the fiber with unique features for *in situ* and *in vivo* applications. Prospectively, it is not so demanding to foresee the development of smart needle-based devices with unprecedented and multiple functionalities at extreme miniaturization levels, able to monitor clinically-relevant parameters in real time. This new attractive technological approach could have a disruptive impact on most cancer and non-cancer diseases, especially those that need localized treatments. Advanced and multifunctional optical fiber-based platforms, completely or partially integrated into needles or catheters, might be able to monitor the early appearance of the disease and also its progression or regression, by quantifying the level of specific biomarkers in close proximity to cancer/tissue/cells or, externally, in liquid biosamples extracted from the patient.

4.3. Optical Fiber SERS-based Sensors for Drug Monitoring

The monitoring of therapeutic drugs in biological matrices is a crucial practice, especially for drugs with pharmacokinetic variability and narrow therapeutic ranges. Specifically, such monitoring assesses drug concentration against duration within a particular biological matrix which will help in the interpretation of drug-drug interactions, drug toxicity, drug efficacy, and compliance. These parameters are essential in drug development, delivery, and precision dosing. Among the common analytical platforms for drug, monitoring includes immunoassay, mass spectrometric, and chromatographic techniques [129–132]. These techniques have been considered as the most accurate, sensitive, and selective method which has been utilized for several years for drug monitoring. Although these approaches are promising, it faces the most significant limitations due to their high cost, time consumption, off-site analyses, and the requirement for skilled technicians.

SERS become a powerful biological analytical tool in recent years [133]. The exploitation of molecule-specific vibrations as Raman signals interact with biological samples has allowed SERS to offer innovative sensing solutions that are highly sensitive and specific for drug monitoring and tracings [134]. Nevertheless, Raman signals are known to be intrinsically weak and thus, require further enhancement techniques for tracing pharmaceutical analytes at very low concentrations. Parameters that affect Stokes Raman scattering intensity can be identified in equation (4) [135]:

$$I_{Stokes} \propto NI_0(\omega_0 - \omega_r)^4 |\alpha|^2 \quad (4)$$

Where, N and I_0 are the number of molecules and incoming excitation intensity, while ω_0 , ω_r and α are Raman excitation frequency, excited vibrational frequency, and polarizability of molecules, respectively. With that said, enhancement of Raman intensity can be achieved with greater I_0 , higher ω_0 , resonance matching of excitation frequency with the electronic

transition of the molecule, and an increase in the number of targeted molecule. As SERS depends greatly on the generation of surface plasmons, fiber configuration, length, coupling efficiency, and laser intensity are factors that would affect the performance of optical fiber SERS-based sensors. Known configurations that were reported to yield high LSPR include single-channel multiplexing optrode [136], liquid-core waveguides [137], and shape-engineered optical fiber probes like D-shaped [138,139] and tapered optical fibers [61,140].

For drug monitoring, hollow-core photonic crystal fiber (HC-PCF) has been reported to achieve fifty times higher sensitivities and LOD improvements for pharmaceutical analyte detection in aqueous solutions [141]. Firstly, the volume of samples needed is significantly reduced as the volume of HC-PCF is minimized. Secondly, the liquid-core configuration allows the guidance of both light and analytes throughout the path length of the optical fiber which increases the number of scattering molecules as shown in Fig. 28. The broadband step-index can be achieved by filling in the central hollow cores with aqueous analytes, which makes excitation wavelengths throughout the whole visible range available to be used. Frosch *et al.* exploited the mentioned configuration and demonstrated ultrasensitive detection of antimalaria drugs, chloroquine, and mefloquine with detection limits of 1.25×10^{-5} and 6.25×10^{-3} , respectively, using UV resonance [135]. The schematic of the fabrication step is shown in Fig. 28. In traditional Raman spectroscopy, the signal is stimulated and gathered within a confined scattering volume, determined by the scattering volume in the focal point of the optical setup, as shown in Fig. 28 (a). This drawback can be overcome by using liquid core optical fibers in which the light and analyte both are guided within the fiber and thus the analyte is efficiently excited upto an extended path length resulting the increment in the number of scattering molecules as show in Fig. 28 (b).

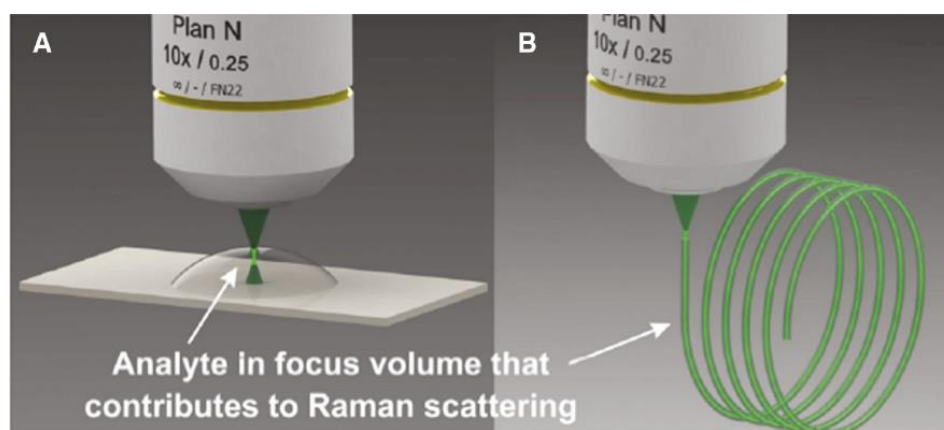


Fig.28. Comparison between limited collection volume in conventional Raman spectroscopy (A) as opposed to the extended interaction length provided by HC-PCF (Reprinted/Adapted from [135]).

Another optical fiber configuration that was investigated for drug monitoring is the end-probe optical fiber configuration. Liu *et al.* fabricated optical tapered shape nano-probes using the spark pull cone method; later the fiber was etched using the chemical etching method to reduce the tip size to 100 nm [142]. Later, the Au nanoparticles of 55 nm diameter were self-assembled electrostatically at the surface of the tip to enable the SERS phenomenon. The fabricated nano-probes were used for the detection of levofloxacin lactate in blood samples

which achieved a LOD of 10^{-4} M. Another study reported a similar sensing configuration where a SERS-active neural end-probe decorated with Au was used for the detection of neurotransmitters [96]. The fabrication of the probe was similar to the previously mentioned work; however, the tip was coated with nano-island Au particles instead of spherical Au nanoparticles. The investigation was investigated both numerically and experimentally which amplified the broadband near-field enhancement from the highly-dense nano-islands allowing the achievement of very low detection limits of 10^{-5} M for serotonin and dopamine, while 10^{-7} M for R6G. Detection of R6G was also shown using an end-probe SERS Au arrays at the tip which were printed using the two-photon polymerization (2PP) technique [27]. 2PP is a microscale 3D printing method without using a mask with lateral and axial resolutions of 100 nm and 300 nm, respectively. The detection limit was achieved of 3.7×10^{-7} M with an analytical enhancement factor of three orders of magnitude.

In 2015, Jin *et al.* applied SERS on an end-probe optical fiber configuration to distinguish between normal and expired tetracycline hydrochloride [143]. The surface of the tip was coated with Au nanoparticles that were 55 nm in diameter. Oxidation of tetracycline hydrochloride due to storage deterioration causes isomerization to the compound. This would result in the production of anhydrotetracycline, anhydrotetracycline, and epianhydrotetracycline of which would yield different Raman spectra from the normal tetracycline hydrochloride. For direct detection, expired tetracycline hydrochloride samples exhibited obvious fluorescence background when compared to normal samples. A probable cause of this could be due to the formation of an anhydrous with two double bonds. When tested via remote detection, loss of peaks was observed from expired tetracycline hydrochloride when compared to Raman spectra retrieved from direct detection. This could be due to transmission attenuation along the fiber. Nevertheless, the disappearance of peak 1450 cm^{-1} was significant in expired tetracycline as the hydroxyl group of the compound was destroyed during the oxidation process. Table 3 summarizes the discussed work on the optical fiber based SERS sensors for drug monitoring.

Table 3. Comparative table showing various SERS-based optical fiber sensors for drug detection

Refs	Type of probe	Target analytes	SERS substrate	Operating range	LOD
[135]	HC-PCF	Chloroquine	-	0 to 0.1 mM	1.25×10^{-5}
[135]	HC-PCF	Mefloquine	-	0 to 0.1 mM	6.25×10^{-3}
[141]	HC-PCF	Moxifloxacin	-	0 to 100 μM	1.7×10^{-6}
[144]	HC-PCF	Ciprofloxacin	AgNPs	10^{-4} to 10^{-10} M	1×10^{-10}
[144]	HC-PCF	Norfloxacin	AgNPs	10^{-4}	1×10^{-11}

				to 10^{-11} M	
[142]	End-probe optical fiber	Levofloxacin	AuNPs	10^{-1} mol/l to 0.5 mol/l	1×10^{-4}
[96]	End-probe optical fiber	Serotonin	AuNPs	10^{-8} M to 10^{-4} M	1×10^{-5}
[96]	End-probe optical fiber	Dopamine	AuNPs	10^{-9} M to 10^{-1} M	1×10^{-5}
[96]	End-probe optical fiber	Rhodamine 6G	AuNPs	10^{-10} M to 10^{-4} M	1×10^{-7}
[27]	End-probe optical fiber	Rhodamine 6G	AuNPs	10^{-6} M to 10^{-3} M	1×10^{-7}
[143]	End-probe optical fiber	Tetracycline hydrochloride	AuNPs	NA	-

4.4. SERS in agricultural and food monitoring:

Agriculture plays an important role in the economy and livelihoods of developing and developed countries. In order to ensure a good growth of the economy and population, it is necessary to focus on the agriculture, which not only includes forestry and animal husbandry, but also encompasses aquaculture and other related industries. A real time and quick monitoring of harmful chemical substances including pesticides, antibiotics, heavy metals and illegal forbidden additives in a various of consumable food products e.g., vegetables, fruit, meat, dairy and aquaculture products, and rapid monitoring of several toxic and pollutants in the plants or crop environments such as heavy metals and other organic pollutants in the soil become a major challenge for the society [145]. Nowadays, there is a growing concern among citizens for the safety and quality of food and agricultural products, as the poor quality of products leads to several diseases and pandemics as witnessed in past decades. Therefore, considering the potential threat, real-time food quality monitoring is recently recognized as a new potential tool in making a healthy nation and economy [146,147]. Due to the growing demand for health safety and food quality monitoring, SERS has gained huge interest in agricultural applications, including the screening of plant seeds, monitoring of crop growth, quality assessment of agricultural products, etc. [148]. In 1987, Alak and Vo-Dinh were reported the early applications of the colloid nanoparticle-based SERS substrates in agriculture [149]. In reported work author utilized silver integrated microspheres as the SERS substrate in order to analyze and detect eight organophosphorus pesticides. Beyond the use of common silver/gold nanoparticles, nanomaterials of various sizes and shapes have been studied widely. In 2020, Pham *et al.* reported work author functionalized silver nanodendrite on microspheres fabricated on the end face of optical fiber for pesticide detection [150]. The common gold and AgNPs with uniformity and easy synthesis procedure have been utilized for the detection of several pesticides [151–153]. Beyond of pesticides, several researchers also reported other types of SERS sensors for heavy metal detection and additive in foods and water. Long *et al.* reported silver coated SERS optical fiber following the special functionalization of the surface with methimazole via a SnCl_2 -sensitized solvothermal method, for the detection of

Cr(VI) ions [154]. In 2022, Zhou *et al.* reported Au-nanorods clusters coated over optical fiber [155]. The Au-nanorods coated optrode showed a improved enhancement factor compared to their previous study [156]. This section will elaborate in detail on the diverse approaches employed in agriculture and food monitoring. The section and sub-sections presents an in-depth discussion of various methods used to develop efficient optical fiber-based SERS devices. It also explores their applications in detecting pesticides, heavy metals, and illegal food additives.

4.4.1. Detection of pesticide:

Permethrin, trans-3-(2,2-dichlorovinyl)-2, 3-phenoxybenzyl (1 RS)-cis, 2-dimethylcyclopropanecarboxylate, methyl parathion, etc. are the most common pesticide generally used in broad range of applications such as insect repellent, insecticide, preventing diseases carrying by mosquitos, e.g., malaria and dengue in the tropical areas. In 2015, Huang *et al.* fabricated a cone-shaped optrode coated with silver nanostructures to improve the performance of SERS substrate and improve the enhancement factor for the detection of methyl parathion pesticides [91]. It was reported the functionalization of the probe with silane, the optrode surface gets charged (either negative or positive) resulting in the uniform deposition of Ag/Au composite nanostructure of desired SPR properties. Four different nanostructures were grown over the fiber probe i.e., Au nanospheres, Ag nanocubes, Au nanorods, and Au@Ag core-shell nanorods, and investigated for their performance. Among various nanostructures, the Au@Ag nanorods assembled optrode exhibited a significantly higher enchantment factor and best SERS activity due to the strong electromagnetic coupling among the neighboring nanorods, whereas the Au nanospheres exhibited extremely poor performance. The obtained results of *in situ* Raman monitoring suggest that from the developed SERS substrate, it is possible to detect concentrations of methyl parathion pesticide as low as 10^{-8} M. In same year of 2015, Liu *et al.* fabricated a SERS active optrode using laser-induced Ag deposition technique to detect biotin/avidin [157]. The investigation over the performance of optrode was performed via an indirect method. The bio-recognition process was based on the SERS response signal of a labeled dye (Atto610) once its fluorescence had been completely extinguished by the deposited Ag nanoparticle membrane. The result exhibited a lowest detection potential of optrode for biotin of low concentration of 1.0×10^{-7} mg/mL within 40 minutes.

In order to detect permethrin pesticide Pham and group reported a series of SERS active optrode in 2019-2022 [150,158,159]. In 2019, Pham *et al.* deposited Ag nanodendrites on the edges of multi-mode fiber utilizing laser-assisted photochemical technique to detect permethrin pesticide [159]. The SERS active optrode was investigated over various concentrations of R6G solutions. The fabricated SERS optrode was investigated for permethrin pesticide ranging from 0.1 ppm to 20 ppm showed a LOD of 0.0035 ppm along with good limit of quantification of 0.1 ppm. Later this enhancement factor was achieved by same group in 2022 following direct deposition of Au nanoparticles over Ag nanodendrite using dual-laser approach [158]. Figure 29 shows the schematic of fabrication step and experimental setup. The fabrication step requires the formation of the spheroid end-facet of the optical fiber using electric-arc method, as shown in Fig. 29(a). The Ag seed solution was synthesized by adding AgNO₃ solution into 20 mL aqueous solution including C₆H₅Na₃O₇·2H₂O, NaBH₄ solution and deionized water

under stirring for 5 min until the solution turn into light yellow, as shown in Fig. 29(c). Figure 29(b) showed the deposition of Ag nanodendrites using diode laser photochemical technique. From the fabricated substrate author achieved a highest enhancement factor for R6G of 2.54×10^7 compared to gold nanoparticles and silver nano-dendrites based SERS substrates. The device also went through the stability test for 40-day resulting 11.16% reduced Raman intensity of R6G for Au-nanoparticles/Ag-nanodendrite which was 44.07% more stable compared Ag-nanodendrite SERS substrate [159]. The fabricated Au-nanoparticles/Ag-nano-dendrites exhibited a rapid detection of fenthion and cypermethrin with a low LOD of 1.7×10^{-4} ppm and 2.87×10^{-4} ppm, respectively.

Fig.29. Schematic diagram of the (a). formation of spheroid end-facet on tip of optical, (b). fiber substrates with AuNPs/AgNDs nanostructures prepared by dual-laser assisted photochemical method, and (c). steps used to synthesize Ag seed solution (Reprinted/adapted from [158]).

4.4.2. Detection of heavy metals:

Nowadays, the water content is experiencing the addition of several pollutants, through both intentional and unintentional means [160]. Heavy metals can potentially affect the surrounding including soil and water used in the farming, planting, and breeding [161]. These SERS substrates play a crucial role in the real time monitoring of such excess contamination in food. Several approaches have been reported so far, among which some notable approach include fiber modal interference [162], fiber Bragg grating [163], optical absorbance technique [164], plasmonic sensing [165], and SERS approach [160]. Heavy metals are considered a group of multiple metallic elements which comprise high densities and atomic weights. Some of the common heavy metals include mercury (Hg^{2+}), lead (Pb^{2+}), cadmium

(Cd^{2+}), arsenic (As^{2+}), and chromium (Cr^{2+}). These metals are naturally found in the crust of Earth and also sometime found to be released into the surrounding environment via human activities e.g., manufacturing, mining, and burning of fossil fuels. In 2014, Cheng *et al.* reported SERS active fiber optrode for real time monitoring of cadmium (Cd^{2+}) ions [100]. The fabricated optrode was five times deposited with Ag nanoparticles using layer-by-layer approach to form SERS substrate. The monitoring of Cd^{2+} in aqueous solution was analyzed by studying the shift in the SERS spectrum occurs after binding the Cd^{2+} ions on the Ag nanoparticles. The presence of Cd^{2+} ion in solution was identified by the appearance of an additional peak at 1020 cm^{-1} which was further evaluated by the relative intensity ratio i.e., I_{1020}/I_{1040} for the concentration varying from $10\text{ }\mu\text{M}$ to $200\text{ }\mu\text{M}$. The recovery rate for $20\text{ }\mu\text{M}$ of Cd^{2+} was observed to be in the range of 69.5–157%.

Most recently, Long *et al.* reported a new type of Ag coated SERS active optical fiber following the special functionalization of the surface with methimazole via a SnCl_2 -sensitized solvothermal method, for the detection of Cr(VI) ions [154]. The working mechanism of the sensor was based on the change in SERS signal in the existence of Cr (VI). The methimazole and Cr (VI) undergo a redox reaction after interacting with Cr (VI), and form a disulphide, resulting decline in SERS intensity. The optrode dually modified by methimazole exhibited extremely high sensitivity of 10^{-11} M and excellent stability for Cr(VI) detection. Figure 30 shows the experimental setup used for characterization and the sensing mechanism of the fabricated optrode. In the measurement process, the laser was launched at the proximal end of the SERS optical fiber (Fig. 30a). Progressing along the core, the laser interacts with AgNPs positioned at the end. This light matter interaction stimulates the surface plasmon polarization (SPP) of silver, significantly boosting the SERS signal of methimazole by amplifying the local electromagnetic field of silver (Fig. 30b). The intensified SERS signal was then conveyed back to the Raman spectrometer through the same fiber (Fig. 30a, b).

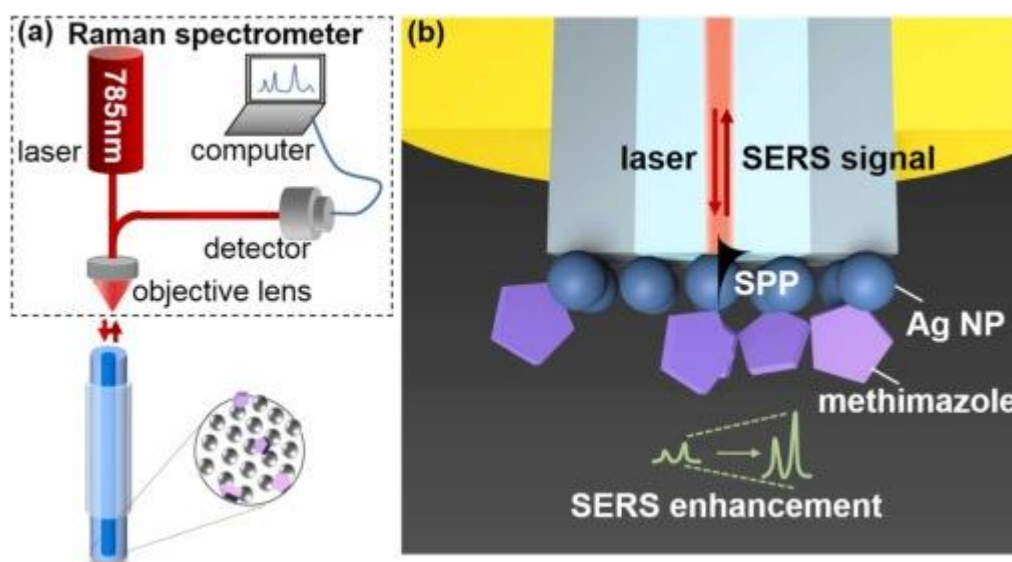


Fig.30. (a) Experimental setup used for the characterization of SERS sensor, and (b) Characterization mechanism of SERS optical fiber probe. (Reprinted/adapted from [154])

Although the SERS approach is considered the most efficient way for various sensing applications, it's not able to gain enough advancement in heavy metal detection. One might be the possible reason for the lack of advancement is the poor reliability and low accuracy arising due to the interference from other ions appearing in the sample matrix. In 2014, F. Cheng *et al.* investigated the potential of SERS active optrode for heavy metal detection. The reported work utilized a metal ion chelating reagent, 4-(4-phenylmethanethiol)-2,2': 6',2''-terpyridine, to modify the end facet of the SERS optrode. The Cd^{2+} was considered as the measurand heavy metal. The binding of Cd^{2+} was with functionalized optrode was reported to produce a unique peak of about 1020 cm^{-1} , which was reported to be reversible by treatment with EDTA. The normalized SERS intensity at 1020 cm^{-1} may be used to quantify Cd^{2+} by carefully selecting an intact band of 4-(4-phenylmethanethiol)-2,2': 6',2''-terpyridine at 1040 cm^{-1} as an internal reference [100].

4.4.3. Detection of dye and illegal additives in food:

In recent times, antibiotics, which belong to the group of organic compounds, have emerged as a potentially dangerous form of pollutant, particularly in the context of pharmaceuticals. Tetracycline, the another most frequently used antibiotic in veterinary and human medicine, have been identified as a target pollutant among various scientific research because of adverse effect on human health [166–168]. Another group of organic compounds that pose a significant risk to both the environment and human health are the organic dyes which possess various carcinogenic properties. These dyes are broadly used in various industrial sectors such as textile, printing, and leather industries. The emission of these organic molecules in the environment causes serious health concerns and potential environmental impacts. Among several classes of dyes, the Rhodamine are considered as a most harmful pollutant with broad industrial applications running from the textile to the food and cosmetic industries [169–171]. Considering the health impact of these dyes several researchers reported an optical fiber SERS probe. In 2007, Lucotti and Zerbi reported the first needle-shaped optimized and compact SERS active optrode for the real time detection of crystal violet in water [76]. Figure 31 shows the fabricated probe and processing technique. The optrode was fabricated using a chemical etching technique in which 40% hydrofluoric acid was used along with organic solvent to form such an optimized needle shape as shown in Fig. 31(d). After an appropriate time interval a partial etching of the fiber has occurred and the fiber has been lifted upward of selected height and held steady in this position until the needle shaped is achieved as shown in Fig. 31(b) and (c). By changing the etching time, the cross-section of the untapered region of the sensing head can be modified by changing the height of the untapered region of reduced diameter, can be varied, as shown in Fig. 31(a). The SERS probe was fabricated by immobilizing Ag nanoparticles on this etched section of fiber. The sensing performance was measured using two different approaches i.e., the 'in-solution' method and a "dip and dry" technique. The fabricated sensor observed to measure the SERS spectra at a low concentration of 0.018 ppb of crystal violets in distilled water. The detection of such a low-concentration molecule claims that the fabricated SERS probe can have potential in the aquaculture industry.

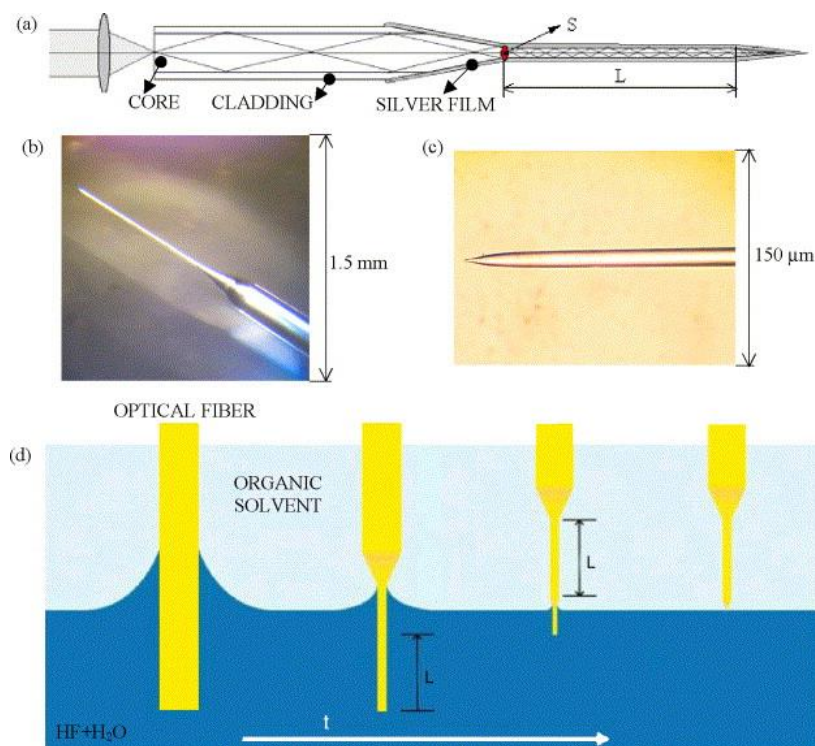


Fig.31. (a) Schematic representation of the geometry-optimized fiber-optic SERS sensor; (b) and (c) photos of the geometry-optimized fiber-optic tip; (d) schematic representation of the two-fold static etching process used to obtain the SERS sensor.

(Reprinted/adapted from [76])

In 2009, Lan *et al.* reported a new approach of the fabrication of a SERS optrode using femtosecond micromachining [172]. The use of femtosecond laser ablation directly onto the perfectly cleaved face of multimode fiber to produce the nanostructures which were later SERS activated using silver chemical plating. A high enhancement factor was observed via back excitation for R6G molecules ranging from 10^{-8} to 10^{-6} M. In 2019, Ran *et al.* reported Ag coated Au nano stars SERS fiber-optrode as a highly enhancing SERS substrate for the direct monitoring of biotargets and food additives [173]. Two types of Au nano stars were synthesized using a seed-mediated method, involving the preparation of a 12 nm citrate gold seed solution. The synthesis process included the rapid addition of Au seed to a solution containing HAuCl_4 , HCl, ascorbic acid, and AgNO_3 , resulting in a color change from pale red to deep blue within a minute. Silver coating on the gold nanostars was obtained by adding 5 μL of AgNO_3 to a Au nano star solution, followed by NH_4OH . After about 5 min, the reaction was complete, and the silver-coated Au nano star samples were labeled based on the volume of AgNO_3 added. The final concentration of the silver-coated Au nano star was identical than the Au nano star solution, allowing for the generation of Au nano star particle solutions with different concentrations through dilution or centrifugation. Figure 32(a) shows the synthesis the steps of Au@Ag nano stars. The fabrication step requires removal of plastic jacket from the fiber using flame heating methods. One end of the fiber was connected to laser source to launch the light. The other end of the fiber was polished to obtain a flat top to collect the maximum laser. The deposition of Au@Ag nano star on flat end was performed following the salinization by immersing it into a 10% 3-aminopropyltriethoxysilane solution, as shown in

Fig. 32(b). The fabricated optrode utilizes the characteristics of the photonic properties of Ag-coated Au-nano stars to achieve an improved sensing performance. The optimization of the sensing configuration was performed by varying the density of Au nano stars and the roughness of the end-face of fiber to maximize the SERS signal. The obtained results exhibited a low LOD for Rhodamine B varying between 10^{-7} and 10^{-8} M.

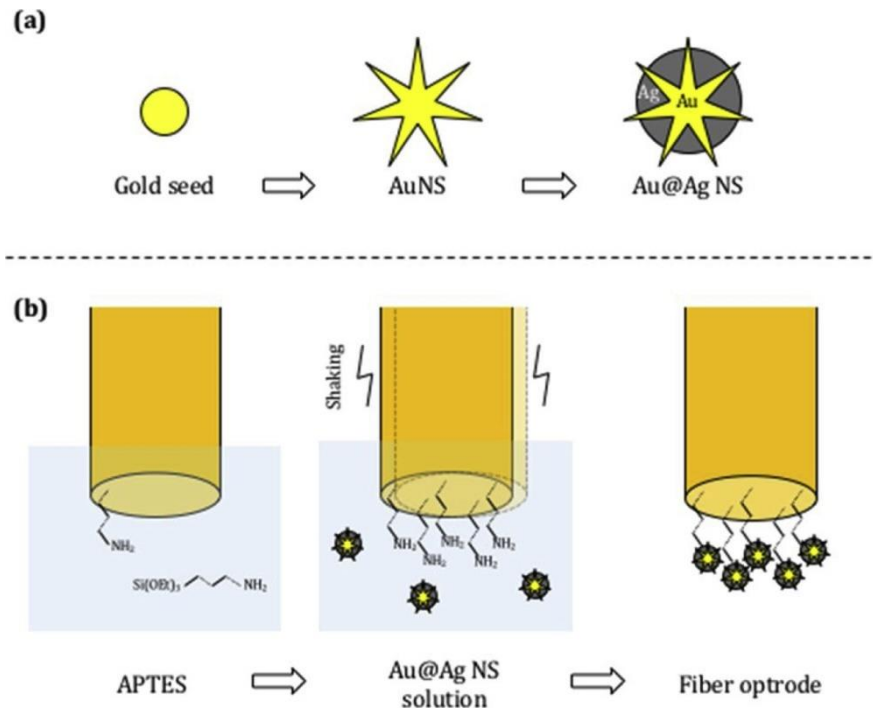


Fig.32. Preparation step of (a) the Ag coated Au nano stars and (b) steps for the used to functionalization of Au@Ag nano star on the optrode. (Reprinted/adapted from [173])

Rhodamine B and xanthenes are most commonly used food additive dye in various countries. A series of experiments was reported by Zhou's group utilizing Au-nanorods on the end face of fiber to determine contaminants in food oils using a laser-induced dynamic dip-coated SERS probe [155,156]. In 2020, Zhou *et al.* reported Au-nanorods clusters coated over optical fiber [156]. The Au-nanorods coated optrode showed a high sensitivity of 10^{-10} M and 10^{-8} for R6G and malachite green, respectively along with excellent reproducibility with a standard deviation of less than 6%. The enhancement factor was further reported to be improved by the same group in 2022 [155]. In the reported work author deposited Au-nanorods clusters on the end surface of fiber using dip-coating. To fabricate end facet optical fiber SERS probes using the laser-induced dynamic dip-coating technique, the optical fiber segment was subjected to multiple dip-pull cycles on the colloid surface while being exposed to laser irradiation. The fabricated device showed a high sensitivity of 2.4×10^{-6} mol/L and 3.6×10^{-7} mol/L for Sudan red and thiram in sunflower oil, respectively. Table 4 summarizes the comparative data on various SERS based fiber sensor used in agricultural monitoring.

Table 4. Comparative table showing various SERS-based optical fiber sensors in agricultural and food monitoring

Refs.	Type of probe	Target analytes	SERS substrate	Operating range	LOD
[91]	Cone shaped fiber	Methyl parathion pesticide	Au@Ag nanorods	NA	10^{-8} M
[157]	Fiber tip	Biotin/avidin	AgNPs	0.49×10^{-3} mg/mL	NA
[159]	Fiber tip	Permethrin pesticide	Silver nano-dendrites	0.1 ppm and 20 ppm	0.0035 ppm
[158]	Fiber tip	Fenthion Cypermethrin	AuNPs/Ag-nano-dendrites	0.005 ppm - 2 ppm 0.001 ppm - 1 ppm	1.7×10^{-4} ppm 2.87×10^{-4} ppm
[100]	Fiber tip	Cd^{2+}	AgNPs	10 μM to 200 μM	NA
[154]	Fiber tip	Cr(VI)	AgNPs	10^{-2} M and 10^{-6} M	0.00001 μM
[76]	Fiber cone tip	Crystal violet	AgNPs	NA	NA
[173]	Fiber tip	Rhodamine B	Silver-coated gold nanostars	10^{-7} and 10^{-8} M	NA
[156]	Fiber tip	Crystal violet solution	Au-nanorod-clusters	10^{-7} M to 10^{-10} M	10^{-8} M
[174]	Fiber tip	Diethylthiatricarbo cyanine and crystal violet	Au nanovoid arrays	0.08 mM and 1 mM	NA

5. Future Prospects and Challenges:

SERS has become an increasingly popular analytical technique for the detection of various analytes in sensing fields due to its high sensitivity, selectivity, and versatility. One of the key advantages of SERS-based optical fiber chemical sensors is their high sensitivity, which can enable the monitoring of various analytes in as low as part per trillion. In addition, the small size and flexibility of optical fibers make them suitable for integration into complex systems, such as microfluidic devices or wearable sensors. There are several perspectives and challenges of SERS in sensing field. SERS has the potential to detect analytes at very low concentrations, even at the single-molecule level which shows a very high sensitivity, making it a valuable tool in many sensing applications. At a time, SERS can detect multiple analytes simultaneously by using different Raman-active molecules as tags, which can increase the throughput of analysis. SERS is a non-destructive technique, which allows the same sample to be analyzed multiple times without losing its integrity. It can be integrated with portable devices, making it ideal for field applications. However, there are also several challenges associated with SERS-based optical fiber chemical sensors. One of the major challenges is the reproducibility of the SERS signal, which can vary depending on the fabrication and functionalization methods of the nanoparticles, as well as the environmental conditions. The reproducibility of the enhancement effect in SERS is also a very important factor that can be controlled in a significant manner.

The enhancement factor can vary significantly between different substrates and even within the same substrate. Therefore, efforts are being made to improve the reproducibility of SERS measurements by developing new substrates and characterization methods. Another challenge is the interference from other molecules in sample matrix, which can affect the specificity and selectivity of the sensors. The signal-to-noise ratio of SERS measurements can be affected by the presence of background fluorescence and other noise sources. The quantification of SERS measurements can be challenging due to the lack of a standardized calibration method. SERS can suffer from non-specific binding of analytes to the SERS substrate, leading to false-positive results. Another challenge is the interference from complex matrices, such as biological samples or environmental samples, which can hinder the detection and identification of target molecules.

Overall, there is a trade-off between maximising SERS enhancement and minimising metal absorption loss in all of the devices that have been shown so far and utilised for distant sensing applications. Therefore, one of the main goals of future research for optical fiber-based probes operating in the optrode configuration would be how to reduce coupling losses and enhance SERS signal intensities. It is a difficult but possibly extremely fruitful undertaking to integrate SERS systems with optical fibre technology. There is still a great deal to be done. Sensitivity and stability are still problems even though SERS optrodes are undoubtedly the most sophisticated optical fibre SERS platform. More highly optimised SERS substrates on optical fibre tips ought to be able to be produced (and replicated correctly). Gaining more knowledge about SERS optrode performance will be facilitated by systematic investigations into how spatial averaging affects sensor repeatability. Simultaneously, technology has advanced to the point where additional useful uses of SERS optrodes and near-field probes may be considered, notably in studies related to biology and medicine where the compact geometry is anticipated to be very helpful. MOFs and PCFs have some potential for distributed SERS sensing and for increasing the sensitivity of SERS detection. This is an interesting yet complicated field that needs more research, especially in the theoretical domain.

Even with a few noteworthy successes, SERS imaging has proven to be a difficult problem thus far. TERS techniques are still somewhat superior to near-field optical fibre approaches. Nonetheless, additional research is unquestionably necessary since optical fibres could offer a more practical and adaptable platform for near-field imaging. However, recent advances in SERS-based sensors and imaging techniques, such as SERS microscopy and SERS mapping, have shown promise in overcoming these challenges. In terms of prospects, the development of new SERS substrates and detection methods is expected to continue. This includes the development of more robust and reproducible substrates, as well as the integration of SERS with other techniques, such as electrochemistry and mass spectrometry. Moreover, the use of artificial intelligence (AI) and machine learning (ML) algorithms for SERS data analysis is also a promising area for future research. These techniques can help to identify patterns in complex SERS spectra and improve the accuracy and speed of SERS data analysis.

A highly intriguing avenue for future research is the integration of SERS substrates into "photonic chips" and opto-microfluidic systems, as well as the miniaturisation of interface optics. The SERS community is expected to gain from the ongoing development of small spectrometers, which are being developed in addition to the technologies now in use for the telecommunications sector. Overall, SERS has great potential as a sensing technique, and overcoming the challenges will allow it to be widely used in various fields, such as environmental monitoring, medical diagnostics, and food safety.

6. Conclusion:

In conclusion, we have provided a comprehensive review of the SERS mechanism and its integration with optical fibers various sensing applications. The integration of SERS systems with optical fiber is still challenging but at the same time, it's potentially rewarding. A systematic study of the influence of spatial averaging on sensor reproducibility will allow a better understanding on the performance of SERS optrode. At the same time, the SERS based fiber technology has gained huge interest leading several practical applications of SERS optrode, specifically in medical and biological studies where the compact geometries are expected to be especially beneficial and advantageous. The optical fiber sensors have shown tremendous potential as a SERS substrate because of their compact size, *in situ* monitoring, and immunity to electromagnetic interference, non-reactiveness, chemical inertness, etc., which are ideally considered for SERS sensing. Through this review, we provided a detailed information allowing readers to progress from fundamental knowledge to advanced concepts, ensuring a clear understanding of each terminology of SERS. Various optical fiber geometries implemented in SERS sensing, their associated applications, and prospects.

7. Author Contributions:

A.K.P. proposed the write up plan, R.K.G., A.K.P., F.C., M.H.A.B., Y.M.K, investigated all the related literatures and wrote original draft; R.K.G., A.K.P., F.C., M.H.A.B revised the whole manuscript. M.A.M. and V.K.S. review and edited the draft. All authors have read and agreed to the published version of the manuscript.

8. Declaration of competing interest:

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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References:

1. K. Liu, X. Pang, H. Chen, and L. Jiang, "Visual detection of microplastics using Raman spectroscopic imaging," *Analyst* **149**, 161–168 (2024).
2. D. L. Jeanmaire and R. P. Van Duyne, "Surface raman spectroelectrochemistry," *J. Electroanal. Chem. Interfacial Electrochem.* **84**, 1–20 (1977).
3. M. G. Albrecht and J. A. Creighton, "Anomalous intense Raman spectra of pyridine at a silver electrode," *J. Am. Chem. Soc.* **99**, 5215–5217 (1977).
4. S. Zhang, Y. Qi, S. P. H. Tan, R. Bi, and M. Olivo, "Molecular fingerprint detection using Raman and infrared spectroscopy technologies for cancer detection: A progress review," *Biosensors* **13**, 557 (2023).
5. Y. Xiao, P. Cheng, X. Zhu, M. Xu, M. Liu, H. Li, Y. Zhang, and S. Yao, "Antimicrobial agent functional gold nanocluster-mediated multichannel sensor array for bacteria sensing," *Langmuir* **40**, 2369–2376 (2024).
6. I. J. Jahn, O. Žukovskaja, X.-S. Zheng, K. Weber, T. W. Bocklitz, D. Cialla-May, and J. Popp, "Surface-enhanced Raman spectroscopy and microfluidic platforms: challenges, solutions and potential applications," *Analyst* **142**, 1022–1047 (2017).
7. S. J. Kim, J. Jeong, G. Ryu, Y. S. Eom, and S. Kim, "Engineered vertically-aligned

- carbon nanotube microarray for self-concentrated SERS detection," *Sensors Actuators B Chem.* **399**, 134861 (2024).
8. N. Nasr, M. Shafi, T. Zhao, R. Ali, I. Ahmad, M. Khan, A. Deifalla, A. E. Ragab, and M. Zahid Ansari, "A two-fold SPR-SERS sensor utilizing gold nanoparticles and graphene thin membrane as a spacer in a 3D composite structure," *Spectrochim. Acta Part A Mol. Biomol. Spectrosc.* **304**, 123331 (2024).
 9. N. N. Kurus, V. Kalinin, N. A. Nebogatikova, I. A. Milekhin, I. V. Antonova, E. E. Rodyakina, A. G. Milekhin, A. V. Latyshev, and D. R. T. Zahn, "Resonant Raman scattering on graphene: SERS and gap-mode TERS," *RSC Adv.* **14**, 3667–3674 (2024).
 10. X. Fan, P. Wu, C. Qu, Y. Gao, and P. Yin, "Functionalized Ag/MOF nanocomposites based on defect engineering for highly sensitive SERS detection of organic dyes," *J. Environ. Chem. Eng.* **12**, 112240 (2024).
 11. P. Mosier-Boss, "Review of SERS substrates for chemical sensing," *Nanomaterials* **7**, 142 (2017).
 12. Z. Zhang, S. Sheng, R. Wang, and M. Sun, "Tip-enhanced Raman spectroscopy," *Anal. Chem.* **88**, 9328–9346 (2016).
 13. D. Cialla-May, X.-S. Zheng, K. Weber, and J. Popp, "Recent progress in surface-enhanced Raman spectroscopy for biological and biomedical applications: from cells to clinics," *Chem. Soc. Rev.* **46**, 3945–3961 (2017).
 14. Y. Fang, N.-H. Seong, and D. D. Dlott, "Measurement of the distribution of site enhancements in surface-enhanced Raman scattering," *Science (80-.)*. **321**, 388–392 (2008).
 15. Y. Zhang, C. Gu, A. M. Schwartzberg, and J. Z. Zhang, "Surface-enhanced Raman scattering sensor based on D-shaped fiber," *Appl. Phys. Lett.* **87**, 123105 (2005).
 16. B. Zhang, F. Mumtaz, M. Roman, D. R. Alla, R. E. Gerald II, and J. Huang, "Miniaturized fluorescence pH sensor with assembly free ball lens on a tapered multimode optical fiber," *Opt. Express* **32**, 4228 (2024).
 17. C. McDonagh, C. S. Burke, and B. D. MacCraith, "Optical chemical sensors," *Chem. Rev.* **108**, 400–422 (2008).
 18. R. A. Lieberman, "Recent progress in intrinsic fiber-optic chemical sensing II," *Sensors Actuators B Chem.* **11**, 43–55 (1993).
 19. R. A. Potyrailo, S. E. Hobbs, and G. M. Hieftje, "Optical waveguide sensors in analytical chemistry: today's instrumentation, applications and trends for future development," *Fresenius. J. Anal. Chem.* **362**, 349–373 (1998).
 20. M. Marazuela and M. Moreno-Bondi, "Fiber-optic biosensors – an overview," *Anal. Bioanal. Chem.* **372**, 664–682 (2002).
 21. S. Managò, G. Quero, G. Zito, G. Tullii, F. Galeotti, M. Pisco, A. C. De Luca, and A. Cusano, "Tailoring lab-on-fiber SERS optrodes towards biological targets of different sizes," *Sensors Actuators B Chem.* **339**, 129321 (2021).
 22. U. S. Dinish, G. Balasundaram, Y. T. Chang, and M. Olivo, "Sensitive multiplex detection of serological liver cancer biomarkers using SERS-active photonic crystal fiber probe," *J. Biophotonics* **7**, 956–965 (2014).
 23. X. Li, Y. Zhang, B. Xue, X. Kong, X. Liu, L. Tu, Y. Chang, and H. Zhang, "A SERS nano-tag-based fiber-optic strategy for in situ immunoassay in unprocessed whole blood," *Biosens. Bioelectron.* **92**, 517–522 (2017).
 24. S. Kim, J.-H. Joo, W. Kim, A. Bang, H. W. Choi, S. W. Moon, and S. Choi, "A facile, portable surface-enhanced Raman spectroscopy sensing platform for on-site chemometrics of toxic chemicals," *Sensors Actuators B Chem.* **343**, 130102 (2021).
 25. P. Pidenko, C. Vakh, A. Shishov, J. Skibina, N. Burmistrova, and A. Bulatov, "Microstructured optical fibers sensor modified by deep eutectic solvent: Liquid-phase

- microextraction and detection in one analytical device," *Talanta* **232**, 122305 (2021).
26. J. Chen, M. Huang, and L. Kong, "Flexible Ag/nanocellulose fibers SERS substrate and its applications for in-situ hazardous residues detection on food," *Appl. Surf. Sci.* **533**, 147454 (2020).
 27. J. A. Kim, D. J. Wales, A. J. Thompson, and G.-Z. Yang, "Fiber-optic SERS probes fabricated using two-photon polymerization for rapid detection of bacteria," *Adv. Opt. Mater.* **8**, 1901934 (2020).
 28. K.-S. Lee and M. A. El-Sayed, "Gold and silver nanoparticles in sensing and imaging: sensitivity of plasmon response to size, shape, and metal composition," *J. Phys. Chem. B* **110**, 19220–19225 (2006).
 29. H. Guo, B. Xing, J. C. White, A. Mukherjee, and L. He, "Ultra-sensitive determination of silver nanoparticles by surface-enhanced Raman spectroscopy (SERS) after hydrophobization-mediated extraction," *Analyst* **141**, 5261–5264 (2016).
 30. Pathak, Rahman, Singh, and Kumari, "Sensitivity enhancement of a concave shaped optical fiber refractive index sensor covered with multiple Au nanowires," *Sensors* **19**, 4210 (2019).
 31. H. Liu, X. Gao, C. Xu, and D. Liu, "SERS tags for biomedical detection and bioimaging," *Theranostics* **12**, 1870–1903 (2022).
 32. A. T. N. Quang, T. A. Nguyen, S. Van Vu, T. N. H. Lo, I. Park, and K. Q. Vo, "Facile tuning of tip sharpness on gold nanostars by the controlled seed-growth method and coating with a silver shell for detection of thiram using surface enhanced Raman spectroscopy (SERS)," *RSC Adv.* **12**, 22815–22825 (2022).
 33. S.-Y. Ding, E.-M. You, Z.-Q. Tian, and M. Moskovits, "Electromagnetic theories of surface-enhanced Raman spectroscopy," *Chem. Soc. Rev.* **46**, 4042–4076 (2017).
 34. S. Schlücker, "Surface-enhanced Raman spectroscopy: Concepts and chemical applications," *Angew. Chemie Int. Ed.* **53**, 4756–4795 (2014).
 35. Pilot, Signorini, Durante, Orian, Bhamidipati, and Fabris, "A Review on surface-enhanced Raman scattering," *Biosensors* **9**, 57 (2019).
 36. Y. S. Yamamoto, Y. Ozaki, and T. Itoh, "Recent progress and frontiers in the electromagnetic mechanism of surface-enhanced Raman scattering," *J. Photochem. Photobiol. C Photochem. Rev.* **21**, 81–104 (2014).
 37. J. Langer, D. Jimenez de Aberasturi, J. Aizpurua, R. A. Alvarez-Puebla, B. Auguie, J. J. Baumberg, G. C. Bazan, S. E. J. Bell, A. Boisen, A. G. Brolo, J. Choo, D. Cialla-May, V. Deckert, L. Fabris, K. Faulds, F. J. García de Abajo, R. Goodacre, D. Graham, A. J. Haes, C. L. Haynes, C. Huck, T. Itoh, M. Käll, J. Kneipp, N. A. Kotov, H. Kuang, E. C. Le Ru, H. K. Lee, J.-F. Li, X. Y. Ling, S. A. Maier, T. Mayerhöfer, M. Moskovits, K. Murakoshi, J.-M. Nam, S. Nie, Y. Ozaki, I. Pastoriza-Santos, J. Perez-Juste, J. Popp, A. Pucci, S. Reich, B. Ren, G. C. Schatz, T. Shegai, S. Schlücker, L.-L. Tay, K. G. Thomas, Z.-Q. Tian, R. P. Van Duyne, T. Vo-Dinh, Y. Wang, K. A. Willets, C. Xu, H. Xu, Y. Xu, Y. S. Yamamoto, B. Zhao, and L. M. Liz-Marzán, "Present and future of surface-enhanced Raman scattering," *ACS Nano* **14**, 28–117 (2020).
 38. K. Kneipp, "Chemical Contribution to SERS Enhancement: An experimental study on a series of polymethine dyes on silver nanoaggregates," *J. Phys. Chem. C* **120**, 21076–21081 (2016).
 39. S. Fateixa, H. I. S. Nogueira, and T. Trindade, "Hybrid nanostructures for SERS: materials development and chemical detection," *Phys. Chem. Chem. Phys.* **17**, 21046–21071 (2015).
 40. J. R. Lombardi and R. L. Birke, "A unified approach to surface-enhanced Raman spectroscopy," *J. Phys. Chem. C* **112**, 5605–5617 (2008).
 41. X.-F. Lang, P.-G. Yin, T.-T. You, and L. Guo, "Chemical effects in SERS of pyrazine

- adsorbed on Au-Pd bimetallic nanoparticles: A theoretical investigation," *ChemPhysChem* **13**, 237–244 (2012).
42. M. M. Dvoynenko and J.-K. Wang, "Finding electromagnetic and chemical enhancement factors of surface-enhanced Raman scattering," *Opt. Lett.* **32**, 3552 (2007).
43. S. Cong, X. Liu, Y. Jiang, W. Zhang, and Z. Zhao, "Surface enhanced Raman scattering revealed by interfacial charge-transfer transitions," *Innov.* **1**, 100051 (2020).
44. B. Dong, L. Liu, H. Xu, and M. Sun, "Experimental and theoretical evidence for the chemical mechanism in SERRS of rhodamine 6G adsorbed on colloidal silver excited at 1064 nm," *J. Raman Spectrosc.* **41**, 719–720 (2010).
45. X. Ling, L. Xie, Y. Fang, H. Xu, H. Zhang, J. Kong, M. S. Dresselhaus, J. Zhang, and Z. Liu, "Can graphene be used as a substrate for Raman enhancement?," *Nano Lett.* **10**, 553–561 (2010).
46. K. L. Kelly, E. Coronado, L. L. Zhao, and G. C. Schatz, "The optical properties of metal nanoparticles: The influence of size, shape, and dielectric environment," *J. Phys. Chem. B* **107**, 668–677 (2003).
47. X. Liu, A. Dang, T. Li, Y. Sun, T.-C. Lee, W. Deng, S. Wu, A. Zada, T. Zhao, and H. Li, "Plasmonic coupling of Au nanoclusters on a flexible mxene/graphene oxide fiber for ultrasensitive SERS sensing," *ACS Sensors* **8**, 1287–1298 (2023).
48. X. Liu, A. Dang, T. Li, Y. Sun, W. Deng, T.-C. Lee, Y. Yang, A. Zada, B. Wang, Y. Liu, S. Wu, and T. Zhao, "Efficient multiplexed label-free detection by flexible MXene/graphene oxide fibers with enhanced charge transfer and hot spots effect," *Sensors Actuators B Chem.* **390**, 133888 (2023).
49. A. Ricciardi, A. Crescitelli, P. Vaiano, G. Quero, M. Consales, M. Pisco, E. Esposito, and A. Cusano, "Lab-on-fiber technology: a new vision for chemical and biological sensing," *Analyst* **140**, 8068–8079 (2015).
50. J. Albert, "A lab on fiber," *IEEE Spectr.* **51**, 48–53 (2014).
51. G. Quero, G. Zito, S. Managò, F. Galeotti, M. Pisco, A. Cutolo, A. C. De Luca, and A. Cusano, "Engineered Lab on Fiber SERS probes by "Self-assembly on fiber" technique," in *26th International Conference on Optical Fiber Sensors* (OSA, 2018), p. TuE7.
52. B. M. A. Rahman, C. Vipavakit, R. Chitaree, S. Ghosh, A. K. Pathak, S. Verma, and N. Sakda, "Optical fiber, nanomaterial, and THz-metasurface-mediated nanobiosensors: A review," *Biosensors* **12**, 42 (2022).
53. J. Kwak, W. Lee, J.-B. Kim, S.-I. Bae, and K.-H. Jeong, "Fiber-optic plasmonic probe with nanogap-rich Au nanoislands for on-site surface-enhanced Raman spectroscopy using repeated solid-state dewetting," *J. Biomed. Opt.* **24**, 1 (2019).
54. M. Li, M. Yan, B. Xu, C. Zhao, D. Wang, Y. Wang, and H. Chen, "A dual-mode optical fiber sensor for SERS and fluorescence detection in liquid," *Spectrochim. Acta Part A Mol. Biomol. Spectrosc.* **290**, 122267 (2023).
55. D. L. Stokes and T. Vo-Dinh, "Development of an integrated single-fiber SERS sensor," *Sensors Actuators B Chem.* **69**, 28–36 (2000).
56. J. Cheng, Z. Zhang, L. Zhang, J. Miao, Y. Chen, R. Zhao, M. Liu, L. Chen, and X. Wang, "Size-controllable colloidal Ag nano-aggregates with long-time SERS detection window for on-line high-throughput detection," *Talanta* **257**, 124358 (2023).
57. C. Viets and W. Hill, "Comparison of fibre-optic SERS sensors with differently prepared tips," *Sensors Actuators B Chem.* **51**, 92–99 (1998).
58. A. Dhawan, Y. Zhang, F. Yan, M. Gerhold, and T. Vo-Dinh, "Nano-engineered surface-enhanced Raman scattering (SERS) substrates with patterned structures on the distal end of optical fibers," in T. Vo-Dinh and J. R. Lakowicz, eds. (2008), p. 68690G.
59. X. Zheng, D. Guo, Y. Shao, S. Jia, S. Xu, B. Zhao, W. Xu, C. Corredor, and J. R.

- Lombardi, "Photochemical modification of an optical fiber tip with a silver nanoparticle film: A SERS chemical sensor," *Langmuir* **24**, 4394–4398 (2008).
60. W. Du, S. Wei, N. Li, Z. Hao, Y. Li, and M. Wang, "Highly sensitive fiber optic enhanced Raman scattering sensor," *Opt. Laser Technol.* **168**, 109879 (2024).
 61. A. K. Pathak, D. K. Chaudhary, and V. K. Singh, "Broad range and highly sensitive optical pH sensor based on Hierarchical ZnO microflowers over tapered silica fiber," *Sensors Actuators, A Phys.* (2018).
 62. P. R. Stoddart and D. J. White, "Optical fibre SERS sensors," *Anal. Bioanal. Chem.* **394**, 1761–1774 (2009).
 63. D. L. Stokes, J. P. Alarie, and T. Vo-Dinh, "Surface-enhanced Raman fiber optic sensors for remote monitoring," in T. Vo-Dinh, ed. (1995), pp. 552–558.
 64. W. Xu, S. Xu, Z. Lü, L. Chen, B. Zhao, and Y. Ozaki, "Ultrasensitive detection of 1, 4-bis(4-vinylpyridyl)phenylene in a small volume of low refractive index liquid by surface-enhanced Raman scattering-active light waveguide," *Appl. Spectrosc.* **58**, 414–419 (2004).
 65. S. Li, L. Xia, W. Li, X. Chen, Z. Yang, and J. Xia, "All-fiber SERS sensing with a depressed double cladding fiber probe embedded in a microfluidic chip," *Appl. Opt.* **58**, 7929 (2019).
 66. A. K. Pathak and C. Vipavakit, "VOC biomarker monitoring for diabetes through exhaled breath using Ag/P-TiO₂ composite plasmonic sensor," *IEEE Sens. J.* 1–1 (2021).
 67. Y. Zhang, C. Shi, C. Gu, L. Seballos, and J. Z. Zhang, "Molecular probe based on photonic crystal fiber (PCF) and surface enhanced Raman scattering (SERS)," in *2007 IEEE Sensors* (IEEE, 2007), pp. 375–377.
 68. X. Zhi-Guo, L. Yong-Hua, W. Pei, L. Kai-Qun, Y. Jie, and M. Hai, "Photonic crystal fibre SERS sensors based on silver nanoparticle colloid," *Chinese Phys. Lett.* **25**, 4473–4475 (2008).
 69. Z. Sun, X. Fang, L. Zha, T. Cheng, C. Kang, Y. Han, and X. Zhang, "Surface mode enhanced by avoided crossing in microstructure fibers for improved SERS sensing," *Sensors Actuators B Chem.* **368**, 132249 (2022).
 70. Y. Han, "Index-guiding liquid-core photonic crystal fiber for solution measurement using normal and surface-enhanced Raman scattering," *Opt. Eng.* **47**, 040502 (2008).
 71. C. Shi, C. Lu, C. Gu, L. Tian, R. Newhouse, S. Chen, and J. Z. Zhang, "Inner wall coated hollow core waveguide sensor based on double substrate surface enhanced Raman scattering," *Appl. Phys. Lett.* **93**, 153101 (2008).
 72. Y. Cao, Y. Cheng, and M. Sun, "Graphene-based SERS for sensor and catalysis," *Appl. Spectrosc. Rev.* **58**, 1–38 (2023).
 73. X.-L. Wei, L. Jiang, Q.-L. Shi, and Z.-H. Mo, "Machine-learning-assisted SERS nanosensor platform toward chemical fingerprinting of Baijiu flavors," *Microchim. Acta* **190**, 207 (2023).
 74. H. V. Chu, Y. Liu, Y. Huang, and Y. Zhao, "A high sensitive fiber SERS probe based on silver nanorod arrays," *Opt. Express* **15**, 12230 (2007).
 75. H. Yan, C. Gu, C. Yang, J. Liu, G. Jin, J. Zhang, L. Hou, and Y. Yao, "Hollow core photonic crystal fiber surface-enhanced Raman probe," *Appl. Phys. Lett.* **89**, 204101 (2006).
 76. A. LUCOTTI and G. ZERBI, "Fiber-optic SERS sensor with optimized geometry," *Sensors Actuators B Chem.* **121**, 356–364 (2007).
 77. Y. Zhang, C. Shi, C. Gu, L. Seballos, and J. Z. Zhang, "Liquid core photonic crystal fiber sensor based on surface enhanced Raman scattering," *Appl. Phys. Lett.* **90**, 193504 (2007).

78. C. Shi, H. Yan, C. Gu, D. Ghosh, L. Seballos, S. Chen, J. Z. Zhang, and B. Chen, "A double substrate "sandwich" structure for fiber surface enhanced Raman scattering detection," *Appl. Phys. Lett.* **92**, 103107 (2008).
79. E. J. Smythe, M. D. Dickey, J. Bao, G. M. Whitesides, and F. Capasso, "Optical antenna arrays on a fiber facet for *in situ* surface-enhanced Raman scattering detection," *Nano Lett.* **9**, 1132–1138 (2009).
80. G. F. S. Andrade, M. Fan, and A. G. Brolo, "Multilayer silver nanoparticles-modified optical fiber tip for high performance SERS remote sensing," *Biosens. Bioelectron.* **25**, 2270–2275 (2010).
81. K. Kneipp, H. Kneipp, I. Itzkan, R. R. Dasari, and M. S. Feld, "Surface-enhanced non-linear Raman scattering at the single-molecule level," *Chem. Phys.* **247**, 155–162 (1999).
82. K. Kneipp, S. R. Emory, and S. Nie, "Single-molecule Raman spectroscopy – Fact or fiction?," *Chimia (Aarau)*. **53**, 35 (1999).
83. J. Cao, D. Zhao, X. Lei, Y. Liu, and Q. Mao, "One-pot hydrothermal synthesis of silver nanoplates on optical fiber tip for surface-enhanced Raman scattering," *Appl. Phys. Lett.* **104**, 201906 (2014).
84. J. Cao and J. Wang, "Development of Ag nanopolyhedra based fiber-optic probes for high performance SERS detection," *New J. Chem.* **39**, 2421–2424 (2015).
85. Y. Liu, F. Zhou, H. Wang, X. Huang, and D. Ling, "Micro-coffee-ring-patterned fiber SERS probes and their *in situ* detection application in complex liquid environments," *Sensors Actuators B Chem.* **299**, 126990 (2019).
86. L. Collard, F. Pisano, D. Zheng, A. Balena, M. F. Kashif, M. Pisanello, A. D'Orazio, L. M. de la Prida, C. Ciraci, M. Grande, M. De Vittorio, and F. Pisanello, "Holographic manipulation of nanostructured fiber optics enables spatially-resolved, reconfigurable optical control of plasmonic local field enhancement and SERS," *Small* **18**, 2200975 (2022).
87. H. L. MacDonald, R. C. Jorgenson, C. L. Schoen, B. F. Smith, S. S. Yee, and K. I. Mullen, "<title>Improving surface-enhanced Raman spectroscopy (SERS) for better sensors</title>," in R. A. Lieberman, ed. (1994), pp. 198–208.
88. C. Viets and W. Hill, "Fibre-optic SERS sensors with angled tips," *J. Mol. Struct.* **565–566**, 515–518 (2001).
89. M. Fan, P. Wang, C. Escobedo, D. Sinton, and A. G. Brolo, "Surface-enhanced Raman scattering (SERS) optrodes for multiplexed on-chip sensing of nile blue A and oxazine 720," *Lab Chip* **12**, 1554 (2012).
90. X. Yang, N. Ileri, C. C. Larson, T. C. Carlson, J. A. Britten, A. S. P. Chang, C. Gu, and T. C. Bond, "Nanopillar array on a fiber facet for highly sensitive surface-enhanced Raman scattering," *Opt. Express* **20**, 24819 (2012).
91. Z. Huang, X. Lei, Y. Liu, Z. Wang, X. Wang, Z. Wang, Q. Mao, and G. Meng, "Tapered optical fiber probe assembled with plasmonic nanostructures for surface-enhanced Raman scattering application," *ACS Appl. Mater. Interfaces* **7**, 17247–17254 (2015).
92. S. S. Gao, S. B. Shang, X. Y. Liu, Z. Li, Y. Q. Sheng, C. Zhang, C. Yang, H. W. Qiu, Y. Y. Huo, and S. Z. Jiang, "An optical fiber SERS sensor based on GO/AgNPs/rGO sandwich structure hybrid films," *RSC Adv.* **6**, 81750–81756 (2016).
93. G. Tsiminis, K. J. Rowland, E. P. Schartner, N. A. Spooner, T. M. Monro, and H. Ebendorff-Heidepriem, "Single-ring hollow core optical fibers made by glass billet extrusion for Raman sensing," *Opt. Express* **24**, 5911 (2016).
94. J. Cao, D. Zhao, and Y. Qin, "Novel strategy for fabrication of sensing layer on thiol-functionalized fiber-optic tapers and their application as SERS probes," *Talanta* **194**, 895–902 (2019).

95. Y. Long, H. Li, Z. Du, M. Geng, and Z. Liu, "Confined Gaussian-distributed electromagnetic field of tin(II) chloride-sensitized surface-enhanced Raman scattering (SERS) optical fiber probe: From localized surface plasmon resonance (LSPR) to waveguide propagation," *J. Colloid Interface Sci.* **581**, 698–708 (2021).
96. D. Zheng, F. Pisano, L. Collard, A. Balena, M. Pisanello, B. Spagnolo, R. Mach-Batlle, F. Tantussi, L. Carbone, F. De Angelis, M. Valiente, L. M. de la Prida, C. Ciraci, M. De Vittorio, and F. Pisanello, "Toward plasmonic neural probes: SERS detection of neurotransmitters through gold-nanoislands-decorated tapered optical fibers with sub-10 nm gaps," *Adv. Mater.* **35**, 2200902 (2023).
97. Y. Liu, J. Guang, C. Liu, S. Bi, Q. Liu, P. Li, N. Zhang, S. Chen, H. Yuan, D. Zhou, and W. Peng, "Simple and low-cost plasmonic fiber-optic probe as SERS and biosensing platform," *Adv. Opt. Mater.* **7**, 1900337 (2019).
98. J. Cao, D. Zhao, and Q. Mao, "A highly reproducible and sensitive fiber SERS probe fabricated by direct synthesis of closely packed AgNPs on the silanized fiber taper," *Analyst* **142**, 596–602 (2017).
99. Z. Chen, Z. Dai, N. Chen, S. Liu, F. Pang, B. Lu, and T. Wang, "Gold nanoparticles-modified tapered fiber nanoprobes for remote SERS detection," *IEEE Photonics Technol. Lett.* **26**, 777–780 (2014).
100. F. Cheng, H. Xu, C. Wang, Z. Gong, C. Tang, and M. Fan, "Surface enhanced Raman scattering fiber optic sensor as an ion selective optrode: the example of Cd²⁺ detection," *RSC Adv.* **4**, 64683–64687 (2014).
101. N. T. Truc Phuong, V. Q. Dang, L. Van Hieu, T. N. Bach, B. X. Khuyen, H. K. Thi Ta, H. Ju, B. T. Phan, and N. H. Thi Tran, "Functionalized silver nanoparticles for SERS amplification with enhanced reproducibility and for ultrasensitive optical fiber sensing in environmental and biochemical assays," *RSC Adv.* **12**, 31352–31362 (2022).
102. X. Zhang, K. Zhang, H. von Bredow, C. Metting, G. Atanasoff, R. M. Briber, and O. Rabin, "Remote chemical sensing by SERS with self-assembly plasmonic nanoparticle arrays on a fiber," *Front. Phys.* **9**, (2022).
103. T. Pan, D. Lu, H. Xin, and B. Li, "Biophotonic probes for bio-detection and imaging," *Light Sci. Appl.* **10**, 124 (2021).
104. F. Chiavaioli, P. Zubiarte, I. Del Villar, C. R. Zamarreño, A. Giannetti, S. Tombelli, C. Trono, F. J. Arregui, I. R. Matias, and F. Baldini, "Femtomolar detection by nanocoated fiber label-free biosensors," *ACS Sensors* **3**, 936–943 (2018).
105. C. Caucheteur, T. Guo, F. Liu, B.-O. Guan, and J. Albert, "Ultrasensitive plasmonic sensing in air using optical fibre spectral combs," *Nat. Commun.* **7**, 13371 (2016).
106. F. Chiavaioli, C. Gouveia, P. Jorge, and F. Baldini, "Towards a uniform metrological assessment of grating-based optical fiber sensors: From refractometers to biosensors," *Biosensors* **7**, 23 (2017).
107. F. Liu, X. Zhang, K. Li, T. Guo, A. Ianoul, and J. Albert, "Discrimination of bulk and surface refractive index change in plasmonic sensors with narrow bandwidth resonance combs," *ACS Sensors* **6**, 3013–3023 (2021).
108. F. Chiavaioli, D. Santano Rivero, I. Del Villar, A. B. Socorro-Lerános, X. Zhang, K. Li, E. Santamaría, J. Fernández-Irigoyen, F. Baldini, D. L. A. van den Hove, L. Shi, W. Bi, T. Guo, A. Giannetti, and I. R. Matias, "Ultrahigh sensitive detection of tau protein as alzheimer's biomarker via microfluidics and nanofunctionalized Optical Fiber Sensors," *Adv. Photonics Res.* **3**, 2200044 (2022).
109. J. Lao, P. Sun, F. Liu, X. Zhang, C. Zhao, W. Mai, T. Guo, G. Xiao, and J. Albert, "In situ plasmonic optical fiber detection of the state of charge of supercapacitors for renewable energy storage," *Light Sci. Appl.* **7**, 34 (2018).
110. P. Li, F. Long, W. Chen, J. Chen, P. K. Chu, and H. Wang, "Fundamentals and

- applications of surface-enhanced Raman spectroscopy-based biosensors," *Curr. Opin. Biomed. Eng.* **13**, 51–59 (2020).
111. C. Zong, M. Xu, L.-J. Xu, T. Wei, X. Ma, X.-S. Zheng, R. Hu, and B. Ren, "Surface-enhanced Raman spectroscopy for bioanalysis: Reliability and challenges," *Chem. Rev.* **118**, 4946–4980 (2018).
 112. V. M. Szlag, R. S. Rodriguez, J. He, N. Hudson-Smith, H. Kang, N. Le, T. M. Reineke, and C. L. Haynes, "Molecular affinity agents for intrinsic surface-enhanced Raman scattering (SERS) sensors," *ACS Appl. Mater. Interfaces* **10**, 31825–31844 (2018).
 113. T. M. Squires, R. J. Messinger, and S. R. Manalis, "Making it stick: convection, reaction and diffusion in surface-based biosensors," *Nat. Biotechnol.* **26**, 417–426 (2008).
 114. Z. Wang, S. Zong, L. Wu, D. Zhu, and Y. Cui, "SERS-activated platforms for immunoassay: Probes, encoding methods, and applications," *Chem. Rev.* **117**, 7910–7963 (2017).
 115. Y. Wang, S. Kang, A. Khan, G. Ruttner, S. Y. Leigh, M. Murray, S. Abeytunge, G. Peterson, M. Rajadhyaksha, S. Dintzis, S. Javid, and J. T. C. Liu, "Quantitative molecular phenotyping with topically applied SERS nanoparticles for intraoperative guidance of breast cancer lumpectomy," *Sci. Rep.* **6**, 21242 (2016).
 116. U. S. Dinish, F. Beffara, G. Humbert, J. Auguste, and M. Olivo, "Surface-enhanced Raman scattering-active photonic crystal fiber probe: Towards next generation liquid biopsy sensor with ultra high sensitivity," *J. Biophotonics* **12**, (2019).
 117. J. P. Scaffidi, M. K. Gregas, V. Seewaldt, and T. Vo-Dinh, "SERS-based plasmonic nanobiosensing in single living cells," *Anal. Bioanal. Chem.* **393**, 1135–1141 (2009).
 118. J. Wang, Y. Geng, Y. Shen, W. Shi, W. Xu, and S. Xu, "SERS-active fiber tip for intracellular and extracellular pH sensing in living single cells," *Sensors Actuators B Chem.* **290**, 527–534 (2019).
 119. X. Yang, C. Gu, F. Qian, Y. Li, and J. Z. Zhang, "Highly sensitive detection of proteins and bacteria in aqueous solution using surface-enhanced Raman scattering and optical fibers," *Anal. Chem.* **83**, 5888–5894 (2011).
 120. X. Yang, Z. Tanaka, R. Newhouse, Q. Xu, B. Chen, S. Chen, J. Z. Zhang, and C. Gu, "Portable fiber sensors based on surface-enhanced Raman scattering," *Rev. Sci. Instrum.* **81**, 123103 (2010).
 121. D. U. S., C. Y. Fu, K. S. Soh, B. Ramaswamy, A. Kumar, and M. Olivo, "Highly sensitive SERS detection of cancer proteins in low sample volume using hollow core photonic crystal fiber," *Biosens. Bioelectron.* **33**, 293–298 (2012).
 122. T. Gong, N. Zhang, K. V. Kong, D. Goh, C. Ying, J.-L. Auguste, P. P. Shum, L. Wei, G. Humbert, K.-T. Yong, and M. Olivo, "Rapid SERS monitoring of lipid-peroxidation-derived protein modifications in cells using photonic crystal fiber sensor," *J. Biophotonics* **9**, 32–37 (2016).
 123. A. Khetani, A. Momenpour, E. I. Alarcon, and H. Anis, "Hollow core photonic crystal fiber for monitoring leukemia cells using surface enhanced Raman scattering (SERS)," *Biomed. Opt. Express* **6**, 4599 (2015).
 124. D. Rithesh Raj, S. Prasanth, T. V. Vineeshkumar, and C. Sudarsanakumar, "Surface plasmon resonance based fiber optic dopamine sensor using green synthesized silver nanoparticles," *Sensors Actuators B Chem.* **224**, 600–606 (2016).
 125. N. La Ngoc Tran, B. T. Phan, H. K. T. Ta, T. T. K. Chi, B. T. T. Hien, N. T. T. Phuong, C. C. Nguyen, T. L. H. Doan, and N. H. T. Tran, "Gold nanoparticles are capped under the IRMOF-3 platform for in-situ surface-enhanced Raman scattering technique and optic fiber sensor," *Sensors Actuators A Phys.* **347**, 113932 (2022).
 126. C. Credi, O. Bibikova, C. Dallari, B. Tiribilli, F. Ratto, S. Centi, R. Pini, V. Artyushenko, R. Cicchi, and F. S. Pavone, "Fiber-cap biosensors for SERS analysis of liquid samples,"

- J. Mater. Chem. B **8**, 1629–1639 (2020).
127. W. Cui, A. Xiao, J. Zheng, P. Chen, J. Liang, Y. Huang, and B.-O. Guan, "Facile preparation of monodisperse silver nanorods with tunable plasmon resonances in the near-infrared region: Implications for SERS-Based Sensing," *ACS Appl. Nano Mater.* **6**, 6345–6353 (2023).
 128. P. Pinkhasova, H. Chen, J. Kanka, P. Mergo, and H. Du, "Nanotag-enabled photonic crystal fiber as quantitative surface-enhanced Raman scattering optofluidic platform," *Appl. Phys. Lett.* **106**, 071106 (2015).
 129. Y. Q. Shi, Z. Xu, L. Wang, K. Wang, L. Xu, and H. Zheng, "The fluorescence and colorimetric dual-readout probe for clinical rapid detection of mycophenolic acid by the poly(ethylenimine)/silica-coated CdTe quantum dots," *Anal. Biochem.* **668**, (2023).
 130. Y. Huo, S. Zhang, C. Pan, H. Shan, Y. Xu, and X. Cai, "A robust procedure for determination of immunosuppressants cyclosporine A and tacrolimus in blood samples with detection of LC–MS/MS," *Chromatographia* **86**, 255–263 (2023).
 131. P. S.-W. Yeung, P. Miller, T. B. Lai-Nyugen, P. Cheng, A. Ibrahim, R.-Z. Shi, R. A. R. Bowen, and R. Y. Luo, "Mass spectrometry quantitation of immunosuppressive drugs in clinical specimens using online solid-phase extraction and accurate-mass full scan-single ion monitoring," *J. Mass Spectrom. Adv. Clin. Lab* **28**, 99–104 (2023).
 132. U. Garg, A. Munar, and C. Frazee, "Quantitation of mycophenolic acid and mycophenolic acid glucuronide in serum or plasma by LC-MS/MS," *Curr. Protoc.* **3**, e730 (2023).
 133. M. Zhang, Y. Lu, L. Zhang, X. Xu, B. Li, X. Zhao, X. Yan, C. Wang, P. Sun, X. Liu, and G. Lu, "Flexible and wearable glove-based SERS sensor for rapid sampling and sensitive detection of controlled drugs," *Sensors Actuators B Chem.* **386**, 133738 (2023).
 134. A. Jaworska, S. Fornasaro, V. Sergo, and A. Bonifacio, "Potential of surface enhanced Raman spectroscopy (SERS) in therapeutic drug monitoring (TDM). A critical review," *Biosensors* **6**, (2016).
 135. T. Frosch, D. Yan, and J. Popp, "Ultrasensitive fiber enhanced UV resonance Raman sensing of drugs," *Anal. Chem.* **85**, 6264–6271 (2013).
 136. L. Meng, L. Shang, S. Feng, Z. Tang, C. Bi, H. Zhao, and G. Liu, "Optical fiber optrodes with silver-coated gold nanocavity ordered arrays for highly sensitive surface enhanced Raman spectrum," *Sensors Actuators B Chem.* **380**, (2023).
 137. P. Sui, A. Zhang, F. Pan, P. Chang, H. Pan, F. Liu, J. Wang, and C. Cao, "High sensitivity refractive index sensor with wide detection range and high linearity based on LSPR in hollow-core anti-resonance fiber," *Opt. Laser Technol.* **155**, (2022).
 138. A. Pathak, C. Vipavakit, B. M. A. Rahman, and V. Singh, "A highly sensitive SPR refractive index sensor based on microfluidic channel assisted with graphene-Ag composite nanowire," *IEEE Photonics J.* **13**, 1–8 (2021).
 139. J. B. Maurya, J. P. Saini, A. K. Sharma, and Y. K. Prajapati, "A localized SPR D-shaped fiber optic sensor utilizing silver grating coated with graphene: Field analysis," *Opt. Fiber Technol.* **75**, (2023).
 140. G. Zhu, L. Singh, Y. Wang, R. Singh, B. Zhang, F. Liu, B. K. Kaushik, and S. Kumar, "Tapered optical fiber-based LSPR biosensor for ascorbic acid detection," *Photonic Sensors* **11**, 418–434 (2021).
 141. D. Yan, J. Popp, M. W. Pletz, and T. Frosch, "Highly sensitive broadband Raman sensing of antibiotics in step-index hollow-core photonic crystal fibers," *ACS Photonics* **4**, 138–145 (2017).
 142. S. Liu, J. Huang, Z. Chen, N. Chen, F. Pang, T. Wang, and L. Hu, "Raman spectroscopy measurement of levofloxacin lactate in blood using an optical fiber nano-probe," *J.*

- Raman Spectrosc. **46**, 197–201 (2015).
143. D. Jin, Y. Bai, H. Chen, S. Liu, N. Chen, J. Huang, S. Huang, and Z. Chen, "SERS detection of expired tetracycline hydrochloride with an optical fiber nano-probe," *Anal. Methods* **7**, 1307–1312 (2015).
 144. P. Teng, D. Gao, X. Yang, M. Luo, D. Kong, S. Gao, Z. Liu, Z. Li, X. Wen, L. Yuan, K. Li, M. Bowkett, and N. Copner, "In situ SERS detection of quinolone antibiotic residues in a water environment based on optofluidic in-fiber integrated Ag nanoparticles," *Appl. Opt.* **60**, 6659–6664 (2021).
 145. P. Jasrotia, B. Priya, R. Kumar, P. Bishnoi, A. Vij, and T. Kumar, "A correlation between fractal growth, water contact angle, and SERS intensity of R6G on ion beam nanostructured ultra-thin gold (Au) films," *Front. Phys.* **11**, (2023).
 146. A. Pathak, K. Swargiary, N. Kongsawang, P. Jitpratak, N. Ajchareeyasoonorn, J. Udomkittivorakul, and C. Viphavakit, "Recent advances in sensing materials targeting clinical volatile organic compound (VOC) biomarkers: A review," *Biosensors* **13**, 114 (2023).
 147. Z. Li, K. Han, A. Zhang, T. Wang, Z. Yan, Z. Ding, Y. Shen, M. Zhang, and W. Zhang, "Honeycomb-like AgNPs@TiO₂ array SERS sensor for the quantification of micro/nanoplastics in the environmental water samples," *Talanta* **266**, 125070 (2024).
 148. C. Liu, D. Xu, X. Dong, and Q. Huang, "A review: Research progress of SERS-based sensors for agricultural applications," *Trends Food Sci. Technol.* **128**, 90–101 (2022).
 149. A. M. Alak and T. Vo-Dinh, "Surface-enhanced Raman spectrometry of organo phosphorus chemical agents," *Anal. Chem.* **59**, 2149–2153 (1987).
 150. T. B. Pham, H. Bui, V. H. Pham, and T. C. Do, "Surface-enhanced Raman spectroscopy based on Silver nano-dendrites on microsphere end-shape optical fibre for pesticide residue detection," *Optik (Stuttg.)* **219**, 165172 (2020).
 151. H. Zhou, J. Qiu, Y. Zhang, Y. Liang, L. Han, and Y. Zhang, "Self-assembled C-Ag hybrid nanoparticle on nanoporous GaN enabled ultra-high enhancement factor SERS sensor for sensitive thiram detection," *J. Hazard. Mater.* 133868 (2024).
 152. S.-S. Zhao, Z.-H. He, X. Liu, Y. Shen, X.-C. Tan, Q. Wang, J. Yan, and W.-W. Zhu, "Dialdehyde starch-enclosed silver nanoparticles substrate with controlled-release "hotspots" for ultrasensitive SERS detection of thiabendazole," *Food Chem.* **436**, 137706 (2024).
 153. Q. Wei, C. Pan, T. Wang, H. Pu, and D.-W. Sun, "A three-dimensional gold nanoparticles spherical liquid array for SERS sensitive detection of pesticide residues in apple," *Spectrochim. Acta Part A Mol. Biomol. Spectrosc.* **304**, 123357 (2024).
 154. Y. Long, H. Li, W. Wang, X. Yang, and Z. Liu, "Ultrasensitive detection of Cr(VI) using a novel SERS optical fiber probe modified by dual-functional methimazole," *J. Alloys Compd.* **910**, 164916 (2022).
 155. B. Wang, Y. Liu, C. Ai, R. Chu, M. Chen, H. Ye, H. Wang, and F. Zhou, "Highly sensitive SERS detection in a non-volatile liquid-phase system with nanocluster-patterned optical fiber SERS probes," *Opt. Express* **30**, 15846 (2022).
 156. F. Zhou, Y. Liu, H. Wang, Y. Wei, G. Zhang, H. Ye, M. Chen, and D. Ling, "Au-nanorod-clusters patterned optical fiber SERS probes fabricated by laser-induced evaporation self-assembly method," *Opt. Express* **28**, 6648 (2020).
 157. C. Liu, S. Wang, C. Fu, H. Li, S. Xu, and W. Xu, "Preparation of surface-enhanced Raman scattering(SERS)-active optical fiber sensor by laser-induced Ag deposition and its application in bioidentification of biotin/avidin," *Chem. Res. Chinese Univ.* **31**, 25–30 (2015).
 158. T. B. Pham, T. H. C. Hoang, V. C. Nguyen, D. C. Vu, H. Bui, and V. H. Pham, "Improved versatile SERS spheroid end-facet optical fiber substrate based on silver

- nano-dendrites directly planted with gold nanoparticles using dual-laser assisted for pesticides detection," *Opt. Mater. (Amst)*. **126**, 112196 (2022).
159. T. B. Pham, T. H. C. Hoang, V. H. Pham, V. C. Nguyen, T. Van Nguyen, D. C. Vu, V. H. Pham, and H. Bui, "Detection of permethrin pesticide using silver nano-dendrites SERS on optical fibre fabricated by laser-assisted photochemical method," *Sci. Rep.* **9**, 12590 (2019).
 160. A. Kumar Shakya and S. Singh, "State of the art in fiber optics sensors for heavy metals detection," *Opt. Laser Technol.* **153**, 108246 (2022).
 161. W. Gao, W. Duan, D. Peng, J. Li, Z. Hu, D. Wang, Z. Gong, and M. Fan, "Surface-enhanced Raman scattering (SERS) microbial sensor for fresh water acute toxicity monitoring," *Microchem. J.* **191**, 108822 (2023).
 162. X. Zhang, C. Liu, J. Liu, and J. Yang, "Single modal interference-based fiber-optic sensor for simultaneous measurement of curvature and strain with dual-differential temperature compensation," *IEEE Sens. J.* **18**, 8375–8380 (2018).
 163. L. S. Laxmeshwar, M. S. Jadhav, J. F. Akki, P. Raikar, J. Kumar, O. Prakash, and U. S. Raikar, "Highly sensitive fiber grating chemical sensors: An effective alternative to atomic absorption spectroscopy," *Opt. Laser Technol.* **91**, 27–31 (2017).
 164. C. H. Tan, S. T. Tan, H. B. Lee, R. T. Ginting, H. F. Oleiwi, C. C. Yap, M. H. H. Jumali, and M. Yahaya, "Automated room temperature optical absorbance CO sensor based on In-doped ZnO nanorod," *Sensors Actuators B Chem.* **248**, 140–152 (2017).
 165. O. Guselnikova, P. Postnikov, M. Erzina, Y. Kalachyova, V. Švorčík, and O. Lyutakov, "Pretreatment-free selective and reproducible SERS-based detection of heavy metal ions on DTPA functionalized plasmonic platform," *Sensors Actuators B Chem.* **253**, 830–838 (2017).
 166. R. Hao, X. Xiao, X. Zuo, J. Nan, and W. Zhang, "Efficient adsorption and visible-light photocatalytic degradation of tetracycline hydrochloride using mesoporous BiOI microspheres," *J. Hazard. Mater.* **209–210**, 137–145 (2012).
 167. H. Fattahimoghaddam, T. Mahvelati-Shamsabadi, and B.-K. Lee, "Efficient photodegradation of rhodamine B and tetracycline over robust and green g-C₃N₄ nanostructures: Supramolecular design," *J. Hazard. Mater.* **403**, 123703 (2021).
 168. S. Kaja, A. V. Mathews, V. V. K. Venuganti, and A. Nag, "Bimetallic Ag–Cu alloy SERS substrates as label-free biomedical sensors: Femtomolar detection of anticancer drug mitoxantrone with multiplexing," *Langmuir* **39**, 5591–5601 (2023).
 169. A. A. Al-Gheethi, Q. M. Azhar, P. Senthil Kumar, A. A. Yusuf, A. K. Al-Buriahi, R. M. S. Radin Mohamed, and M. M. Al-shaibani, "Sustainable approaches for removing Rhodamine B dye using agricultural waste adsorbents: A review," *Chemosphere* **287**, 132080 (2022).
 170. J. Neng, Y. Wang, Y. Zhang, P. Chen, and K. Yang, "MIPs–SERS sensor based on Ag NPs film for selective detection of enrofloxacin in food," *Biosensors* **13**, 330 (2023).
 171. H. Wang, L. Zhang, C. Chen, G. I. N. Waterhouse, Y. Sun, and Z. Xu, "SERS sensor based on core–shell Au@Ag nanoparticles for the sensitive detection of acrylamide in foods," *Food Anal. Methods* (2024).
 172. X. Lan, Y. Han, T. Wei, Y. Zhang, L. Jiang, H.-L. Tsai, and H. Xiao, "Surface-enhanced Raman-scattering fiber probe fabricated by femtosecond laser," *Opt. Lett.* **34**, 2285 (2009).
 173. Y. Ran, P. Strobbia, V. Cupil-Garcia, and T. Vo-Dinh, "Fiber-optrode SERS probes using plasmonic silver-coated gold nanostars," *Sensors Actuators B Chem.* **287**, 95–101 (2019).
 174. S.-H. Chang, J. Nyagilo, J. Wu, Y. Hao, and D. P. Davé, "Optical fiber-based surface-enhanced Raman scattering sensor using Au nanovoid arrays," *Plasmonics* **7**, 501–508

(2012).