Chapter

Chiral Hybrid Nanosystems and Their Biosensing Applications

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Abstract

The presented chapter is devoted to chiral biosensing using various metal nanostructures and their hybrid nanosystems with optically active bio- and organic molecules. Plasmonic nanosystems and nanostructures provide an excellent platform for label-free detection of molecular adsorption by detecting tiny changes in the local refractive index or amplification of light-induced processes in biomolecules. Based on recent theoretical and experimental developments in plasmon-enhanced local electric fields, we consider the main types of molecular-plasmonic hybrid systems capable of generating an amplified chiroptical signal for such applications as detecting the presence of certain biomolecules and (in some cases) determination of their orientation and higher-order structure.

Keywords: plasmonics, chiral nanosystems, biosensors, surface plasmon resonance, chirality

1. Introduction

Plasmonic nanostructures attract increasing attention as signal amplifiers and transducers for optical sensing. The local plasmon-induced enhancement of electric fields affects various optical processes in molecular systems and therefore finds multiple applications in enhanced spectroscopic techniques, such as Surface-Enhanced Raman Scattering (SERS), Plasmon-Enhanced Fluorescence (PEF), Surface-Enhanced Infrared Absorption (SEIRA), etc. These plasmon-enhanced spectroscopic methods have been described in several recent review articles [1–3].

A wide number of naturally occurring biomolecules, including amino acids, sugars, and nucleotides, are chiral and often exist only in one of the two possible enantiomeric forms [4–6]. It is known that the therapeutic effect of chiral drugs is associated with one of enantiomer's form, while the other one can lead to highly undesirable effects [6]. This fact highlights the necessity of enantiomers detection and separation as well as the need for stereoselective synthesis. Circular dichroism (CD) spectroscopy is usually used for analyzing molecular chirality. It determines small differences in the interactions between left- and right-circularly polarized light (CPL) with a molecular system. Molecular chirality can also reveal itself by rotating a polarization plane of linearly polarized light, an effect called optical rotational dispersion (ORD). These chiroptical responses define each other through Kramers-Kronig relations [7]. Unfortunately, their experimental detection is possible only in highly concentrated analytes because the chiroptical signals are usually very weak. Thus, there is great interest in chiral plasmonics nowadays, especially in using plasmon-enhanced near fields in order to increase the sensitivity of chiroptical

spectroscopy [8–9]. Many chiral plasmonic nanostructures are studied both experimentally and theoretically. The nature of plasmonic chirality and the chiroptical effects in plasmonic nanostructures are described in several extensive reviews [10–12].

This chapter is dedicated to the applications of different plasmonic metal nanostructures and their hybrid nanosystems with optically active organic and biomolecules in chiral biosensing. We focus on the recently published results of using plasmon-induced evanescent fields and consider the main types of molecular plasmonic systems capable of generating amplified chiroptic signal in order to detect the presence of certain biomolecules and (in some cases) to determine their orientation and high-order structure.

2. Chiral molecules coupled to a single plasmonic nanoantenna

The absorbance of an achiral excitonic system can be strongly enhanced via the interaction with plasmonic particles due to the antenna effect [13]. Similar phenomena can amplify the chiroptical response of a chiral molecular system coupled to a plasmon, which is highly desirable for (bio)sensing, as it can increase the sensitivity and lower the detection limit of a sensor.

It was experimentally demonstrated that silver nanoparticles induce nearly two orders of magnitude amplification of chromophore's CD. Besides, the CD signal appeared at the same wavelength as the Localized Surface Plasmon Resonance (LSPR) of the nanoparticles [14]. These results initiated thorough theoretical studies of the nature of plasmon-induced CD amplification [15–18]. It has been found that binding of a chiral molecule to a small achiral plasmonic nanoparticle (particle size ≈ 10 nm) can enhance the molecular CD signal in conjunction with the appearance of a new CD signal at the plasmon resonance wavelength. The suggested model is presented in **Figure 1**.

The charge is localized in the small gap between the molecule and the nanoparticle and the Coulomb interactions between their electronic systems can be very strong. As a result, the CD signal induced by molecular transition can be boosted by plasmonic

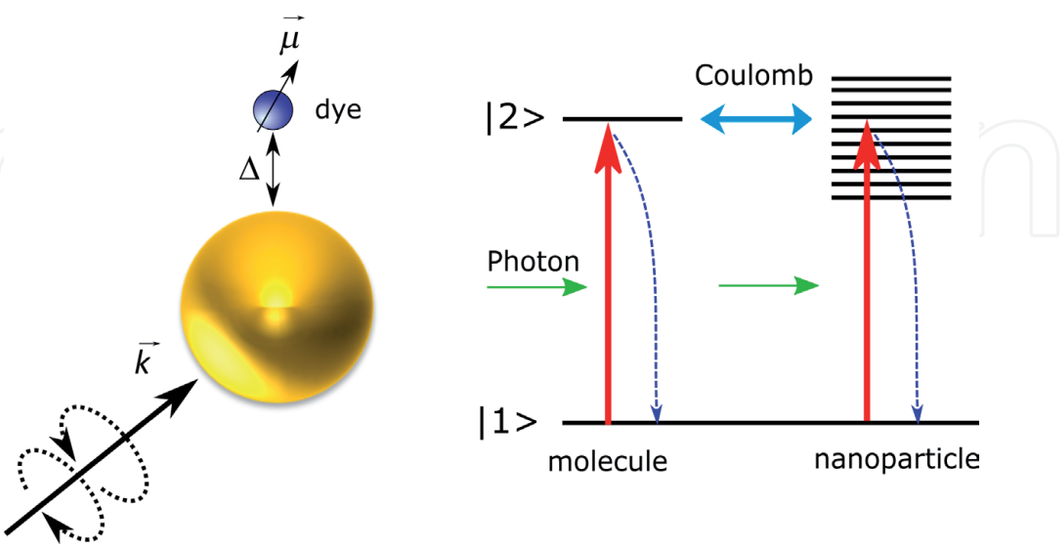

Figure 1.
The model of the metal nanoparticle-dye molecule assembly (left) and the scheme of excitation-deexcitation processes (right) with solid vertical (horizontal) arrows representing light (Coulomb)-induced transitions. The dotted vertical arrows show the relaxation processes. Adapted with permission from Govorov et al. [15], Copyright 2010 American Chemical Society.

resonance, and, at the same time, the surface current in plasmonic nanoparticle becomes chiral due to the chiral molecule, resulting in a new CD signal [15]. With increasing distance (d) between the metal nanoparticle and the molecule, the near field intensity decreases as d^{-3}. Since most biomolecules have CDs in the UV range, the appearance of the CD peak in the visible range is important for practical purposes as it can be easily detected.

A number of experimental studies support these findings. The CD peak in the visible range, generated by an adsorption of peptide molecules on spherical gold nanoparticles with 10 nm radius, is presented in **Figure 2** [19].

Similar results were obtained for a bilayer of riboflavin 50-monophosphate and polylysine molecules adsorbed on gold island films [20]. For cysteine and its derivatives in the presence of 45 nm spherical silver nanoparticles [23], for glutathione molecules adsorbed on 45 nm silver nanocubes [24] and for tobacco mosaic virus uniformly covered by spherical 5 nm gold nanoparticles [25] the enhanced chiroptical signals in the visible spectral range were also detected. The authors of the latter work achieved near-field amplification of the induced CD signal controlling by the separation between the molecule and the metal nanoparticle. The adsorbed chiral molecules were found to be in resonance with plasmon for the new appeared CD peak. Though, matching the wavelengths of molecular absorption and plasmon resonance intensified the effect, which suggests the use of nanostructures with plasmon resonance in UV for biosensing [21, 22].

Thus, to amplify CD signal of small chiral molecules a plasmonic nanoantenna can be used. But practical application of this approach in biosensing is limited by strong sensitivity to separation distance. It was shown that the induced CD can be sensitive to the orientation of the transition dipole moments of the adsorbed molecule relative to the local plasmon polarization of the nanoparticle [26]. Two orders of magnitude enhancement coefficients of CD were observed for 42 ± 2 nm gold/silver core-shell nanocubes coated with DNA molecules [21]. Additionally, the induced CD signal can be sensitive to the orientation of the transition dipole moments of the adsorbed molecule relatively to the local plasmonic polarization of the nanoparticle [26].

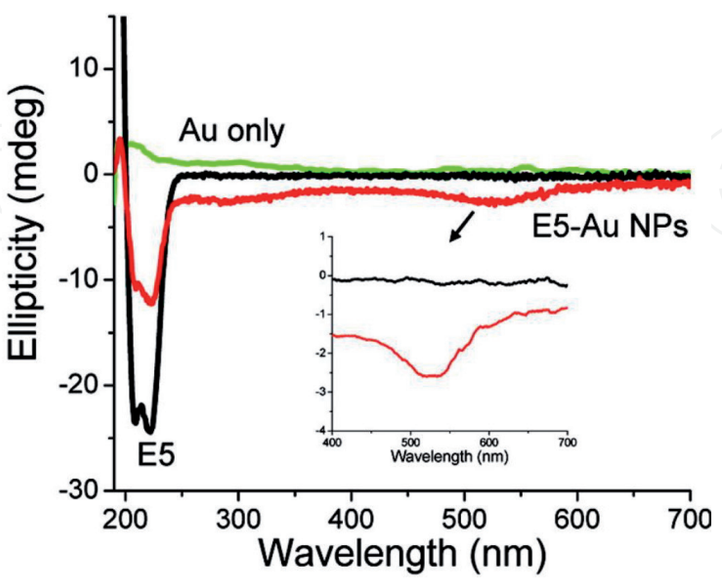

Figure 2.
CD spectra of E5 peptide (black line), gold nanoparticles (green line), and their assembly (red line). The inset shows the appearance of the CD peak in the visible range. Reproduced with permission from Slocik et al. [19]. Copyright 2011 American Chemical Society.

3. Chiral molecules in the gap of dimers of plasmonic metal nanoparticles

A similar chirooptical phenomenon is theoretically predicted for chiral molecules located in the gap of dimers of plasmonic nanoparticles for both resonant and nonresonant CD signals [27–30]. Strongly amplified electric field localized in the gap of such nanostructures results in a strong CD amplification. The enhancement factors up to 3000 can be expected for 5 nm gap. **Figure 3a,b** demonstrate the schematic image of the system and the correlation of CD enhancement with electric field in the gap [31].

This effect was experimentally observed in several systems of aggregated metal nanoparticles (NP), such as spherical gold nanoparticles conjugated to oligonucleotides [32–34], cysteine-modified gold nanorods [35, 36] and nanospheres [37, 38], as well as cholate-coated silver nanoparticle [39], etc. The CD signal is greatly enhanced by particle agglomeration, which leads to the formation of nanometer-sized gaps.

A demonstration of chiral biosensing based on the formation of asymmetric plasmon dimers has been reported recently [40]. The authors detected CD signal generated by self-assembly of gold nanorods using an antigen-antibody recognition reaction. The low detection limit for bisphenol A of 0.02 ng/mL was reached. To assemble nanoplasmon dimers with a tunable chiroptical response, the immobilization of highly specific complementary DNA primers on their surface were

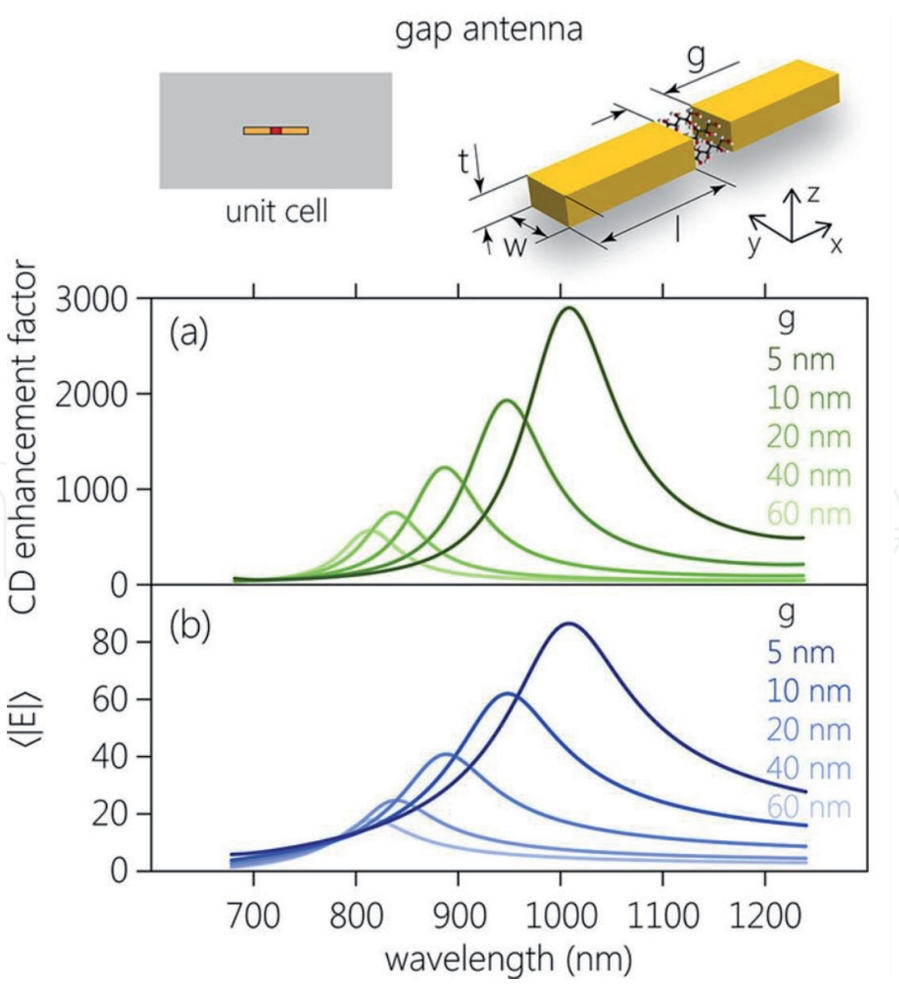

Figure 3.
Chiral molecules in the gap of a plasmonic dimer: schematics (top), (a) calculated CD enhancement factor for different gap size; (b) corresponding values of average electric field in the gap volume. Reproduced with permission from Nesterov et al. [31].

fulfilled [34]. Using this method and its modifications, various analytes were successfully being detected. For instance, self-assembly of silver ions was carried out with a detection limit of 2 pM by inducing the nanodimer assembly reaction [41]. By triggering the DNA-based chiroplasmonic assembly of gold nanoparticles and endonuclease H-paII the methyltransferase activity and inhibition has been studied [42]. Self-assembly technique has been used for the detection of ochratoxin A with the reported limit of detection as low as 0.15 pg/mL. In this experiment the construction of heterogeneous system with Au core and Ag satellites was created [43]. For the demonstration of the zeptamolar DNA detection the multimetal shell-engineered assemblies had been used [44].

Recently an alternative sensing scheme was demonstrated on an example of the alpha-fetoprotein (AFP) detection. NP dimers were formed by AFP aptamer binding to its complementary sequence immobilized on gold nanoparticles and display strong chiroptical activity. The addition of AFP aptamer led to its strong binding to immobilized aptamers and to the destruction of the aptamer-DNA hybrid accompanied by the decrease of CD signal. The authors reported the detection limit as low as 11 pg mL^{-1}. Since AFP is a marker of liver cancer, such detection scheme is of high practical interest [45].

Similar approach was used for the detection of 8-hydroxy-2′-deoxyguanosine, a well-known biomarker for the oxidative DNA damage, in human serum [46]. CD intensity showed log-linear correlation with the concentration of the analyte molecules, and the limit of the detection as 33 pM was reported.

The same strategy has been applied for monitoring the intracellular concentration of analyte molecules. For instance, the detection of adenosine-5′-triphosphate

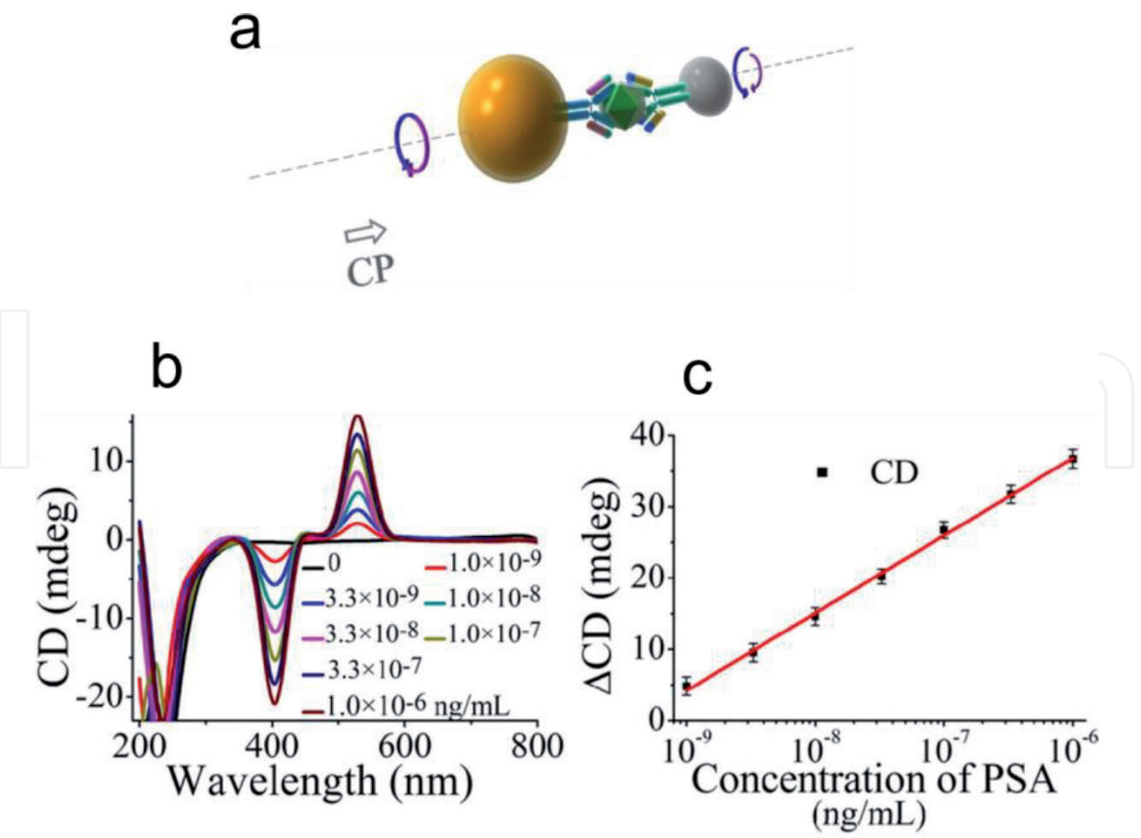

Figure 4.
Schematics of the Au-Ag heterodimer bridged by immunocomplex with prostate-specific antigen (PSA) (a); (b) the CD spectra for different concentrations of PSA; (c) the CD calibration curve for PSA detection as a function of logarithmic PSA concentrations. Reproduced with permission from Wu et al. [32], Copyright 2013 American Chemical Society.

in living cells with a detection limit of 0.2 mM has been demonstrated [47]. The results of telomerase activity study were reported: a limit of detection as 1.7×10^{-15} IU in a single HeLa cell was reached [48]. **Figure 4a–c** demonstrates another general approach to the formation of sensitive plasmonic dimers by using antibody-antigen interactions. For the chiroplasmonic detection of an environmental toxin, microcystin-LR, and a cancer biomarker, prostate-specific antigen (PSA), a silver-gold nanoparticle heterodimer was used [32]. The PSA limit of detection as 5×10^{-10} ng/mL (1.5×10^{-20} M) has been determined.

Recently, the detection of DNA molecules (with concentrations below 100 pM) located in the gap of two gold nanoparticles was successfully demonstrated [49]. The effects of the particle's gap size, shape, etc. were analyzed. In this way, for the detection of small chiral molecules, enzymes and proteins plasmonic dimers can be used. This approach is highly promising for biomedical applications such as biorecognition and intracellular detection. The use of DNA contributes to high sensitivity and selectivity in practical applications.

4. Chiral assemblies of achiral plasmonic nanoparticles

Consider sensing approach basing on geometrical chirality of chiral molecules. Physically, the generation of chiroptical response is due to both exciton-plasmon interaction, as described in previous section, or plasmon-plasmon coupling between achiral nanoparticles, arranged in a chiral superstructure [50]. In the latter case, the molecules play a role of a template and define handedness of the resulting assemblies. Eventually, the presence of the chiral molecules can be detected by the appearance of the CD signal.

Currently, several techniques were used to arrange plasmonic metal nanoparticles in chiral superstructures. As an example, DNA molecules can serve as such a template and chiral DNA-based structures are considered in recent reviews [51–56]. This method is often called "DNA origami." Besides, promising results have been achieved using peptide-directed assembly of gold nanoparticles into single-helix [57, 58] and double-helix superstructures [59, 60] (see **Figure 5**).

In order to arrange metallic nanoparticles in chiral assemblies, cholesteric liquid crystals were also used by the authors [61–63]. The elongated nanofibers obtained in cholesteric liquid crystalline mesophase are demonstrated in **Figure 6** [62]. Firstly, silver nanoparticles (2.5 nm in size) were formed and then their helical ordering was resulted due to the specific interactions of ligand molecule's functional thiol- groups with the surface atoms of silver nanoparticles. This process was resulted in hybrid spirals formation. In the case of a thiocholesterol ligand, concentrated organosols of such aggregates have high optical activity, as demonstrated by CD spectra. The optical spectra of these systems exhibited the absorption at about 430–450 nm, attributed to the LSPR bands of silver nanoparticles, and long-wavelength absorption at 700–1000 nm, which is characteristic of linear aggregates. This near infrared region is suitable for in vivo imaging and biosensing.

Anisotropic plasmonic nanoparticles, such as nanorods, offer some additional advantages, including better near-field focusing and high sensitivity to relative particle orientation [60]. The generation of optical activity in a dimer of gold nanorods was theoretically investigated. It was shown that hybrid plasmon modes, binding and antibinding, contribute to the CD signal [64]. Increased chirooptic activity was shown also by dimers and larger aggregates of gold nanorods initiated by immobilized DNA oligomers during PCR [65], which made it possible to detect DNA attomols [66]. The chiral response arose due to a slight twist between the nanorods. In the process of self-assembly, both enantiomers were formed, but one

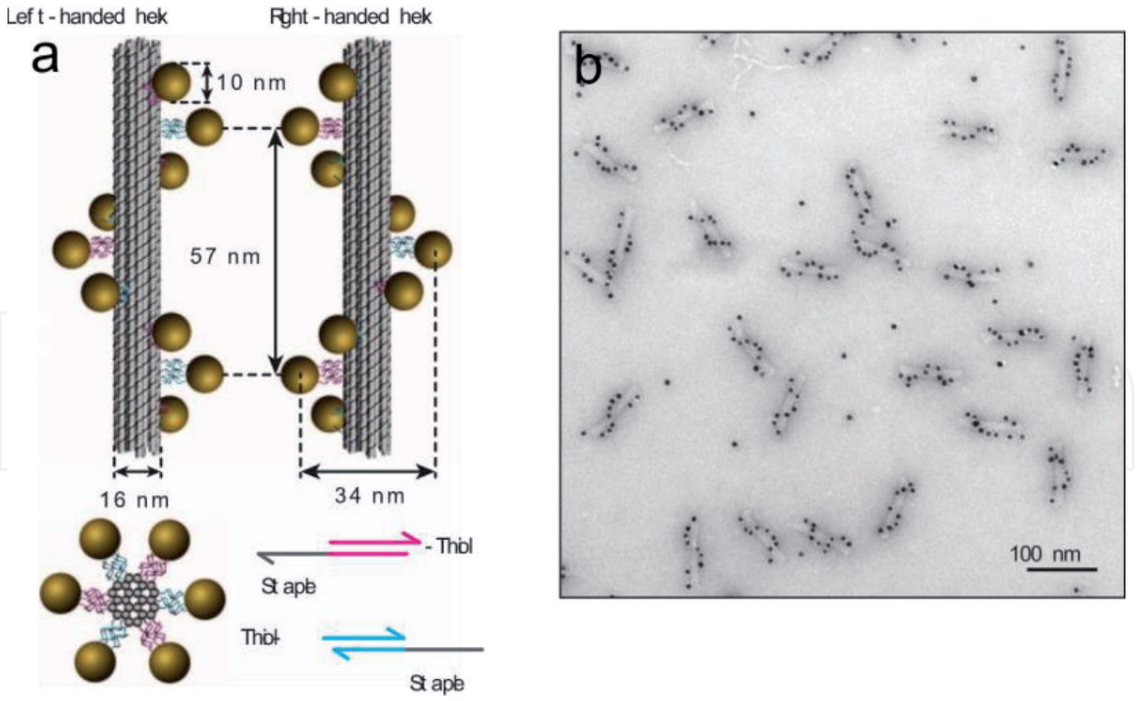

Figure 5.
Chiral assemblies of gold nanoparticles and DNA origami in left- and right-handed nanohelices: (a) schematics, (b) TEM image. Reproduced with permission from Kuzyk et al. [53], Copyright 2012 Springer Nature.

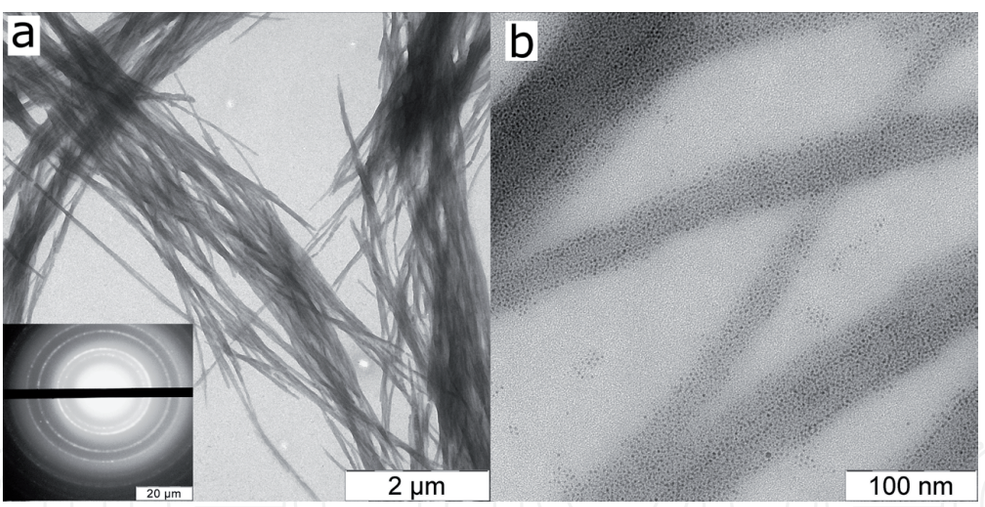

Figure 6.
TEM images of silver nanoparticle aggregates stabilized by thiocholesterol (after 24 h storage in mesophase): (a) general view, (b) internal structure, and (c) the formation scheme of silver-thiocholesterol chiral 3D-aggregates. Reproduced with permission from Shabatina et al. [62], Copyright 2013 Springer.

of them was thermodynamically more favorable. Glutathione molecules supported by cetylammonium bromide micelles directed the self-assembly of gold nanorods and the formation of chiral nanochains with end-to-end contacts [67].

A strong chiroptical signal can be generated by plasmon nanorods assembled into a three-dimensional spiral structure by supramolecular fibers, such as anthraquinone based oxalamide [68]. The DNA origami approach allowed you to adjust the chiro-optical response by carefully controlling of the plasmonic superstructure. Dynamic switching between different configurations of the nanorod spirals led to a change in the chiro-optical response [69].

Other biomolecular matrices also can be used to order plasmonic nanoparticles in three-dimensional chiral assemblies, such as proteins or their aggregates. So, it

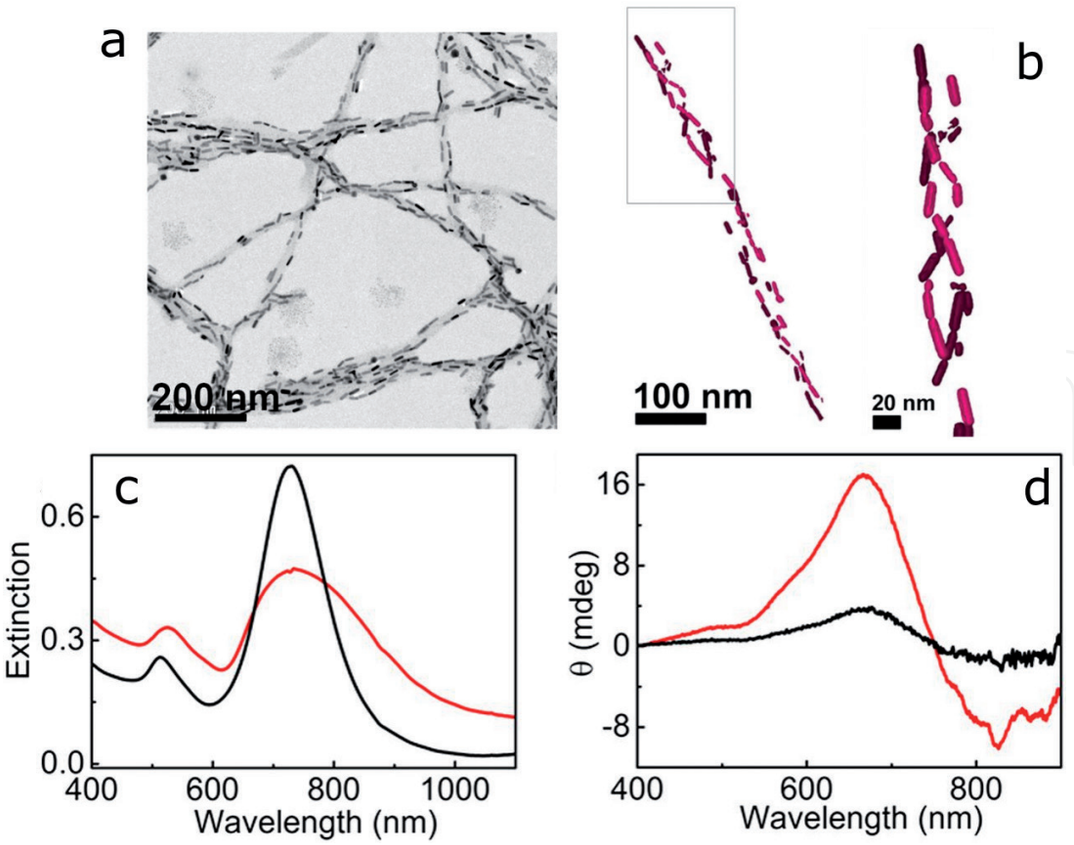

Figure 7.
Composite α-synuclein fiber with 3D chiral arrangement of Au nanorods: (a) TEM image, (b) cryo-TEM tomography reconstruction, (c) extinction, and (d) CD spectra of Au nanorods monitored 30 min after the addition of 30 μL of purified brain homogenates from healthy (black) and Parkinson-disease-affected (red) patients. Adapted with permission from Kumar et al. [60], Copyright 2018 National Academy of Sciences.

was reported that amyloid fibrils of α-synuclein CD were detected using helically arranged gold nanorods (see **Figure 7**) [60]. At the same time, chiro-optical activity was not detected when only α-synuclein monomers were present. This technique can be further expanded to detect infectious recombinant prions.

There are cases of aggregation of plasmonic nanoparticles, leading to the sharp optical changes upon initiation by only one enantiomer. D-glutamic acid led to the aggregation of gold nanoparticles coated with CTAB, which followed by a significant change in color, while for the L-enantiomer there were practically no changes [70]. Similarly, the enantioselective detection of D-cysteine by silver nanoparticles was recently demonstrated in the solution and in the special bacterial cellulose matrix [71].

5. Biosensing with 3D chiral nanostructures

To amplify the CD signal of a chiral molecule, the differential absorption of the chiral molecule must be increased. For an analytical estimate of the speed of light absorption, one can use the relation [72]:

$$A \propto \frac{\omega}{2}\left(\alpha''\left|\tilde{E}^*\right|^2 + \chi''\left|\tilde{B}\right|^2\right) - G''\omega Im\left(\tilde{E}^* \cdot \tilde{B}\right) \quad (1)$$

where ω is the angular frequency of electromagnetic wave, α'', χ'' and G'' are the imaginary parts of electric polarizability, magnetic susceptibility and mixed

electric-magnetic polarizability of the molecule, and $\tilde{E}$ and $\tilde{B}$ are the complex electric and magnetic field, respectively. CD is determined by the second term, which is defined by both the intrinsic chirality of a molecule ($G'' \neq 0$) and by local electromagnetic field ($\mathrm{Im}\left(\tilde{E}^* \cdot \tilde{B}\right)$), which needs to have nonorthogonal components of electric and magnetic field vectors.

Thereby, to enhance the CD response of a chiral molecule one can modify the electromagnetic field to maximize the local optical chirality C, the quantity originally introduced in 1964 [73] and recently revised [72].

$$C = -\frac{\varepsilon_0 \omega}{2} \mathrm{Im}\left(\tilde{E}^* \cdot \tilde{B}\right) \tag{2}$$

The present subsections consider the research directed at constructing plasmonic systems with enhanced near-field chirality and examples of biosensing based on these nanostructures.

The efforts of many groups of scientists have been expended in order to increase the optical chirality C (Eq. (2)) using chiral plasmonic nanostructures. One of the chiral structures that scientists have studied both theoretically and experimentally is nanohelix. The numerical modeling of such structures determined a strong CD effect [74]. However, for gold nanohelices 400 nm high, 400 nm in diameter, and 80 nm thick nanowires, the chirality enhancement factor was determined as 10, so the use of such structures in biosensing is limited [75]. This problem was solved by fabricating superstructures with several nanohelices [76] using direct laser recording methods [77, 78] or ion- and electron beam lithography [79–81]. The use of such structures made it possible to increase the optical chiral amplification factor up to two orders of magnitude and to adjust the CD signal from IR to the visible region of the spectrum. A schematic representation of the structure and the field distribution are shown in **Figure 8**. In addition, this approach made it possible to create core-shell nanohelices with adjustable dissymmetry coefficients and CD [82].

Recently, another method using three-dimensional chiral plasmonic nanohelices for probing was demonstrated [83]. Instead of using enhanced near-field chirality, the CD signal of Pd nanohelices was used to detect a (0.1–1%) hydrogen content. Large-area arrays of Pd and Pd-Au hybrid nanostructures were obtained using the angular nanoglancing deposition method [84], which combines block copolymer micellar nanolithography [85] with glancing-angle deposition (GLAD) [86].

The last considered approach for synthesis of chiral lattice is adsorption of chiral organic molecules on growing nanocrystals. The following review demonstrated

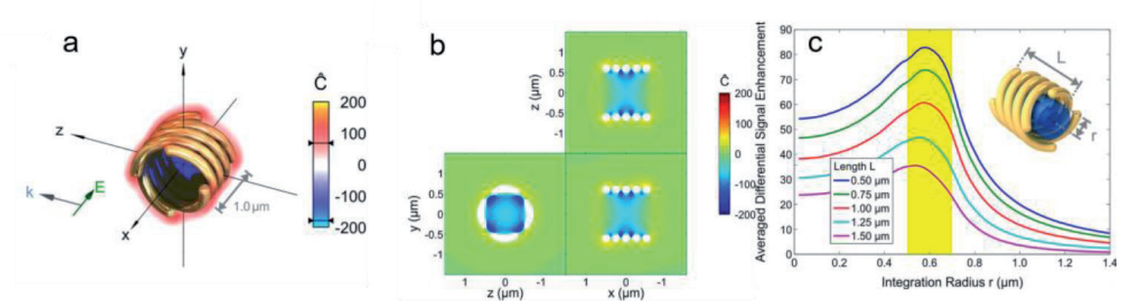

Figure 8.
3D chiral plasmonic nanostructures: (a, b) simulated four-helix gold nanostructure showing strongly confined optical chirality within the helices and (c) the graph presenting the enhancement of differential absorption signal depending on the radius of integration, for different length of a structure. Adapted with permission from Schäferling et al. [76], Copyright 2014 American Chemical Society.

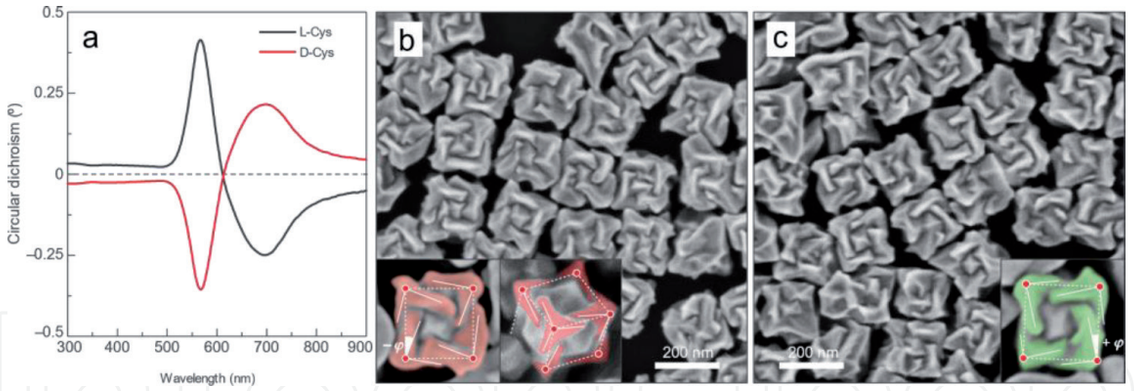

Figure 9.
Three-dimensional plasmonic helicoids controlled by cysteine chirality transfer: (a) CD spectra and (b–c) SEM images of chiral nanoparticles synthesized using L-Cys and D-Cys. The insets highlight the tilted edges (solid lines), cubic outline (dashed lines), and tilt angles (−φ and +φ). Reproduced with permission from Lee et al. [77], Copyright 2018 Springer Nature.

the formation of chiral nanocrystals of Te and Se, which can be used as a matrix for growing nanostructures of gold and silver tellurides [87]. Also, there was presented the growth of chiral gold nanoparticles in the opposite direction induced by amino acids and peptides [77]. The effect of different growth rates on the chiral morphology of gold nanocrystals in the presence of L-Cys or D-Cys was observed. The structure and CD spectra of these nanocrystals are shown in **Figure 9**. It has been revealed that in the presence of L-glutathione (GSH) growing nanocrystals have different morphologies. The proposed mechanism involves specific adsorption of Cys or GSH on the high-index planes of growing particles.

6. Planar chiral nanostructures and metasurfaces

Next perspective structures are planar plasmonic nanostructures with thickness less than the wavelength of the incident light. They are very attractive from a technological point of view because of a possibility of mass production using conventional lithographic methods. As well as for truly chiral forms with enantiomers that cannot be superimposed by any rotation in 3D space, the left and right enantiomers of a flat chiral shape are not superimposed on each other by the rotation in a plane. Handling in the latter case has been determined by the viewing side, which leads to inverted CD spectra when the planar structure is illuminated from the opposite normal direction. In contrast to three-dimensional spiral structures, the differential light absorption of LCP and RCP by planar plasmon nanostructures is due to the difference in LSPR-induced near-field distributions [88]. Similar effects were observed in the study of 2D chiral plasmon nanostructures (see **Figure 10**), such as G- [89], S- [90], L-shaped [91] nanostructures, gammadions [92, 93], nanohelix [75] asymmetric nanoparticles [94], checkerboard nanorods [95] and also for flat metamaterials, including thin metal films with two-dimensional chiral holes, such as dimers with nanogap [96, 97].

Chiroptical response of planar chiral plasmonic nanostructures can be highly sensitive to the presence and to the specifics of tertiary structure of biomolecules, as in the case of arrays of gold gammadion nanostructures [99]. These effects can be viewed in plasmonic peak shifts for RCP and LCP light upon adsorption of proteins and in the difference of the values $\Delta\Delta\lambda = \Delta\lambda RCP - \Delta\lambda LCP$, and can been used as an analytic signal. The parameter $\Delta\Delta\lambda$ becomes zero: $\Delta\Delta\lambda = 0$ for achiral adsorbed molecules. In this way, the picogram levels of proteins were detected.

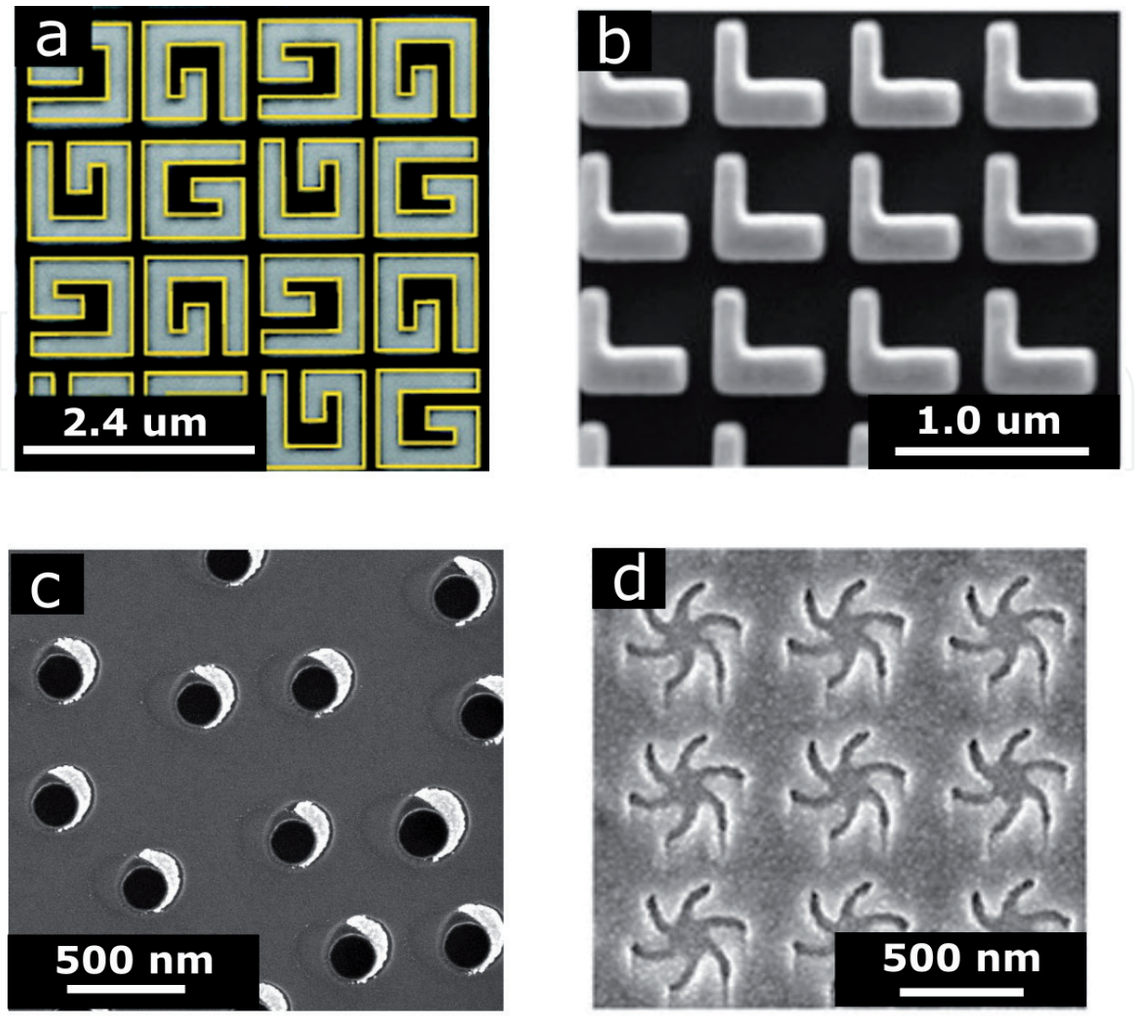

Figure 10.
Examples of planar chiral nanostructures: (a) arrays of G-shaped gold nanoparticles. Adapted with permission from Valev et al. [89], Copyright 2009 American Chemical Society. (b) Arrays of L-shaped gold nanoparticles. Adapted with permission from Ye et al. [91], Copyright 2017 American Physical Society. (c) Short-ordered arrays of comma-shaped gold nanoparticles [94]. (d) Gold metafilm with arrays of "shuriken" nanostructures. Adapted with permission from Kelly et al. [98], Copyright 2018 American Chemical Society.

Furthermore, the proteins with different content of β-sheets give different CD response, so, providing information about the structure of the adsorbed biomolecules. This feature has been studied in detail using chiral "shuriken"-like gold-covered indentations created on polycarbonate templates using injection molding method and gold deposition [100]. The chiroptic properties of the far-field were characterized by the collection of ORD spectra in the reflection mode for linearly polarized incident light. The observed peak shifts demonstrated picogram limit of detection of protein. Conformational changes associated with protein binding to ligands can be accompanied by the changes in the asymmetry factor $\Delta\Delta\lambda$, demonstrating sensitivity to the tertiary and domain (quaternary) structure of proteins [101].

More recent studies have shown that these chiral plasmon substrates can distinguish between proteins that have similar structures but have primary sequences that differ in one amino acid [102]. So, it can provide information about the structural order in complex biointerfaces [98].

Thus, the "superchiral" fields generated by 2D chiral nanostructures can provide a unique opportunity to probe the chirality of adsorbed biomolecules at such levels, as conformation, orientation, molecular structure, and supramolecular ordering.

7. Conclusions

Unique properties of plasmonic nanostructures open exciting new possibilities for increasing the sensitivity of molecular chirality. There are several common approaches among different experimental and theoretical studies benefiting in biosensing. Despite moderate CD enhancement factors, the formation of complexes with small achiral nanoparticles can be useful for detecting chiral organic molecules and peptides.

An alternative approach based on the formation/destruction of chiral plasmon dimers, constructed using target-specific aptamers, makes it possible to detect a wide range of biomolecules, including enzymes and proteins, in complex biological environments and even inside living cells. For detection of supramolecular biological structures, such as amyloid fibrils, the formation of self-organizing three-dimensional chiral assemblies of achiral plasmon nanoparticles can be used. This fact is very useful for early diagnosis of various concomitant diseases. Sophisticated fabrication and a moderate increase in optical chirality make it difficult to use three-dimensional chiral plasmon nanostructures, while flat chiral metasurfaces that can be conveniently obtained using lithographic methods demonstrate a high potential for ex-vivo detection of chiral biomolecules, further allowing the study of their tertiary and domain structure.

Currently, the field of chiral plasmonic biosensing is of great interest for various biosensor applications [103]. One can expect new developments in this area and unique results in the future. Due to the theoretical basis developed by scientists in understanding the nature of the interaction of chiral molecules with plasmon-induced near-fields, the creation of more advanced nanostructures requires even greater care. Variation of the geometry and assembly of nanostructures, as well as the use of new, primarily dielectric [104] and hybrid materials and alloys with specified dielectric functions [105]—these are the ways of increasing sensitivity of chiral biosensors. Moreover, the use of combinations of various types of chiral nanostructures allows the simultaneous detection of chirality at various scales or the detection of various chiral molecules in the complex biological media.

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