Review article

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Plasmonic nano-arrays for ultrasensitive bio-sensing

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Abstract: Surface plasmon resonance (SPR) and localized SPR (LSPR) effects have been shown as the principles of some highly sensitive sensors in recent decades. Due to the advances in nano-fabrication technology, the plasmon nano-array sensors based on SPR and LSPR phenomena have been widely used in chemical and biological analysis. Sensing with surface-enhanced field and sensing for refractive index changes are able to identify the analytes quantitatively and qualitatively. With the newly developed ultrasensitive plasmonic biosensors, platforms with excellent performance have been built for various biomedical applications, including point-of-care diagnosis and personalized medicine. In addition, flexible integration of plasmonics nano-arrays and combining them with electrochemical sensing have significantly enlarged the application scenarios of the plasmonic nano-array sensors, as well as improved the sensing accuracy.

Keywords: LSPR; nano-array; plasmonics; sensing; SPR.

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1 Introduction

As the demands of environmental monitoring, medical diagnostics, and food safety control increase, researchers have explored many techniques for developing cost-effective and highly sensitive transducers. Plasmonic-based sensors are becoming the method of choice in label-free detection of biomolecules [1–3]. Because surface plasmon resonance (SPR) is inherently sensitive to a small change in the refractive index (RI) of the dielectric environment, enormous attention has been drawn to its potential in sensing applications. Surface plasmon sensing is often divided into two categories: SPR and localized SPR (LSPR). When the RI of the environment changes, the plasmonic resonance shifts, resulting in the shift of resonant wavelength or detection angle [4]. Based on this principle, SPR- and LSPR-based sensors have been widely used for numerous applications, for example, power harvesting, biological sensing, medical treatment, and subwavelength imaging [5, 6]. LSPR-based sensing technology using metallic nano-particles requires simpler instruments compared with SPR sensors, but its low uniformity and irreproducibility limit the application since the spatial distribution, particle sizes, and shapes are difficult to control precisely, which results in its sensitivity being lower than SPR sensors [7].

In practical application, compactness, high-uniformity, ultrasensitivity, and cost-effectiveness are important and needed characteristics of plasmon resonance sensors. Thus, nano-particles with good controllability are a viable candidate. From the perspective of manufacturability, chemical synthesis cannot produce uniform nanoparticles with good consistency, directly affecting LSPR resonance [8, 9] and making it far from a good candidate for real-life application. Nano-sphere-based lithography produces better consistency, but its unavoidable defects over a large scope limit its practical application [10]. Electron beam lithography and ion beam milling provide high-quality structures but are limited by high cost [11]. In 2013, Gartia et al. [12] demonstrated a metal-coated nano-well array

for ultrasensitive RI sensing, which was fabricated by inexpensive large-area nano-replica technique. Moreover, the large absolute peak wavelength shift from nano-array device enables the opportunity for colorimetric sensing by using a common microscope system, a camera on a smartphone, or naked eyes instead of complicated spectrometers, which opens a new avenue for researchers to explore the feasibility of using nano-plasmonic array for ultrasensitive plasmon resonance sensing.

In this review, we focus on plasmonic nano-arrays that have the potential for real-life applications in bio-sensing and have high-sensitivity, good uniformity, and cost-effectiveness. After reviewing the related theories of plasmonic nano-arrays for bio-sensing, we review works and research advances in bio-sensing applications. Two aspects of the applications are focused on in this review: (1) RI sensing based on nano-array structure and (2) sensing assisted by enhanced field from the plasmonic nano-array structure. We hope this review brings readers the most updated summary of the design, application, and performance of practical bio-sensing orientated plasmonic sensing devices.

2 Theories for nano-array plasmonic sensors

A surface plasmon is the collective oscillations of the free electrons at the interface of dielectric and metal materials. Noble metals like gold (Au) and silver (Ag) have been reported to exhibit strong surface plasmon polariton (SPP) in the visible wavelength when the condition of momentum match is satisfied [2]. This condition can be expressed as follows:

$$\mathbf{k}_0 \sin \theta = \mathbf{k}_{\text{spp}}$$

where $\mathbf{k}_0$ is the wavevector of incident light, θ is the incident angle, and $\mathbf{k}_{\text{spp}}$ is the wavevector of SPPs mode [13, 14], which is expressed as

$$\mathbf{k}_{\text{spp}} = \mathbf{k}_0 \sqrt{\frac{\varepsilon_m \varepsilon_d}{\varepsilon_m + \varepsilon_d}}$$

where ε_m and ε_d are the dielectric constants of surface metal and surrounding materials, respectively [12, 14–16]. Although prism coupling could satisfy this condition, this massive configuration is out of date for convenient bio-sensing applications. Nano-array structures otherwise could achieve this momentum match in the form of sub-wavelength grating without bulky optical components.

The matching condition can be described by Bragg's coupling equation:

$$\mathbf{k}_0 \sin \theta \pm \nu \mathbf{G} = \mathbf{k}_{\text{spp}}$$

where ν is the grating order for the reciprocal grating vector $\mathbf{G}$ ($\mathbf{G} = \frac{2\pi}{a}$, a is the grating period) [12, 14, 15]. Therefore, the resonance of SPP can be tuned by changing the incident angle (θ), the period of nano-array structure (a), or the optical constant of the dielectric material (ε_d). It should be noted that the minimum condition of $\varepsilon_m(\omega) + \varepsilon_d(\omega)$ is the foundation for RI sensing [14, 17].

Nano-array structures with specifically designed sizes and shapes can even exhibit localized surface plasmon (LSP) which is normally confined to metal particles or curved surface [13, 14, 18]. The resonance condition for LSP is quite different from that of SPP due to the different boundary conditions (planar vs. spherical). If an ideal sphere metal nano-particle with sub-wavelength size is analyzed, the scattering field will reach a resonant enhancement under the condition when $|\varepsilon_m(\omega) + 2\varepsilon_d(\omega)|$ is at minimum [14]. This resonance mode derived from noble metal particles can also be estimated from Mie scattering. Due to the strong confinement of LSP resonance (LSPR), the short decay length is an intrinsic property, which means the enhanced scattering field is just within a short distance (~10 nm) of the metal surface, leading to ultra-sensitivity when the analyte is positioned very close to the metal particle surface [19].

Compared with LSPR, SPR usually shows a stronger signal due to grating structure, but its relatively large decay length limits its sensitivity. So, it is often more favored in the sensing application of ions in solution or large bio-target. LSPR carried by noble metal nanocrystals and nanostructures can concentrate light into nanoscale spatial regions, which were simple, cost-effective, and suitable for measuring local RI changes caused by the adsorption of target molecules at the metal surface. So, LSPR can often be utilized for ultrasensitive bio-sensing especially for ultra-small targets at low concentration. Due to the ultrasensitivity of LSPR-based sensors, it is critical to distinguish the LSPR mode from the other existing modes in the nano-array structure, in order to boost the performance for real applications.

Based on the SPP and LSP theory, in the following, we introduce the two aspects of the applications for ultrasensitive bio-sensing: RI sensing based on nano-array structure and sensing assisted by enhanced field from the plasmonic nano-array structure. The RI sensing is usually based on the principle of either SPR or LSPR, where the peak shift in optical spectrum is detected. The

other application is usually based on LSPR because of its requirement for locally enhanced field. The magnitude amplification at the resonance frequency is usually detected.

3 Refractive index sensing based on nano-array structure

Plasmonic nano-array structure was commonly used for RI sensing. The performance is typically evaluated by the figure of merit (FOM), defined as the ratio of the sensitivity (S) to the width of the spectral peak (the full-width at half-maximum (FWHM) at the resonant peak).

$$\text{FOM} = \frac{S(\text{nm/RIU})}{\text{FWHM (nm)}}$$

The sensitivity S is calculated by the wavelength shift per RI unit (RIU), which is often determined by the structures' intrinsic parameters like period, depth, and metal coverage. The FWHM indicates the ability to confine electromagnetic fields at resonance mode, which determines sensing resolution. It is important to have high RI sensitivity and low resolution for effective ion or bio-target quantification. In terms of common ion quantification, the SPR-based sensor with high sensitivity often displays its advantage in stronger signal than LSPR, since the change of target concentration is uniform within the decay length of wave propagation. But for the case of certain metal ions or bio-targets which accumulate or bind closely at the nano-array surface, LSPR sensors show ultrasensitive response to low concentration change [4, 20, 21]. By

fine-tuning the spatial distribution with proper geometric design, the state of the art LSPR plasmonic sensors can achieve as high as 1900 nm/RIU or FOM of 14.2 at the near-infrared (NIR) region [22–24]. However, working at IR range has prevented them from broader application with low-cost and common equipment to observe. At visible spectrum, the sensitivity for LSPR nano-array sensor is about hundreds of nanometer per RIU [25, 26]. Table 1 presents a comparison of sensitivity of different plasmonic nano-array sensors. The trend for increasing the sensitivity is enabled by increasing the aspect ratio and introducing multipolar resonances. For example, the sensitivity generally improves by increasing the aspect ratio from sphere to disk, and to nanorods (NRs). Also, using nanocrescents (multipolar resonances) [28] instead of nanospheres or nanodisks (dipolar resonances) [27] also achieves high sensitivity. Fano resonance, where weak coupling and interference occur between bright and dark plasmon modes, has emerged as another method to improve the sensitivity. Since periodic nanohole arrays in thick metal film have been shown to observe extraordinary optical transmission (EOT) [29], this structure has been extensively used for surface-based bio-sensing as opposed to colloidal-based sensing. LSPR has also been incorporated in order to improve the sensitivity of EOT structures [30].

With the advances of nano-fabrication technology, ultrasensitive plasmonic devices based on z-direction metal coverage variation (3D plasmonics) have demonstrated exceptional performance. For example, Shen et al. [15] reported plasmonic gold mushroom arrays with sensitivity of 1015 nm/RIU and FOM of 108. Sreekanth et al. [31] demonstrated an extremely sensitive

Table 1: Comparison of sensitivity of different nano-array plasmonic sensors [26].

Structure	Wavelength (nm)	Structural dimensions (nm)	Principle	Sensitivity (nm/RIU)	RI range (μm)	Reference
Gold nanodisk	500–1000	p: 162, 340	LSPR	167–327	1.32–1.42	[27]
Nanocrescents	800–2800	d: 410; AR: 4	LSPR	879	2–3.5	[28]
Nanocross and bar	1200–1900	L: 380; W: 76	Fano resonances	710–1000	1.333–1.38	[24]
Nanohole	450–950	d: 200; p: 500; t: 200 (Au)	EOT	481	1.33–1.36	[29]
Double-hole	500–680	d: 200	EOT-LSPR	600	1–1.4	[30]
		C-C spacing: 190				
		p: 500–600				
		t: 100				
Nano-bowl	600–1000	d: 202–294	LSPR	1200–1600	1–1.6	[25]
		h: 297–340				
		p: 280–370				
		t: 60 (Au)				

d, Diameter; h, height; p, period; t, thickness; W, width; L, length; AR, aspect ratio; C-C, center-to-center; EOT, extraordinary optical transmission; LSPR, localized surface plasmon resonance; RI, refractive index.

platform (30,000 nm/RIU with FOM of 590) by combining a normal Au-2D grating with layered metamaterial (Au and Al_2O_3) in z-direction. This metamaterial substrate achieved a hyperbolic dispersion of permittivity in parallel and perpendicular polarization, which introduced highly confined bulk plasmon polaritons. Meanwhile, some of the fabrication technologies are also at affordable cost for potential real applications and mass manufacture [12, 32–35]. For instance, Gartia et al. [12] reported a nano-Lycurgus cup array (NanoLCA) device with ultra-high sensitivity, fabricated with large-area and cost-effective nano-replica technique. More importantly, the large absolute peak wavelength shift in visible spectrum has enabled the possibility of colorimetric sensing by naked eye or simply a common camera system. In this section, we will review the relevant applications for RI

sensing based on ultrasensitive plasmonic devices with z-direction variation.

In previous literature [36], it has been theoretically shown that compared with a circular array, a square array, or a toroid structure on a flat substrate, a multi-layer circular array with a cylindrical hole structure has higher sensitivity and better signal-to-noise ratio (SNR). This study demonstrated that plasmonic devices with z-direction variation have higher sensitivity and tunable SNR. In this part we will review some articles related to these kinds of 3D plasmonic structure. In Chang and Gartia's work [12, 35], noble metals (Au, Ag) were coated on a nano-well array with the depth of 500 nm (Figure 1A), produced by nano-replica from a silicon oxide mold of nano-pillars fabricated by interference lithography. Because the sidewall of the nano-well is not vertical, nano-particles were formed after

Figure 1: Ultra-sensitive plasmonics sensors for refractive index.

(A) Top view and (B) tilted view of SEM images of nanoLCA plasmonic sensor. (C) Optical images of different concentrations of glycerol on nanoLCA (A–C adapted from Ref. [35]). (D) Optical transmission mode images of nanoLCA with 14 different chemicals with varying refractive indices. (E) Colorimetric variations due to different concentrations of target and probe DNA strands immobilized from nanoLCA sensor (D and E adapted from Ref. [12]). (F) SEM image of the surface of FlexBrite. (G) Photograph of a piece of FlexBrite sample. (H) Detection of antibody-antigen reaction (biotin-streptavidin binding) with plasmonic colorimetry of FlexBrite: the process of functionalization of thiolated biotin on the surface of FlexBrite and conjugation with streptavidin (top); colors of FlexBrite in the wet state with water, after functionalization with thiolated biotin and after binding of biotin with streptavidin (bottom) (F and G adapted from Ref. [34] with permission from The Royal Society of Chemistry).

noble metal coating with e-beam evaporation, as shown in Figure 1B. In Chang's research [35], one can clearly see distinct colors after different concentrations of glycerol were dropped on the device (Figure 1C). In addition, the ability to differentiate chemical solutions has been shown in Figure 1D. Moreover, the ultrasensitive sensor can also be used to monitor DNA hybridization with DNA's concentration as low as $0.1 \mu\text{M}$ (Figure 1E) [12]. Further study was also accomplished with finite difference time domain simulation, where nano-wells covered with metal films are studied. In the simulated transmission result, configuration with metal covering top rim, bottom of the nano-well, and sidewall nanoparticles showed good agreement compared with the measured transmission spectra. The fine tuning of the sizes of the sidewall nanoparticles shows that the measurement data have highest similarity with 30 nm and 40 nm silver nanoparticles. After optimizing the geometric specifications by matching simulated data with experimental data, the simulation of sensitivity was performed by changing the RI of surrounding material (glycerol 0%–40%) in Figure 2C. This simulation data successfully matched the measurement data of glycerol with different concentrations, where we could see a red shift of the resonance peak as concentration increases. The sensitivity here was calculated to be 796 nm/RIU with the peak at 465 nm when the concentration of glycerol is 0%. The corresponding FOM was calculated to be 12.7. Unlike traditional laser spectrometer optical system, this sensitive response in the visible spectrum enables a portable solution in which a simple digital camera can be applied to detect the RI change with a uniform light source applied under the sample [39–41].

Instead of a concave structure, FlexBrite consisting of nano-pillar array was fabricated with a similar approach. After metal coating by e-beam evaporation, the pillars look like nano-mushrooms, with the tip and sidewalls covered with metal film and nano-particles, respectively, as shown in Figure 1F. FlexBrite also demonstrated strong sensing capability, which is mainly ascribed to the densely distributed nano-particles along the sidewalls. The actual appearance of this device is shown in Figure 1G. When FlexBrite is used to test liquid with different refractive indices, different colors can be easily identified. Different from the NanoLCA sensor, FlexBrite is more sensitive in reflection mode. As a sensing system, reflection setup can be implemented by integrating the light source and detection within the same device, which is easier to accomplish. Figure 1H shows a concrete application using FlexBrite to test water, monolayer-biotin, and biotin binding with streptavidin. The color differences between the samples clearly signify the additional layer's binding

to the previous layer. In many situations, it is very difficult for researchers to be sure that the new layer binds with the previous layer firmly. FlexBrite, NanoLCA, and similar ultrasensitive plasmonic devices provide researchers with a new paradigm to monitor the bio-process easily from the color change!

One application of these ultrasensitive plasmonic devices is to combine them with the microfluidic technique characterized by the engineered manipulation of fluids at submillimeter scale, which has shown considerable promise for improving biology and diagnostics research [42]. This technique enables rapid sample processing and precise control of fluids in an assay, yet due to the limited volume of the sample, non-disturbing monitoring techniques are required. *In situ* detection capability within the microfluidics devices is quite important as it can increase the functionality of microfluidics devices extensively. Besides the advantages above, the *in situ* detection ability meets the anticipated market demand for portable devices for environmental monitoring, medical diagnostics, and chemical-weapon detection. To meet this demand, the fusion of microfluidics and optics is a suitable technique. However, it requires a lot of work for the integration design of the optics, which may increase the cost significantly [43]. On-chip electrochemical is a good alternative for *in situ* monitoring, as the low-cost electrodes are easy to integrate with the microfluidics devices [44]. However, the sophisticated external devices and complicated signal analysis requirement limit its feasibility more or less.

After introducing the ability of ultrasensitive 3D plasmonic sensors to detect RI change, we are aware that it is a suitable technology to integrate with microfluidics for *in situ* detection purpose. Figure 2A shows a series of video snapshots where glycerol is injected into the microfluidic channel after water [34]. The micro-channel is incorporated on the FlexBrite sensor. Under reflection mode, we can clearly observe the process by which the center part of the glycerol was flushed away by water first. Then the glycerol around the side of the channel was flushed away gradually. This observation actually obeys Fick's second law of diffusion. For another example, Figure 2B shows that the NanoLCA device was used to observe the process of water-in-oil droplets traversing across a microfluidic channel where oil pressure is applied to modulate water into small droplets through the channel [37]. We can easily see the distribution of oil and water in the microfluidic channel since water shows more yellowish color while oil looks greenish on top of the NanoLCA device. Hsiao et al. [37] also showed the application of using NanoLCA combined with microfluidic channel to perform kinetic

Figure 2: Ultra-sensitive plasmonics for microfluidic sensing.

(A) A series of video snapshots to demonstrate the real-time sensing functionality of FlexBrite in microfluidics. In a microfluidic channel (width = 500 μm) with FlexBrite in the bottom, glycerol is replaced with water (adapted from Ref. [34] with permission from The Royal Society of Chemistry). (B) Schematic of the microfluidic droplet generation nozzle region with top inlet for water and side inlets for oil (solid arrow indicates the direction of the flow); time-lapse reflection images of water (W) droplet formation, release, and re-formation in oil (O) emulsion at the nozzle region. (C) Streptavidin (SA)-biotin representative association curve on nanoLCA sensor immobilized with biotinylated thiol where two concentrations (100:1 and 200:1 dilution ratio) of streptavidin solution were used. BSA association curve on Au nanohole array sensor via adsorption (B and C reproduced from Ref. [37] under Creative Commons License). (D) Spectral blue shift from a high and low concentration of ebastine binding with immobilized CYP2J2-ND. Inset: Schematic of the CYP2J2-ND system with CYP2J2 protein (blue) incorporated into the nanodisk. The nanodisk consists of a phospholipid bilayer (gold) and two membrane scaffold proteins (red) (C and D adapted from Ref. [38] with permission from Elsevier).

measurement of biomolecule interaction on the surface of NanoLCA. Streptavidin solution was flowed into the microfluidic channel using a syringe pump. The time trace measurement of light spectrum was continually recorded for 40 min. Figure 2C shows the typical sensorgram with the association and dissociation stages of the binding event between the streptavidin-coated microspheres

and the biotin moiety on the surface. After treating a 3D plasmonic device with different functioning agents, it can detect more biological elements on its surface as an ultrasensitive biosensor. In the work by Plucinski et al. [38], CYP2J2-ND (nanodisks) were immobilized on the nanoLCA, and different elements were binding to the active site of CYP2J2 proteins as the inset shows. With high

concentration of binding elements, the transmission peak showed larger shift (Figure 2D). The author has also demonstrated the detection of seven other different chemicals at high and low concentration according to their spectral blue shifts by CYP2J2-ND-coated nanoLCA sensor [38]. These spectra shifts can also produce large enough Red-Green-Blue change to be detected by a camera. Researchers from Spain also demonstrated their work of integrating NR plasmonic sensor into microfluidic system, which achieved the detection of cancer bio-markers (human alpha-feto-protein and prostate specific antigen) down to concentrations of 500 pg/ml in human serum [45].

By virtue of its extraordinary optical sensitivity as well as the promising conductivity, plasmonic nano-arrays have also become an emerging tool for electrochemical studies [46]. Traditionally, signals obtained through electrochemistry could only represent the electrochemical process of the entire system in an averaged manner, while in reality most electrochemical systems are heterogeneous. Thus, plasmonic sensors were increasingly utilized as electrodes in order to reveal single-entity electrochemical reactions. For example, Cheng et al. used arrays of gold nanotriangles, decorated on indium tin oxide surface, for the electrochemical and optical monitoring of α -synuclein, a substantial protein related to Parkinson's disease [47]. The gold nano-array was proved to be a promising dual-detection platform for small molecules interaction monitoring. However, Cheng's work studied the optical and electrochemical signals separately.

For this reason, the interaction of plasmonic and electrochemical responses was then studied. Most electrochemical processes derive their signals through charge transfer and mass transport within the electrolyte: for example, the current signals in cyclic voltammetry were generated in accordance with the formation of diffusion layers of the analytes [48, 49]. Usually the transfer of charge and mass transport during electrochemistry will result in RI change near the electrodes, therefore making such electrochemical processes sensible with plasmonic devices. By utilizing plasmonic nano-arrays as working electrodes, the SPR/LSPR phenomenon integrated with electrochemistry could offer a promising method to simultaneously exploit optical and electrochemical properties during the redox reactions. Li et al. reported a novel spectroelectrochemical method for the detection of neurotransmitters, in which NanoLCA was set as the working electrode in the standard three-electrode system [50, 51]. Cyclic voltammetry was applied to observe the characteristic current for oxidation and recovery of dopamine and serotonin within the electrolyte, and LSPR responses of NanoLCA during

such process were observed to have corresponding wavelength fluctuation in accordance with the oxidation currents of neurotransmitters. In comparison with traditional electrochemistry, electrochemical-enhanced LSPR provided better SNR and lower detection limits, along with immunity against interference factors like ascorbic acid.

Fang et al. took a further step by visualizing electrochemical reactions of single nanoparticles based on SPR imaging [52, 53]. In their recent works, a plasmonic sensor was utilized as the working electrode in the standard three-electrode system, and an object with RI matching oil was used for electric field monitoring as the electrochemical process proceeded [54]. Two modes of imaging were presented, i.e. electrochemical current imaging and interfacial impedance imaging, each associated with faradaic current and double-layer charging current. During the electrochemical process, the changes in concentrations of reactant and product on the surface of the electrode could be visualized in real time by virtue of SPR sensing, providing an alternative for improving the spatial and temporal resolution of traditional electrochemistry. Another recent research accomplished by Hu et al. [55] used the NanoLCA device to monitor the layer-by-layer molecular deposition process by colorimetric imaging, which is largely due to the improved sensitivity for RI detection with the newly designed plasmonic nano-array.

Most RI plasmonic sensing requires the comparison of transmission or reflection spectrum, which in turn usually requires expensive spectrometry for quantification. Recently, researchers [56, 57] have designed a metal-insulator-metal structure on top of 3D plasmonic nano-well array structure to quantify RI change using the transmission at a single wavelength. This new technology can lower the complexity of the equipment needed for accurate bio-sensing.

4 Sensing assisted by enhanced field from nano-array structure

In addition, the electrochemical scanning could change the redox reaction species around the nano-sensor surface and elicit RI changes, finally enhancing the LSPR signals. Thus, the RI sensing, nano-array plasmonic structure can be utilized for ultrasensitive sensing owing to locally enhanced electromagnetic field [32, 58–61]. Here we review the applications of fluorescence/absorbance amplification and surface-enhanced Raman spectroscopy (SERS) with such nano-array structure.

4.1 Field-enhanced fluorescence and absorbance

As mentioned above, enhanced electromagnetic field within the decay length of nano-array structure could be utilized for ultrasensitive bio-sensing. The near-field enhancement has been studied and well known for application of metal-enhanced fluorescence (MEF) in bio-sensing. The theory of MEF was developed and illustrated in a lot of previous work [62–64]. The enhancement was mainly affected by three mechanisms: energy transfer quenching by the nearby metal; concentrated local field near metal particles, which leads to enhanced emission intensity; and the increase of intrinsic radiative decay rate (Γ_0) due to nearby metal. The quantum yield was then modified to be

$$Q = \frac{\Gamma_0 + \Gamma_m}{\Gamma_0 + \Gamma_m + k_{nr} + k_q}$$

where Γ_m is the modification of radiative decay rate, k_{nr} is the nonradiative decay rate, and k_q is the rate of quenching process. The lifetime of the fluorophore is the average of these rates:

$$\tau = \frac{1}{\Gamma_0 + \Gamma_m + k_{nr} + k_q}$$

The enhanced fluorescence can normally be indicated by larger radiative decay rate ($\Gamma = \Gamma_0 + \Gamma_m$), increased quantum yield (Q), or decreased lifetime (τ). The period and curved nano-array structures covered by noble metal not only lead to a metal increased radiative decay rate, but also provide a locally confined field which amplifies the emission intensity from fluorophores nearby. The requirement of this MEF on nano-array structures should satisfy an overlap of absorbance and emission spectra as well as an overlap within the LSPR mode of the metal structure. Additionally, an optimized separation distance between fluorophore and metal surface to prevent quenching should also be considered.

Cui et al. have published their work on metal MEF by coupling SPR to fluorophore's emission spectrum [65]. They realized enhanced fluorescence intensity on 2D grating nano-array structure as early as 2010. The grating structure they demonstrated was a conventional nano-hole array (Figure 3A). Compared with ordinary MEF based on 1D grating or planar metal surface before, they

Figure 3: Metal-enhanced fluorescence on different nano-array structures.

(A) Scanning probe microscopy images of 1D and 2D gratings after metal deposition. Grating pitch = 400 nm. (B) Enhancement factor (EF) of the fluorescence intensity on different substrates using plane glass as reference (EF = 1.0) (A and B adapted from Ref. [57] with permission from John Wiley and Sons). (C) Schematic (overview and cross section) of disk-coupled dots-on-pillar antenna array (D2PA) plate without an immunoassay. D2PA has an array of dense three-dimensional (3D) resonant cavity nano-antennas (formed by the gold disks on top of periodic nonmetallic pillars and the gold backplane on the pillar foot) with dense plasmonic nanodots inside and couples the metallic components through nanogaps. (D) Measured area average fluorescence intensity spectrum of the human-IgG labeled with IRDye800CW captured by the assay on the D2PA (red line) and the glass plate (blue line, which is amplified 1000 times to be visible at given scales), respectively. (C and D reprinted with permission from [58]; copyright (2012) American Chemical Society). (E) SEM images of Au nanostructure with 5s oxygen plasma etching. (F) Fluorescence spectra intensity change with etching time (E and F reproduced from Ref. [61] with permission from The Royal Society of Chemistry).

demonstrated an enhancement factor (EF) of 100, which is significantly larger than the previous methods (Figure 3B).

Apart from nano-hole array, Zhou et al. have demonstrated a disk-coupled dots-on-pillar antenna array structure with a molecular spacer, which enhanced the average fluorescence of an immunoassay of protein A and human immunoglobulin G (IgG) by over 7400-fold [66]. This array was formed by 3D resonant cavity nano-antennas with dense plasmonic nanodots inside and nano-gaps between top disks and pillar foot (Figure 3C). The average fluorescence enhancement covered a dynamic range of eight orders of magnitude, and it improved the sensitivity by 3,000,000-fold (Figure 3D).

Nano-antenna structure was already reported to produce single-molecule fluorescence enhancement up to a factor of 1340 by Moerner's group [67]. The sharp metal tips introduce highly enhanced optical fields with ultra-compact mode volume which causes fluorescence enhancement. Brown et al. made use of this advantage and modified such nano-antenna structures into a

rotation of two pairs and have demonstrated enhanced absorption by a factor of more than 12,000 [68]. To achieve fluorescence enhancement in large scale, Xie et al. made tunable periodic nano-structures using colloidal lithography, by which the distance between Au sharp tips could be adjusted (Figure 3E). Both the enhancement and quenching were studied by adjusting the etching time after colloidal lithography. The gap between the tips should be neither too close due to quenching effect nor too far away due to short decay length of LSPR. The EF was optimized to 69 in large scale (Figure 3F) [69].

Seo et al. have developed nano-cup array structure which achieved tunable enhanced fluorescence by varying surrounding fluidic refractive indices [70]. The nano-cup array was covered by Au (Figure 4B), which showed obvious plasmonic phenomenon with high RIU. Based on this property, HEX (hexachloro-fluorescein) and TEX (sulforhodamine 101 acid chloride) were utilized to demonstrate the integrated fluorescence's dependence on fluid environment change. When the emission peak of

Figure 4: Fluorescence enhancement on nanocup array structure (nanoLCA).

(A) A schematic representation of the fluorescence enhancement on the nanocup array structure is presented. The nanocup array polymer substrate is in gray, gold layer deposited on the substrate is in yellow, and two different refractive indexed media are in blue and purple color. Green and red point sources are HEX and TEX dye, respectively. In different media, reflected light intensity ($h\nu_{ref}$) and scattered light intensity ($h\nu_{scat}$) differ despite the same excitation light intensity ($h\nu_{ex}$), resulting in different fluorescence emission intensities ($h\nu_{em}$). (B) The SEM image of nanocup arrays. (C) The scattering peak position shifts to red with increasing concentration of glycerol. (D) Dynamic fluorescence image brightness response with alternate flows of air (A) and water (W). (E) The radiative decay rate on the surface of the nanocup structure with different surrounding refractive indices. (F) Integrated fluorescence emission curves of HEX and TEX show their maxima at different refractive indices. HEX has maximum integrated fluorescence intensity with 20% glycerol, but TEX has it with 80% glycerol (A–F adapted from Ref. [62] with permission from The Royal Society of Chemistry).

fluorescent dye matches plasmonic scattering peak, the emission will be enhanced due to the locally enhanced electromagnetic field (Figure 4A). Upon changing the concentration of glycerol, the corresponding plasmonic resonance peak displayed a red shift, which can cover the emission peak positions of both HEX and TEX (Figure 4C). This property was demonstrated by changing the surrounding media alternately (air and water) to see the fluorescence intensity change periodically (Figure 4D). The peak value of quantum efficiency and radiative decay rate were optimized by changing the surrounding media's RI when the fluorescence intensity of HEX and TEX was under investigation. The peak radiative decay rate indicates an enhanced fluorescence with optimized RI (Figure 4E). The most fluorescence enhancement could thus be validated by tuning the glycerol concentration shown in Figure 4F. This tunable property of the nano-cup array structure opened a door for multi-target fluorescence-based bio-sensing without modifying sensing substrate dimension.

Besides fluorescence bio-sensing, the enhanced scattering electromagnetic field from LSPR could also benefit the sensing mechanism which utilizes the target's absorbance property. A plasmonic nano-antenna has been proved to have near-field enhancement which facilitates molecular sensing by absorbance measurement [16, 71]. Seo et al. demonstrated this absorbance enhancement phenomenon for bovine serum albumin (BSA) sensing with the nano-cup array structure [72]. Covered by Au on nano-cup array (Figure 5A), the device showed plasmonic scattering peak (absorbance dip in Figure 5B) at 600 nm,

which was close to the absorbance peak (595 nm) of Bradford assay. Here the chromophore which absorbs light acts as an acceptor while the plasmon acts as an energy donor, similar to Foster resonant energy transfer [73]. By matching the chromophore's absorbance peak and the plasmonic resonance peak of the device, the absorbance of the chromophore could be enhanced (Figure 5C). This mechanism could be used for ultrasensitive bio-sensing especially at low concentration, since the decay length of LSPR is only 10 nm near the metal surface. By comparison of the case with and without nano-cup array structure in Figure 5D, the sensitivity of the detection improved significantly with the device. The enhanced absorbance property enabled quantification for low volume and low concentration sensing, which showed obvious advantages over other absorption detection methods. Seo et al. also demonstrated the potential for mass-productive detection by integrating such a device into a 96-well plate.

Furthermore, NIR emitting fluorescent detection has provided another valuable tool for bio-imaging, especially for the detection of disease markers *in vivo* [74–76]. To form images deeply into the organs and soft tissues of living systems, a relatively large penetration depth of NIR light was needed. Researches showed that noble-metal nanoparticles and nanostructures with unique, remarkably vivid optical properties were a highly promising approach to enhance the emission of currently available NIR fluorescent molecules by decreasing their radiative lifetime, thereby increasing their quantum yield [62, 63, 77, 78]. The lifetime of a molecular excited state changed

Figure 5: Absorbance amplification on nanocup array structure (nanoLCA).

(A) SEM image of the nanocup array structure in top-down view and in a cross-section view. (B) Absorbance spectra of the nanocup array structure in air and in water. (C) Schematic representation of energy diagram to show energy transfer mechanism between plasmon and dye molecule. (D) Relative absorbance changes with increasing BSA concentration with and without the nanocup array structure (A–D reprinted with permission from [64]; copyright (2015) American Chemical Society).

with the distance from the surface of a noble metal. The modifications of the enhanced absorption, radiative decay rate, and nonradiative decay channels of the noble-metal nanoparticles and nanostructures would also influence the fluorescence detection [79–81]. With the increase of the fluorophore-metal distance, oscillatory enhancement and quenching behavior would occur in bulk metals. And the molecular fluorescence could return to its unperturbed value under large separation distances. In addition to image enhancement, metal-enhanced fluorescence showed high sensitivity and selectivity in many emerging applications such as immunostaining, DNA hybridization, and single-molecule detection [64, 80, 82]. Consequently, designing and developing metal-enhanced fluorescence of colloidal nanocrystals with nanoscale control to enhance NIR fluorescence is of broad interest and general importance.

4.2 Surface-enhanced Raman spectroscopy

SERS is a powerful vibrational spectroscopy technique that is capable of detecting low-concentration analytes by amplifying the electromagnetic fields produced by the excitation of localized surface plasma [83]. The strength of the SERS signal is of the fourth order of the magnitude of electrical field strength [84–86]; thus, the strong enhanced field is essential for SERS substrate. As one important category of SERS substrates, plasmonic nano-array SERS substrate has the advantages of outstanding uniformity, good reproducibility, ease of use, and high EF [87]. One of the best demonstrated examples is that by Wu et al. [88] where a metal-coated nano-dome has been finely tuned and EF of 8.1×10^7 was achieved. Compared with traditional 2D-based SERS substrates which mostly only have one layer of hot spots such as metallic nanoparticles and NRs, nano-array plasmonic SERS devices with 3D structures have the strength of creating more hot spots in z-direction. As a result, higher EF has been achieved with those substrates. Moreover, by fine-tuning the surrounding RI or the geometric parameters of the 3D plasmonic devices, we can move the resonant wavelength closer to the excitation wavelength so as to gain higher EFs [20]. In this part, we review SERS based on 3D plasmonic structures.

The two 3D plasmonic devices in Figure 1 have also been shown to provide good SERS performance. The NanoLCA device has an EF of 2.8×10^7 , while the FlexBrite device has an EF of 4.81×10^8 . In the simulation for FlexBrite at wet state (Figure 6A), the reflection dip corresponding to the resonant mode is closer to excitation

laser wavelength (633 nm) [34]. However, the EF at dry state is only 6.85×10^7 , which is only 1/7 of that at wet state. The EF could be further improved by 3.4 times in the following research by fine-tuning the diameter of the nano-pillars [33]. As previously mentioned, the biotin conjugation process could be monitored using colorimetric method; therefore, the combination of streptavidin with biotin can also be easily identified (Figure 1H). Since the colorimetric method often relies on RI, which is a nonspecific parameter of the target, it is usually only applicable for quantification sensing. In contrast, owing to specific vibration information from chemical bonds and symmetry of different target molecules, SERS is a perfect candidate for qualitative sensing. Furthermore, the strong SERS EF of FlexBrite improves its feasibility for molecule identification. Figure 6B shows the SERS signals on FlexBrite for water, biotin monolayer, and biotin binding with streptavidin, respectively. According to the Raman signal database, we can easily identify the chemical categories from the characteristic peaks. In another research, Hackett et al. [90] deposited metal-insulator-metal cap structure on top of polymer nano-pillars, and fine-tuned the hot spots to be located primarily on top of the nano-pillars. For the authors' application of cancer biomarker antigen 125 detection, the enhancement at the surface is essential for good detection result. This research demonstrates the tenability of 3D plasmonic sensors for variant applications. As a result, the 3D plasmonic device has the power to identify both the concentration from colorimetric measurement and the characterization of the chemical agent from SERS measurement.

In most recent researches, adding additional structure on top of 3D SERS structures increased the SERS EF significantly by forming additional “hot spots”. For example, Seo et al. [91] added 50 nm gold nanoparticles to the top of the metal-coated nano-well structure of the NanoLCA device to increase the EF by up to 60.94-fold. Similarly, Chang et al. [92] integrated 5 μm SiO_2 microspheres onto a random silver-nano-sphere-coated silicon nano-pillar array substrate, where the SiO_2 not only increased the electromagnetic field at its interface between silver and SiO_2 spheres but also concentrated the target molecules around the “hot-spots” based on the Marangoni effect. As a result, this research drastically increased the EF to 3.6×10^{10} , which is enough to achieve single-molecule detection and has superseded the EF of the SERS devices built upon the optical antenna principle [93].

With the similar concept of adding extended hot spots along z-direction, Tang et al. [89] reported the array of cone-shaped NRs decorated with silver nanoparticles as 3D surface-enhanced Raman scattering substrates which

Figure 6: 3D plasmonics SERS sensors.

(A) Measured (solid curves) and simulated (dashed curves) FlexBrite in dry state (blue curves) and wet state (red curves). Both measured and simulated reflection spectra show a dip around 633 nm, the excitation laser wavelength. This indicates the resonance at 633 nm. (B) SERS spectra of FlexBrite with water, biotin and biotin-streptavidin conjugate on the surface of FlexBrite (A and B reproduced from Ref. [34] with permission from The Royal Society of Chemistry). (C) An array of ZnO-NRs decorated with Ag-NPs (on the NRs side surface) and Ag spheres (on the NRs tops) on Si wafers. There are three kinds of “gaps” between the Ag-NPs to form 3D “hot spots” as indicated as 1st, 2nd, and 3rd schematically. “1st” stands for the gaps between the Ag-NPs located on the side surface of the same NR; “2nd” stands for the gaps between the two Ag-NPs located on the side surface of two neighboring NRs; and “3rd” stands for the gaps between the two large Ag spheres located on the tops of two neighboring NRs. (D) Top: SEM image of the ZnO-NRs after an Ag-sputtering for 135 s; Bottom: SEM image of small Ag-NPs on the side surface of the ZnO-NRs after an Ag-sputtering for 12 min (C and D adapted from Ref. [89] with permission from John Wiley and Sons).

achieved the EF of 3.6×10^7 . To fabricate this sensor, after growing ZnO NRs on planar Si wafer, they assembled small Ag nano-particles onto the side surface of the NRs by top-view ion-sputtering and decorated large Ag spheres onto the tip of each NR by elongation of the ion-sputtering duration. Figure 6C shows the schematic of the SERS substrate, and Figure 6D includes two scanning electron microscope (SEM) images of the silver-decorated ZnO NRs. Similarly, instead of extending hot spots in z-direction, Shen et al. who made full use of 3D space to add more hot spots, developed a highly sensitive (10-fold amplification) nano-grass structure with integrated grating, which significantly increased SPP coupling [94].

Overall, in order to produce large-scale SERS substrate with good uniformity, high-sensitivity plasmonic

substrates with extended hot spots in z-direction are a good candidate.

5 Conclusion and future prospects

In summary, most recent developments in plasmonic nano-array structures were reviewed for ultrasensitive bio-sensing. The sensing mechanisms based on RI change and surface field enhancement were discussed separately. The development of plasmonic nano-array sensors has advanced dramatically in the past few years mainly due to the advances in nano-fabrication technology, especially in biomedical applications. The ultrasensitive

plasmonic biosensors here provide foundation for further development in point-of-care based diagnosis and personalized medicine, which will make biosensors ubiquitous in the near future. Better specificity and more flexibility will be the challenge for future plasmonic sensing. Labeling techniques based on fluorescence or Mie scattering will be coupled with plasmonic nano-array substrate, such that lower limit detection with specificity can be achieved. With optimized parameters for both labeling particles and plasmonic nano-structure [95], the enhanced surface electromagnetic field and resonance mode matching may facilitate better sensitivity. Greater flexibility will definitely bring such plasmonic biosensors closer to real point-of-care diagnosis. The research in the area of flexible materials and innovative fabrication methods has already shown the advantages in tunable plasmonic sensing [96, 97]. Such flexible platforms will be pushed to achieve better stability and repeatability. With further integration to flexible electronics, the ultrasensitive plasmonic biosensors will drive the revolution in personal healthcare approaches, such as cost-effective, portable, or wearable sensors. In addition, by combining a metallic plasmonic nano-array with electrochemical detection that can be integrated with smart-phone-based platform or portable techniques [98–101], not only can extended detection targets be included but also the sensing accuracy, anti-interference capabilities, SNR, and limit of detection can be improved.

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