Resonant Metasurfaces for Spectroscopic Detection: Physics and Biomedical Applications

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Received 14 January 2022; Accepted 20 May 2022; Published 6 July 2022

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Metasurfaces are ultrathin metamaterials consisting of subwavelength scatterers (e.g., meta-atoms) arranged in a specific sequence that generates low radiation losses and fantastic optical resonances. According to the electromagnetic response properties, metasurfaces can be divided into two categories: metallic nanostructures based on the response of plasmonic excitations (e.g., noble metals and graphene) and all-dielectric nanostructures based on near-field scattering (e.g., Mie scattering). Metasurfaces supporting various optical modes possess optical localization and electromagnetic field enhancement capabilities on the subwavelength scale, making them a promising platform for label-free detection in biomedical sensing. Metasurface-based optical sensors offer several outstanding advantages over conventional spectroscopic detection solutions, such as planar structures, low loss, miniaturization, and integration. Recently, novel sensing and even imaging tools based on metasurfaces have widely loomed and been proposed. Given recent advances in the field of metasurface spectroscopic detection, this review briefly summarizes the main resonance mechanisms of metasurfaces and the notable achievements, including refractive index sensing, surface-enhanced Raman scattering, surface-enhanced infrared absorption, and chiral sensing in the ultraviolet to terahertz wavelengths. Ultimately, we draw a summary of the current challenges of metasurface spectroscopic detection and look forward to future directions for improving these techniques. As the subject is broad and growing, our review will not be comprehensive. Nevertheless, we will endeavor to describe the main research in this area and assess some of the relevant literature.

1. Introduction

Metasurface is usually an artificial planar electromagnetic material consisting of a large number of periodically arranged sub-wavelength scale structures (i.e., meta-atoms), drawing a great deal of attention in different fields such as materials science and electromagnetism. By carefully designing the structure and arrangement of the meta-atoms and integrated functional materials, arbitrary modulation of the electromagnetic (EM) response from microwave to visible and even ultraviolet (UV) wavelengths can be achieved. Planar metasurfaces can be manufactured in bulk using existing technologies including photolithography and nanoimprinting, which has prompted the enrichment of many single-layer or multilayer metasurface devices with optical functions such as wavefront shaping [1, 2], metasens [3, 4], electromagnetic cloaking [5, 6], holographic imaging [7–9], polarization modulation [10], and biochemical sensing [11–16]. These planar devices driven by metasurfaces represent a novel class of optical elements that are ultracompact, ultrathin, and low loss. In the field of sensing, optical sensing technology offers fast and robust methods for detecting, differentiating, and quantifying targets from a wide range of samples, even probing their molecular structure. Spectroscopic analysis of biochemical molecules, biological tissue, proteins, cells, and germs/viruses is of great significance in biomedical sensing applications. Spectroscopic detection techniques are primarily used to explore and analyze the interaction between target molecules and electromagnetic waves, with the core capability of detecting and even decoding the spectroscopic response to external environmental stimuli. Metasurfaces that support the confinement of light to the subwavelength range and highly localized field enhancement...
are extremely sensitive to surrounding target analytes, allowing the detection of these target molecules at the nanoscale or even lower. Compared with conventional spectroscopic detection equipment, metasurface-based spectroscopic detection devices show undeniable advantages, including the ability to provide truly label-free, nondestructive measurements and the potential for multiplexing and miniaturization, offering great promise for highly integrated detection devices. For instance, plasmonic metasurfaces in the mid-infrared (mid-IR) can monitor changes in trace drugs inside the body by extracting generic molecular vibrational fingerprints, truly enabling wearable and noninvasive detection, which is challenging with traditional surface-enhanced Raman scattering spectroscopy methods [17]. Another recent work has used plasmonic metasurfaces as nanomicroscope slides for cellular imaging of breast cancer tissue and combined with colorimetric histology techniques to achieve naked eye differentiation between cancerous and normal tissue [18]. The combination of metasurface detection elements with laboratory and even human structures is transformative in bringing metasurface-based spectral detection devices to the market.

Up to now, a large number of advances in resonant metasurface-based spectroscopic detection have been successively reported. Based on the physical properties of the material, research on the spectroscopic detection of metasurfaces has focused on three main categories: plasmonic metasurfaces, all-dielectric metasurfaces, and hybrid metasurfaces (i.e., plasmonic-dielectric metasurfaces). Recent advances in micro-/nanooptics and nanophotonics have led to the application of spectroscopic detection techniques in diverse fields ranging from drug analysis to disease diagnosis, including (i) refractive index (RI) sensing for nonspecific sensing of RI changes in the surrounding dielectric environment, (ii) surface-enhanced Raman scattering (SERS) for the specific enhancement of unique vibrational signals of molecules, (iii) surface-enhanced infrared absorption (SEIRA) for the specific identification of molecular absorption fingerprints, and (iv) chiral sensing for the identification and quantification of chiral molecules. These efforts are broadly focused on four main areas: performance improvements, miniaturization, integration of systems, the addition of new features, and cost reductions [12]. There have also been several shifts in improving the performance of metasurfaces, such as the replacement of plasmonic materials with all-dielectric materials to reduce absorption losses [19, 20], or the exploration of new resonance mechanisms such as quasi bound states in the continuum (quasi-BIC) [21, 22], Fano resonance [23, 24], and surface lattice resonance (SLR) [25] to achieve high quality (Q) resonances. In terms of miniaturized devices, the integration of metasurfaces with complementary metal-oxide-semiconductor (CMOS) or microfluidic systems offers the possibility of miniaturized devices [26–28]. From the perspective of functional enrichment multilayer metasurfaces [29, 30], or hybrid metasurfaces [31, 32] are used to obtain additional optical functionality. From the aspect of cost-effectiveness, wavelength-based interrogation is transformed into an intensity interrogation detection scheme to eliminate the need for cumbersome wavelength scanning or expensive spectrometers [27].

Herein, this review intends to propose a simple framework for resonant metasurface-based spectroscopic detection schemes and to help designers quickly understand and select the most suitable detection techniques for different micro- and nanosensing fields. Figure 1 gives an overview of the various main light-matter interaction mechanisms and applications of metasurface-based spectroscopic detection. Firstly, the physical mechanisms of resonant metasurfaces will be presented, including localized surface plasmon resonance (LSPR), SLR, Fano resonance, and quasi-BIC. Materials involved include noble metals, dielectrics, and two-dimensional (2D) materials (e.g., graphene). Next, we review research advances in the metasurface-based spectroscopic detection in the UV to the THz range, including RI sensing, SEIRA, SERS, and chiral sensing. Finally, the current challenges of metasurface spectroscopic detection are summarized and future directions for improving these techniques are forecasted.

2. The Mechanisms of Resonant Metasurface

Careful design of the interaction between EM waves and artificial meta-atoms enables complex wavefront modulation, including the modulation of multiple parameters such as amplitude, phase, wavelength, and polarization. The multiple optical modes or resonances generated by this process are one important mechanism for achieving modulation of these parameters [33]. Around the properties of meta-atomic resonance, how to manipulate these complex arrangements of meta-atoms in metasurfaces to achieve modulation of the spectrum has been a topical concern in recent years for nanooptical sensing. The spectroscopic properties of metasurfaces, including the absorption, reflection, transmission, and phase spectra, are closely related to EM field modes excited by meta-atoms themselves or between meta-atoms. Numerous works have demonstrated that modulation of EM field modes can be achieved by tuning parameters such as the material, structure, and arrangement of the meta-atoms, thus enabling spectroscopic modulation of the metasurfaces. Based on the EM response properties of the material, metasurfaces can be divided into two categories: metallic nanostructures based on plasmonic response (e.g., noble metals and graphene) and all-dielectric nanostructures based on near-field scattering (Mie scattering). Metallic nanostructures exploit plasmonic effects to generate large electric or magnetic field enhancements, while all-dielectric nanostructures with high refractive indices use near-field coupling (e.g., Mie resonance) to generate strong electrical and magnetic resonances simultaneously. All-dielectric metasurfaces can exhibit some similar properties as plasmonic metasurfaces, while their special design and parameter engineering make them outperform lossy plasmonic metasurfaces. Overall, blocks formed by resonant plasmonic and dielectric nanostructures bring unique and abundant optical functionalities to optical sensor devices. In this section, we will briefly describe the principles, characteristics, and influencing factors of several major resonance modes generated by the interaction of EM waves with plasmonic and dielectric meta-atoms, commonly utilized in the field of spectroscopic detection, including LSPR, SLR, Fano...
resonance, and quasi-BIC, as shown in Figures 1(a)–1(d). It should be mentioned that the optical resonance modes used for spectral detection are not limited to the abovementioned ones, but also surface plasmon polariton (SPP), guided-mode resonance (GMR), ring resonance, electric dipole (ED) or magnetic dipole (MD) resonance, electric/magnetic multipole resonance, etc. The type, function, and operating band of optical resonance can be effectively adjusted by changing the material, geometry, and arrangement of the unit.

2.1. Localized Surface Plasmon Resonance. When the size of the metallic nanostructure is smaller than the wavelength of the incident EM wave, a collective but nonpropagating electronic oscillation phenomenon is generated in the single metallic nanostructure, which is known as LSPR [34, 35], as shown in Figure 1(a). These LSPs have the remarkable ability to localize incident EM waves within a deep subwavelength volume (or within a thin layer), and after multiple scattering can increase the intensity of light (or multiple of the local electric field of nearby molecules) to more than about \(10^3\) [36]. This capability to capture light into nanoscale EM hotspots and to strongly enhance the field strength highly beneficial for improving the sensitivity of spectroscopic detection techniques, especially for single-molecule spectroscopy [37]. The LSPR depends strongly on the geometry and size of the plasmonic nanoparticles, their composition, and the RI of the surrounding medium, which means that it can be used to design meta-atoms with a wide range of optical properties [38]. In addition to metallic nanomaterials, graphene also exhibits a strong plasmonic response in the IR as a loss-free, zero-volume, optically, and electrically tunable material [37, 38]. Furthermore, graphene has good biocompatibility (or high overlap of molecular vibrational fingerprints) with nanobiomolecules. Therefore, several dielectric or plasmonic structures coupled to graphene have been proposed for attempted applications in spectroscopic detection, including the specific identification of biological components such as proteins and lipids [39–41].

2.2. Surface Lattice Resonance. Another strategy for the preparation of metasurfaces with strong optical properties is the arrangement of meta-atoms in a defined lattice. By arranging the meta-atoms in 1D or 2D periodic arrays, the near-field can be strongly enhanced due to near- and far-field coupling between the arrays, resulting in an array-induced SLR [42], as shown in Figure 1(b). SLRs, also known as collective resonances, can strongly enhance field localization and high Q-factor resonance [25]. The Q-factor of SLRs is commonly related to the period, arrangement, mate-atomic size, and the surrounding dielectric environment [43]. For instance, when the resonant wavelength is close to the product of the lattice period (\(P\)) and the RI of the dielectric environment (\(n\)), \(\lambda_{SLR} \approx nP\), a relatively high Q-factor SLR can be produced [42]. The latest results of using
SLR to obtain plasmonic metasurfaces with ultrahigh Q-factor of 2340 in the communication bands are exciting [44].

2.3. Fano Resonance. According to Mie theory, Fano resonance arises from the light scattering effect of a single dielectric/plasma nanoparticle [45]. They destructively and constructively interfere at the energy close positions, resulting in sharp and asymmetrical transmission/reflection curves (Figure 1(c)) [33]. There is a view that almost all resonances can be depicted in terms of Fano resonances because since can be treated as quasidiscrete states with complex frequencies [46]. The spectral response of the Fano resonance is strongly dependent on the structural asymmetry parameter and incident angle of the EM wave. Spectral positions and resonance line shapes of Fano resonances are highly sensitive to the geometry or dielectric constant of the local environment, where small perturbations can cause violent resonances or line shapeshifts [46]. This effect, combined with appropriate biomarkers, facilitates approaching the detection limits of single-molecule binding events and can make a new generation of label-free biochemical detection elements suitable for ultrasensitive applications.

2.4. Bound States in the Continuum. A recent strategy for obtaining ultrahigh Q-factor resonance modes is to use the theory of BIC [47]. In the field of electromagnetism, as a localized state coexisting with extended waves in the continuous spectral range, BIC has no energy leakage and an infinite lifetime [48]. There are two main mechanisms for BIC to limit mode energy leakage, including symmetry protection [49] and resonant coupling [50]. BIC can theoretically produce an infinite radiation Q-factor and lifetime. In practice, BIC can be turned into a “quasi-BIC” or “supercavity mode” by changing attention to the vicinity of the parameter space of BIC[51–53], whose Q-factor and resonant bandwidth become finite values, as shown in Figure 1(d). There are two main types of symmetry-breaking methods for quasi-BIC, including structural symmetry (e.g., in-plane asymmetry parameters, α), and excitation field symmetry (e.g., the angle of the incident light). Meta-atomic arrays with different symmetry mismatches have been demonstrated for the excitation of high Q-factor resonances, including asymmetrically tilted strip pairs [27], nanodisks with asymmetric holes [54], split-ring structures [55], and square split-ring structures [56]. Interestingly, from the point of view of spectral characteristics, quasi-BICs can be seen as the posterity of Fano resonances [46]. The quasi-BIC allows for fabrication defects and a limited range of structures to break the ideality of the system, while greatly suppressing radiation losses in micro-nanophotonic devices.

3. Spectroscopic Detection
Applications with Metasurfaces

3.1. Refractive Index Sensing. RI sensing provides highly sensitive detection of variations in the surrounding dielectric environment caused by changes in the composition of the target analyte, molecular interactions, etc. These changes are mainly in the local dielectric properties and can be detected and quantified by monitoring variations in resonant wavelength or transmission/reflection intensity, as shown in Figure 1(e). RI sensing enables label-free and direct detection as no chemical modification of the target or subsequent combination of other factors is required to generate a signal. Factors that need to be considered simultaneously when designing a metasurface for spectroscopic detection include the operating wavelength (or resonant wavelength, \( \lambda_{res} \)), resonant bandwidth (or full-width at half-maximum (FWHM)), and electrical/magnetic near-field resonance enhancement intensity. The main indicators used to evaluate and compare the sensing performance of RI sensors are sensitivity (S) and figure of merit (FOM). Wavelength sensitivity (S_\lambda) and intensity sensitivity (S_I) describe the ability of a nanostructure to sense changes in RI in a homogeneous environment, S_\lambda = \Delta \lambda_{res}/\Delta n, S_I = \Delta I/\Delta n [57]. FOM describes the accuracy of the measurable resonance minimum [58], FOM = S/FWHM. The limit of detection (LOD) is a complex system performance metric, determined by a combination of spectral resolution, contrast and sensitivity, and detection system [59].

One of the initial explorations of using metasurfaces to try to achieve nanoscale RI sensing is to investigate plasmonic modes. A plasmonic metasurface consisting of two mirror-image gold split-ring resonators is proposed that supports ring resonance and achieves a sensitivity of 485.3 GHz/RIU, as shown in Figure 1(a) [60]. When different concentrations of three types of lung cancer cells (Calu-1, A427, and 95D) are placed on the metasurface, a 2D “fingerprint” of the frequency and intensity changes in the resonance spectrum is obtained, allowing for rapid and direct differentiation of cell types and concentrations. The combination of wavelength and intensity provides a unique barcode for analytes with different refractive indices, which is also demonstrated in the visible wavelength. Abbey’s team proposed a plasmonic metasurface consisting of a silver supercavity film with cross-holes on a glass substrate, as shown in Figure 2(b) [61]. Combined with microfluidics, the metasurface supports dual resonance and enables polarization-dependent continuous dynamic modulation of the spectrum in the visible spectrum. Using its filtering function, it enables the “color” output of RI variations for different chemicals and obtains a unique chemical barcode consisting of the transmission and wavelength values of each RI together \((n = 1.0003~1.4707)\). Recently, this stark difference in color output has been used for the naked eye identification of cancer cells. Abbey’s team further proposed a metasurface consisting of a glass substrate, a silver film with periodically arranged hole-like patterns, and an ultrathin protective layer [18]. The metasurface is considered a nano-microscope slide for biological tissue imaging. Combined with colorimetric histology techniques, the metasurface translates changes in spectral characteristics caused by the local thickness and dielectric constant of the sample into distinct color differences, enabling the differentiation of healthy from nonhealthy tissue in early spontaneous breast cancer. Moreover, in the same individual, the existence of overlapping regions between healthy cells and cancerous cells suggests that this plasmonic metasurface has a predictive diagnostic capability for the early stage of cancer.
The Q-factors of the two plasmonic metasurface sensors proposed above are not significantly high due to the presence of attenuation channels in plasmonic modes, including ohmic losses, external coupling of their radiation, and intrinsic dipole moment [24]. Gallinet et al. demonstrated that the Fano resonance-based system can be used as an effective RI sensing platform due to its controlled radiation losses. Bin-Alam et al. also proposed a plasmonic metasurface induced by periodically aligned Au meta-atoms and based on SLRs to obtain a record high Q-factor of 2340 in the communication band [44]. Although the two aforementioned efforts have sought to improve plasmonic metasurface Q-factor.
from different perspectives, there are still serious limitations to the potential applications of plasmonic metasurface RI sensors. The dielectric nanoparticles with good biocompatibility, low loss, and high RI supporting strong Mie resonance provide new ideas for enhancing the interaction between near-field light and matter. Yang et al. illustrated a Q-factor of 483 and a FOM of 103 RI sensors using silicon-based metasurfaces [23]. The near-field coupling of the rod and the ring resonator leads to collective oscillation of the resonator, resulting in a high Q-factor resonance. Combined with a reduction in absorption losses, it made to the minimization of both radiative and nonradiative losses. Yesilkoy et al. combined a BIC-supported all-dielectric silicon-based metasurface with hyperspectral imaging to demonstrate the first large-scale, high-throughput, label-free, and nondestructive detection of individual biomolecules in the visible range [62]. The metasurface with a Q-factor of 144 exhibits a sensitivity of 263 nm/RIU when used to detect analytes in aqueous solutions. Combined with hyperspectral imaging and advanced data processing methods, it allows for immuno-noglobulin G (IgG) detection of fewer than 3 molecules per μm². This portable system for spectroscopy-based RI sensing consists of a narrow-band light source (~2 nm), readily available optics, and CMOS imager without the need for an expensive and bulky spectrometer, enabling a disruptive technology based on metasurface spectroscopic detection. TM mode achieves LOD as low as 1 pg/ml for IgG proteins, and TE mode enables imaging of individual Escherichia coli bacteria at a spatial resolution of less than 1 μm. Yesilkoy and colleagues then went on to achieve the same high Q-factor (701) near-field resonance for the diatomic Si all-dielectric metasurface using another symmetry-breaking approach [27], as shown in Figure 2(d). It enables a single-wavelength imaging optofluidic biosensor that can allow real-time detection of an average of 0.41 nanoparticles per μm² and measurement of breast cancer cell exosomes combined with encapsulated exosomes as small as 204 femtomolar solutions. In contrast to spectral interrogation, single-wavelength-based intensity interrogation eliminates the need for cumbersome and time-consuming wavelength scanning systems. And more appealingly, it can also be used to collect both spatial and time-resolved image measurements of molecular binding kinetics. Nevertheless, the consequent low noise tolerance of this scheme will need to be addressed in subsequent studies.

The vast majority of the above work is based on single-layer metasurfaces or single resonance mode. Multilayer metasurfaces and hybrid metal-dielectric metasurfaces offer comparable or even better performance in RI sensing applications. A bilayer plasmonic metasurface consisting of Au-Si₃N₄ nanopillars arrays on silicon substrate was proposed and applied to detect various amyloid β (Aβ) proteins, as shown in Figure 2(e) [63]. Compared to the single-layer nanostructure, it can support the excitation of Fano resonance by backside irradiation to enhance the electromagnetic field and reduce the effect of temperature on enzyme activity. Meanwhile, the metasurface was functionalized with enzymes to allow the captured exosomes to form insoluble optical deposits on the surface. The multilayered and functionalized metasurface further increases the detection sensitivity, enabling LOD as low as 200 exosomes. In another work, Nugroho et al. proposed an Ag-SiO₂-Ag multilayer plasmonic metasurface that excites two spatially located and spectrally separately tunable LSPR resonances with a bulk sensitivity of 180 nm/RIU and 133 nm/RIU, respectively [30]. It demonstrates for the first time plasmonic sensing in three dimensions (3D) space, allowing simultaneous detection of local chemical or physical processes at different spatial locations. Subsequently, Dong et al. proposed a hybrid metal-dielectric metasurface consisting of TiO₂ nanopillars arrays on a metallic reflector, supporting both SLR and plasmonic resonance modes [32]. The bulk sensitivities obtained experimentally were 449 nm/RIU and 273 nm/RIU, respectively. Another hybrid metasurface consisting of a silicon cylinder and an aluminum disk enables spatial RI sensing with a sensitivity of 208 nm/RIU [31]. Those metal-dielectric hybrid nanostructures combine the advantages of strong field enhancement of plasmonic metals and several low-loss radiation channels of dielectric resonators. Besides, the multiple mode combination allows for a simultaneous combination of bulk sensitivity, surface sensitivity, and LOD, which is beneficial for the identification of changes in substances occurring at different spatial locations (e.g., internal or external) in biological systems. Most current multilayer metasurface sensors do not currently enable true spatial resolution 3D sensing because they are not yet combined with imaging techniques (e.g., hyperspectral imaging).

3.2. Surface-Enhanced Raman Scattering. As each molecule has a unique vibrational Raman spectrum, relying on the inelastic scattering of photons by molecules with quantized vibrational characteristics, Raman spectroscopy can be used as an ideal research technique to probe the structural information of a given molecule, including small molecules, nucleic acids, and proteins. However, the inelastic photon scattering efficiency of the molecule is low and its Raman signal may also be affected by background luminescence [65]. By increasing the local electromagnetic intensity (i.e., hot spot) at the analyte, SERS allows the detection of low concentrations of biological and chemical molecules, even single molecules [66, 67]. The enhanced surface Raman scattering intensity is calculated as [68]

\[
I_{\text{SERS}} \approx \left| \frac{E_{\text{det}}(\omega_{\text{det}})E(\omega_{\text{ext}})}{E_{0}(\omega_{\text{ext}})} \right|^2,
\]

where \(\omega_{\text{ext}}\) and \(\omega_{\text{det}}\) are excitation and detection frequencies and \(E\) and \(E_{0}\) are the electric field strength before and after the enhancement of the plasmonic structure, respectively. The enhancement factor (EF) is defined as \(\text{EF}(\omega) = \left| \frac{E(\omega)}{E_{0}(\omega)} \right|^2\). Raman EF can be expressed as \(\text{EF}_{\text{SERS}} = \text{EF}(\omega_{\text{det}})\left(\text{EF}_{\text{det}}(\omega_{\text{det}})\right)^{-1}\). The resonance of the maximally enhanced SERS signal occurs between the excitation and the Raman scattering wavelengths [69]. Meanwhile, the spatial uniformity of \(\text{EF}_{\text{SERS}}\) is directly related to the electric field. To obtain more accurate results, achieving high spatially uniformly distributed field enhancement is in need.
Resonators with a periodic structure allow EM energy to be concentrated at any specified frequency. Such resonators can be used to achieve SERS enhancement and increase the selectivity of SERS sensors. Shioi et al. proposed a dual-resonant plasmonic substrate consisting of the Au-dielectric-Au structure [70]. A maximum average NIR SERS EF of $7.2 \times 10^7$ was obtained experimentally when 4-amino thiophenol (4-ATP) was detected. Recently, a plasmonic metasurface consisting of inverted pyramidal arrays was proposed, as shown in Figure 3(a) [71]. Using the Raman probe 4-mercaptobenzoic acid (4-MBA) probe, the metasurface substrate achieved a signal EF of more than $10^6$ for different samples. Biofunctionalization of the metasurface allowed the detection of the hepatitis A virus (HAV) at a minimum concentration of 13 pg/ml in a low sample volume of 2 μl. Another plasmonic metasurface consisting of an ordered arrangement of silver nanosquares was proposed and realized for the detection of multiple drug components in human sweat [17], as shown in Figure 3(b)). The metasurface can detect characteristic Raman spectra of crystal violet (CV) molecules at ultralow concentrations ($10^{-9}$ M) with a SERS EF of about $10^7$. As a sensing element, it has also been successfully integrated with a wearable sensing device to accomplish SERS spectra of lidocaine, cocaine, methotrexate, and other drugs.

Although high field EF can be achieved using nanostructures with metals, it comes at the cost of high optical absorption losses, severely limiting practical applications. Caldarola et al. established a novel all-dielectric metasurface consisting of Si-dimer nanoantennas on an insulating substrate (Figure 3(c)), improving the Raman scattering signal of the polymer film by a factor of $10^3$ in the NIR wavelength [72]. It has been demonstrated that the heating losses and nonradiative fluorescence quenching caused by plasmonic devices are greatly reduced in dielectric systems. To further improve the ability of nanophotonics to enhance the SERS signal, a BIC-type all-dielectric metasurface consisting of silicon nitride ($\text{Si}_3\text{N}_4$) nanopores were explored (Figure 3(d)), achieving a Raman signal enhancement of molecules of CV dye $10^7$-fold enhancement [73]. Cambiasso et al. prepared silicon dimers on alumina substrates and used them for Raman detection of β-carotene monolayers [74], as shown in Figure 3(e). Two characteristic Raman peaks for β-carotene were obtained at 1522 cm$^{-1}$ and 1154 cm$^{-1}$ with SERS EF of 1380 ± 300 and 1720 ± 300, respectively. It can be seen that even though plasmonic metasurfaces currently still have higher field EF and SERS signals, dielectric metasurfaces could have the potential to produce SERS enhancements equivalent to plasmonic substrates through several future optimizations. Simultaneously, the combination of the dielectric and plasmonic metasurface is a reliable solution for enhancing light trapping and near/far-field coupling, and overcoming the inherent losses and thermal effects of the plasmonic.

Most metasurfaces are designed to be arranged periodically, but narrowband resonance is not tunable for multiplexing SERS. In particular, for multipath in situ SERS, broadband, or tunable metasurfaces can be used to achieve uniform signal enhancement in different Raman modes [75]. In addition, combined with the SERS effect to provide ultrahigh signal-molecule detection sensitivity and unique SERS spectral fingerprints, the wearable metasurfaces integrated sensing platform can realize real-time tracking of multiple analytes in the body [76]. The realization of plasmonic or dielectric metastructures on flexible substrates will greatly promote the development of metasurface devices with SERS activity in wearable technology.

3.3. Surface-Enhanced Infrared Absorption. Different molecules have their characteristic absorption frequencies or molecular fingerprints in the mid-IR, which can be used for unique detection and identification of large molecules, including the four major classes of biomolecules: proteins, lipids, nucleic acids, and carbohydrates. However, due to the mismatch between the mid-IR wavelength (2-6 μm) and the size of biochemical molecules (<10 nm), the vibrational absorption signal detected by the mid-IR spectroscopy is extremely weak when the number of molecules bound to the nanosample, biofilm, or surface is small [77]. This limitation can be effectively overcome by using SEIRA. In contrast with SERS, the metasurface-based SEIRA nanosensors are suitable for multilayer detection due to their deeper bior-elevant sensing depth (tens of nanometers) [78], monitoring larger analytes and providing their detailed biochemical information in a nondestructive and label-free strategy.

Surface-enhanced infrared spectroscopy is a specific detection technique whose performance is related to the strength of the metasurface-enhanced local electromagnetic field [79]. When the resonant peaks of subwavelength resonators overlap with the vibrational fingerprint of target molecules, the highly localized electromagnetic hotspot provided by the engineered metasurface can enhance the coupling between the target molecules and the resonators, resulting in a change in resonant intensity to extract the molecular fingerprint. In some complex applications, particularly the differentiation and monitoring of individual components in heterogeneous mixtures, it is necessary to design a broad bandwidth resonance or multiresonant structure to simultaneously extract multispectral fingerprint features of different chemical or biological components. Although the strong optical near-field of metal nanostructures enables high-sensitivity detection, it also brings the shortcomings of reduced spectral bandwidth and poor field localization capability of metals in the mid-IR [80]. One avenue to alleviate this deficiency and extend the functionality of the sensor is through the use of graphene-based metasurfaces to achieve dynamic tunability. A graphene-based tunable mid-IR biosensor for chemically specific label-free detection of protein monolayers. A graphene-based tunable mid-IR biosensor is proposed and used to detect protein monolayers [40], as shown in Figure 4(a). Selective detection of proteins at different LSPR wavelengths and extraction of their complex refractive indices is achieved through modulating the external electrostatic bias. Specifically, after binding the protein to graphene, the resonance peak has a redshift of more than 200 cm$^{-1}$, while two important vibrational fingerprints of the protein emerge at 1660 cm$^{-1}$ and 1550 cm$^{-1}$. Furthermore, when the device surface is covered by a thin protein
bilayer, graphene shows tighter near-field intensity confinement than gold. These results suggest that graphene, with its stronger light-protein interaction in the mid-IR, will provide higher sensitivity and spectral resolution, as well as dynamic tunability than advanced metal plasmonic sensors. Nevertheless, the strong plasmons-phonon coupling between graphene and substrates (e.g., SiO₂ and h-BN) leads to a low near-field intensity at the top of the graphene
surface and severely limited spectral tunability [81]. In 2016, the proposed hybrid metasurface structures of graphene nanoribbon array on the CaF$_2$ nanofilm avoids the strong coupling of plasma-phonon hybridization [41], as shown in Figure 4(b). This wide resonant design covers the entire molecular fingerprint region (600-1500 cm$^{-1}$) for
the first time, enabling the simultaneous recognition of multiple nanoscale molecular fingerprints. Taking advantage of graphene’s active electrical tuning, broadband resonance, and substrate-free coupling effects has enabled the detection platform to achieve high sensitivity and selectivity for nanomolecular fingerprinting applications in several complex situations. Subsequently, Rodrigo et al. continue to investigate multiresonant metasurfaces for enhanced molecular vibrational fingerprinting in the mid-IR. A metasurface with an electromagnetic response independently modulated by two sets of gold nanodipoles was proposed [82], as shown in Figure 4(c). It provides more than 3 orders of magnitude local near-field intensity enhancement and allows for the simultaneous detection of characteristic absorption bands of lipids (~2900 cm\(^{-1}\)) and peptides (~1600 cm\(^{-1}\)). To further provide a large amount of signal enhancement and cover all absorption bands of biomolecules within a wider spectrum, John-Herpin et al. have designed a highly sensitive multiresonant plasmonic metasurface consisting of gold nanoantenna arrays on a transparent GaF\(_2\) substrate and integrated the plasmonic chip with a polydimethylsiloxane (PDMS) microfluidic device [83], as shown in Figure 4(d). The resonance point positions are designed by adjusting the geometrical parameters of the two arrays (i.e., 1200, 1600, and 2900 cm\(^{-1}\)) and the electric near-field enhancement is boosted by tuning the \(y\)-period. The broadband metasurface covered the spectral range from below 1000 cm\(^{-1}\) to above 3000 cm\(^{-1}\) and the multiple resonances overlapped well with the absorption bands of polypeptides, nucleic acids/nucleotides, lipids, and polysaccharides. More interestingly, deep learning methods were introduced to extract signals from the metasurface to efficiently and reliably discriminate between all simultaneously present biomolecules. The team went on to propose a suitable low-cost, high-throughput wafer-scale nanofabrication method that can be applied to the production of plasmonic metasurfaces [26]. The metasurface based on aluminum nanoantenna arrays proposed by Leitis et al. achieved high sensitivity real-time monitoring of protein (1600 cm\(^{-1}\)) and lipid (2900 cm\(^{-1}\)) interactions.

As thermal effect due to metallic ohmic loss is always an unavoidable problem, high refractive all-dielectric metasurfaces capable of producing both electrical and magnetic resonance modes are also considered for sensing applications in the mid-IR. An alternative approach was taken by Tittel et al. using a 2D pixelated dielectric metasurface to engineer a series of narrow resonant peaks at discrete frequencies [84], as shown in Figure 4(e). These discrete resonances maintain the “broadband” character while catering to molecules in certain molecular vibrationally dense spectral regions. The metasurface consists of zigzag arrays of anisotropic \(\alpha\)-Si: H resonators on the MgF\(_2\) substrate, whose resonant frequency is tuned by a scaling factor of the cell size. The high Q-factor resonance without additional resonance background comes from BIC-driven supercavity mode, allowing spectrally selective enhancement of molecular fingerprint signals. This technique, eliminating the need for spectroscopy and wavelength scanning, promises to enable highly sensitive and multifunctional miniature mid-IR spectroscopy devices. Leitis et al. demonstrate another germanium-based metasurface sensor with a high Q-factor, which combines angular scanning refractometric to achieve broadband IR detection (Figure 4(f)) [85]. The enhancement of the electromagnetic field and angular regulating of the resonant wavelength is achieved by toggling different incident angles and polarizations. By retrieving the angularly resolved signals of this metasurface before and after binding to analyte molecules, the detection of broad-spectrum molecular fingerprinting information from 1100 to 1800 cm\(^{-1}\) was achieved. Both methods provide new approaches to the miniaturization of highly sensitive, multifunctional, and label-free mid-IR spectrometers.

3.4. Chiral Sensing. Chirality is one of the fundamental properties of all living organisms that describes structures that cannot be overlapped with their mirror image by translation, rotation, or combination. Many molecular systems, such as DNA and nucleic acids, exist as two enantiomers, one labeled as “left-handed (LH)” and the other as “right-handed (RH)” [29]. Sometimes, although the two enantiomers have the same functional group and composition, they may exhibit opposite biological effects on cells. Therefore, it is crucially significant to sense and discriminate the forms of LH and RH and to quantitatively analyze trace concentrations of RH amino acids particularly in the fields of analytical chemistry, biomedicine, pharmaceutical industry, and toxicology. Spectroscopic measurements using molecular chiral optics allow label-free, noninvasive, and low-cost identification of chiral molecules [86, 87]. A common means of distinguishing chiral molecules is the circular dichroism (CD) method, which is based on the difference in absorption of left/right circularly polarized light (L-/R-CPL) by opposite enantiomers [88]. However, since the scale mismatch between the helical pitch of chiral molecular and the optical wavelength, the conventional CD enantiomer spectroscopic methods appear low sensitivity perception of the weak chiroptical signal. This means that high-concentration solutions, strong lasers, or high-precision analytical instruments are required to accurately detect the weak chiral signals of molecules. Lately, due to the strong optical localization (in sub-wavelength volumes) and field enhancement capabilities of metasurfaces, it has proved to be unique and powerful platforms for enhancing optical chirality [89], \(C\), described as [12]

\[
C(E, \mathbf{H}) = \frac{-k_0}{2\varepsilon_0} \text{Im}(E \mathbf{\cdot H}^*),
\]

where \(k_0\) and \(\varepsilon_0\) are the wavenumber and speed of light in free space and \(E\) and \(\mathbf{H}\) represent the complex electric and magnetic field vectors, respectively.

In 2010, Hendry et al. used the metasurface composed of a single-layer gold gammadions structure for the first time for the chiral detection of various proteins [90]. The main detection principle of this research is the measurement of spectral shifts caused by near-field interactions between chiral molecules and metasurfaces. Another detection device
consisting of two plasmonic metasurfaces with different rotation angles is proposed and used to enhance enantiomers’ CD effects (Figure 5(a)) [89]. The CD signal is significantly enhanced at the plasmon resonance frequency and the detection sensitivity of chiral molecules up to 55 zeptomoles. Another plasmonic metasurface consisting of asymmetrical gold nanorods on a silicon substrate was proposed and used for chiral detection of alanine [91]. Under the excitation of linear polarization, left-handed and right-handed chiral fields are selectively generated at 1600 cm⁻¹, while functional groups such as COO, NH3, CH3, and CH exhibit strong vibrational absorption. Due to the interference of the background CD spectrum of the chiral metasurface and the spectral drift caused by the introduction of molecules in the near-field of the plasmonic structure, the further improvement of the detection sensitivity of chiral molecules is still limited. Therefore, the achiral metasurface is beneficial to avoid being disturbed by the chiral response of the nanostructure itself. Mohammadi et al. proposed an all-dielectric metasurface composed of silicon nanodisks for CD signal enhancement and extraction analysis in chiral biolayers (Figure 5(b)) [92]. This metasurface shows two resonance drops caused by the excitation of two ED and MD in response to the excitation of the RCP and LCP. The differential absorption of the obtained CD spectrum is only determined by the imaginary part of the pasture. This platform eliminates the effects of background noise and dielectric constant and obtained up to ~30 fold enhancement of the CD signal. Subsequently, Solomon et al. achieved ~138 fold local C enhancement of this metasurface [88], as shown in

Figure 5: Different metasurfaces for chiral sensing. (a) A bilayer metasurface consisting of two interleaved plasmonic metasurfaces was used to measure and enhance the CD spectral signal of a chiral anticancer drug (irinotecan hydrochloride at a concentration of 1 mg/ml). “MTM w/w” indicates the metasurface with water, “MTM w/D” indicates the metasurface with chiral drug, and the blue curve indicates that the test substance is “left-handedness.” Reproduced under a Creative Commons Attribution 4.0 International License (CC BY 4.0). http://creativecommons.org/licenses/by/4.0/ [89]. (b) All-dielectric metasurface consisting of silicon nanodisks for CD signal enhancement and extraction analysis in chiral biolayers. Reproduced with permission. Copyright 2018, American Chemical Society [92]. (c) A dielectric metasurface consisting of silicon nanodisk arrays for local enhancement of C. Reproduced with permission. Copyright 2018, American Chemical Society [88]. (d) A dielectric metasurface consisting of a porous dielectric disk is used to generate electromagnetic overlapping super-chiral fields. Reproduced with permission. Copyright 2019, American Chemical Society [93]. (e) A dielectric metasurface consisting of asymmetric diamond arrays for UV chiral near-field enhancement. Reproduced with permission. Copyright 2019, American Chemical Society [94]. (f) A high-Q hybrid metasurface consisting of asymmetric rectangular columns on thin gold film is used to identify the enantiomers and to analyze their composition (molar concentration). Bottom panel: chiral sensing combined with refractive index sensing for molar chiral sensing. Reproduced with permission. Copyright 2020, American Chemical Society [95].
4. Conclusions and Outlook

To conclude, this paper reviews recent advances in resonant metasurface-based spectroscopic detection in biomedical sensing and is aimed at providing the reader with the latest overview of this exciting new topic. Firstly, in the field of spectroscopic detection, the main resonance mechanisms for plasmonic and dielectric metasurfaces include LSPR, SLRs, Fano resonance, and BICs. Recent advances in the spectroscopic detection of plasmonic and dielectric metasurfaces are listed, including RI sensing, SERS, SEIRA, and chiral sensing in the UV to THz wavelength. A bright future can be foreseen for a subject that started only ten years ago and has now reached a relatively mature stage of development.

Both plasmonic and dielectric metasurfaces demonstrate their powerful appeal as components for new types of optical sensing devices. Plasmonic metasurfaces show strong electric field enhancement due to resonant oscillations of free electrons, but their intrinsic damping leads to high losses. Dielectric metasurfaces show lower field enhancement than the plasmonic metasurfaces but with low loss. The hybrid plasmonic-dielectric structure allows simultaneous strong field enhancement and low-loss radiation, which is a promising approach to achieving high-performance optical sensing. From the UV to THz wavelengths, the metasurface-based spectroscopic detection system demonstrates excellent experimental performance for liquid biopsies (including nucleic acids, biomarkers, proteins, cytokines, extracellular vesicles, and pathogens), tissue biopsies (cells, etc.), drug small molecules, gases, and other substances. A comprehensive set of requirements for detection equipment performance development based on practical application, including miniaturization, intelligence, real-time, multiplexing, low cost, usability, high throughput, and high sensitivity. Simultaneously, although we focus on resonant metasurfaces in this review, nonresonant metasurfaces of plasmonic and dielectric also present promising pathways [96, 97].

4.1. Metasurfaces Based on Novel Optical Phenomena and Surface Functionalization. Novel concepts of manipulating particles or molecules at the nanoscale deserve to be continuously innovated to keep the field of spectroscopic detection vibrant and thriving. At present, the design of metasurface for spectroscopic detection mainly focuses on how to improve the extreme electromagnetic control of light fields, that is, the nanophotonic resonators restrict the light to subwavelength and produce high near-field enhancement contributed by the photonic hot spots. The transfer of most of the analytical molecules to the hot spot is essential to improve the detection sensitivity. While most current methods use drops or rotating coatings to disperse analytes across the entire surface of the device, meaning that only a few molecules undergo field enhancement. Inspired by the mechanism of liquid evaporation, some works effectively enrich target molecules near the hot spot of the optical nanoantenna, thus significantly improving the spectroscopic response and sensitivity performance of the sensor [98]. Another external means to increase the sensitivity is to perform appropriate surface biological functionalization of the sensing platform. It is specifically embodied in the suppression of nonspecific interactions, forcing the interactions between biomolecules to occur only in the electromagnetic hotspots of the nanostructure [99]. Furthermore, metasurfaces based on novel optical phenomena deserve to be explored and developed for spectroscopic detection.

4.2. Tunable or Reconfigurable Metasurfaces. Once customized, metasurfaces have been made, and their material response and resonance characteristics cannot be altered. Dynamically tunable devices are becoming increasingly important in the face of demands such as inspection complexity and cost control. The addition of 2D materials (e.g., graphene), phase change materials (e.g., VO₂), and functional materials (e.g., liquid crystals) can temporarily alter the optical or electrical response of nanostructures.
4.4. Artificial Intelligence- (AI-) Based Design Methods and Data Processing Algorithms. The vast majority of current metasurface designs require multiple full-wave electromagnetic simulations to optimize the required optical response and functionality. Design methods based on deep learning can predict the spectral response, specific geometry, and dimensions of nanostructures with high accuracy. This approach accelerates the optimization process and saves the design cost of the device. Several works have now demonstrated and validated the feasibility of using deep neural networks to design silicon-based metasurfaces with enhanced Fano resonance and plasmonic-based metasurfaces [105, 106]. In addition to the design optimization of device intrinsic characteristics, more algorithms and applications deserve to be developed and applied to the analysis and processing of data [107]. Many applications, including tumor tissue detection and crop disease assessment, are significant for the acquisition of spatial distribution information, suggesting that the combination of metasurfaces and spectral imaging technology is a major development trend. For instance, in the field of medical diagnosis, various deep learning model-based image segmentation methods have been developed for image segmentation of spectral images [108]. Since spatial and spectral data are usually obtained by different methods, it increases the complexity of the system and the simultaneous acquisition of information in 3D. Therefore, metasurface-based spectroscopic detection methods will inevitably utilize various AI algorithms to process a large amount of information generated, which is one of the most promising ways to realize the miniaturization and ubiquity of spectroscopic detection systems in the future.

Conflicts of Interest

The authors declare that there is no conflict of interest regarding the publication of this article.

Authors’ Contributions

All the authors have accepted responsibility for the entire content of this submitted manuscript and approved submission.

Acknowledgments

We acknowledge the financial support from the National Natural Science Foundation of China (Grant Nos. 52005175 and 52111530233), Shenzhen Science and Technology Program (Grant No. RCBS20200714114855118) and the Tribology Science Fund of State Key Laboratory of Tribology (SKLTKF20B04).

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