Technologies for Plasmon-Based Fluorescence Enhancement

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Fluorescence is a widely used phenomenon in various scientific and technological fields, including biology, chemistry, medicine, and materials science. The fluorescence signal provides valuable information about molecular interactions, concentrations, and structural changes. Fluorescence exhibits numerous valuable applications, encompassing the detection of single molecules, fluorescence nanoscopy, biological labeling, and optoelectronic device functionality, among many others. Fluorescence enhancement is imperative for enhancing the sensitivity and precision of a wide range of scientific and technological applications that heavily rely on fluorescence detection. It is a crucial requirement to elevate the performance and reliability of these applications.

plasmonics SPR LSPR infectious disease biosensors fluorescence

1. Introduction

Fluorescence sensors operate on the principle of fluorescence, a photophysical process where a molecule, known as a fluorophore, absorbs light at a specific wavelength and then emits light at a longer wavelength. The mechanism involves the excitation of electrons to a higher energy state followed by their return to the ground state, accompanied by the emission of light. This characteristic emission is highly sensitive to the local environment of the fluorophore, making fluorescence sensors powerful tools for detecting specific ions, molecules, or changes in the physical conditions of their surroundings [1]. Enhancement and quenching effects are two critical phenomena in the operation of fluorescence sensors [2]. Enhancement refers to the increase in fluorescence intensity, which can be due to various factors, including changes in the fluorophore's environment that stabilize the excited state or reduce non-radiative decay pathways, thereby increasing the efficiency of fluorescence emission [3]. Molecular interactions that lead to a more rigid fluorophore environment can also enhance fluorescence by restricting internal rotational movements that would otherwise dissipate energy non-radiatively [4]. Quenching, on the other hand, involves the decrease in fluorescence intensity [5]. Quenching mechanisms can be dynamic, where the quencher molecule interacts with the fluorophore in its excited state, or static, where the fluorophore and quencher form a non-fluorescent complex [6]. Quenching is particularly useful in fluorescence sensors for detecting the presence of quencher molecules, as the reduction in fluorescence directly correlates to the concentration of the quencher. Both enhancement and quenching effects are exploited in the design of fluorescence sensors to achieve high sensitivity and selectivity towards specific analytes. By understanding and manipulating these effects, advanced sensors can be developed for a wide range of applications, from medical diagnostics to environmental monitoring.

2. Fundamentals of Surface Plasmons

The study of plasmonics focuses on the collective electron oscillations in metallic media, known as “plasmons”, and their interactions with external electromagnetic fields, referred to as “polaritons”. Within this domain, plasmon polaritons are categorized primarily into two types: surface plasmon polaritons (SPPs) and localized surface plasmons (LSPs) [7]. SPPs are electromagnetic fields that propagate along the interface between metal and dielectric materials, while LSPs represent oscillations of electrons confined to the surface of isolated metallic nanostructures [8]. Metallic nanostructures demonstrate exceptional optical characteristics, primarily due to the excitation of their surface plasmons when exposed to light. This interaction significantly enhances the electromagnetic field at the nanoparticles’ surfaces. This enhanced near-field effect is useful in building very sensitive chemical and biosensors that can be finely controlled by manipulating the shape of the nanoparticles. Metallic nanoparticles have been found to increase fluorescence emissions while decreasing the excited-state lifetimes of adjacent fluorophores. The observed rise in fluorescence is due to a number of causes, including increased absorption by the fluorophore, changes in the molecule’s radiative decay rate, and better efficiency in coupling the fluorescent emission into the far field [9]. Generally, metallic nanoparticles that exhibit LSP resonances are preferred over metallic layers or surfaces that support propagating modes, known as SPPs. This preference stems from LSPs’ simpler coupling with excitation and emission light beams, as well as their relative lack of sensitivity to geometry or momentum conservation restrictions. This versatility allows LSPs to be used in a variety of configurations [10]. In contrast, while uniform layers that enable SPP modes have been used, there has been less research on connected metallic surfaces such as hole gratings. Importantly, the opto-plasmonic features of such structures arise from the interaction of LSP and SPP modes, resulting in the development of mixed modes such as Fano resonances [11]. Upon examining the transmission behavior relative to the characteristics of the electric field, it has been observed that the spectral region with the most significant relative enhancement aligns closely with the most pronounced indicators of plasmonic modes. Moreover, the mechanism of field coupling displays a notable directional quality in the propagation of the electric field, moving from the substrate’s backside to the nanostructured surface on the top and in the reverse direction. This directional behavior facilitates the effective design of the structure for optimal pumping and collection, making it highly suitable for sensing applications. This characteristic becomes crucial in the context of utilizing a plasmonic structure for the creation of a sensing device that leverages surface-enhanced fluorescence.

3. Plasmon-Enhanced Fluorescence (PEF)

3.1. Metal-Enhanced Fluorescence (MEF)

Plasmon-enhanced fluorescence (PEF) technology utilizes the increased electromagnetic (EM) field intensity near metal nanostructures to significantly enhance molecular fluorescence [12]. Metal-enhanced fluorescence (MEF) can be explained by two key factors. Firstly, it is attributed to the enhancement of excitation through the presence of strong local electric fields resulting from the excitation of localized surface plasmon resonance (LSPR). Secondly, MEF involves an increase in the radiative decay rate originating from the excited state of the fluorophore, which is coupled with surface plasmon resonance [13]. Despite its ease of implementation, LSPR biosensing frequently

demonstrates constrained spectral sensitivity, presenting a hurdle for practical LSPR sensors that solely depend on spectral shifts for detecting biomolecules at ultra-low concentrations [14]. Tang et al. demonstrated that Fe_3O_4 magnetic nanoparticles (MNP) can significantly boost LSPR of metal nanoparticles. This enhancement is attributed to the high refractive index and substantial molecular weight of the Fe_3O_4 MNPs, rendering them potent enhancers for the plasmonic response to biological binding events. Using Fe_3O_4 MNPs to enhance LSPR assays, their practicality is tested with cardiac troponin I (cTnI) as a model protein for diagnosing myocardial infarction. This resulted in six-times-stronger spectral responses compared to direct cTnI adsorption on the GNR sensor, lowering the detection limit to approximately 30 pM in plasma samples. As a result, this breakthrough facilitates a notable enhancement in sensitivity, reliability, dynamic range, and calibration linearity when conducting LSPR assays to detect minute quantities of small molecules. However, it is important to note that fluorescence quenching effects have limited the progress of PEF in sensitive applications [3]. To address this, an innovative gold nanorod (GNR) array biochip was developed to systematically explore the enhancement of LSPR-coupled fluorescence [15]. The ordered assembly of GNRs on a glass surface dramatically intensified LSPR between adjacent nanoparticles. This resulted in a surface-plasmon-enhanced excitation and radiative mechanism for signal amplification. The appropriate choice of GNR size allowed for tunability, enabling overlap with the fluorophore's excitation and emission wavelengths greater than 600 nm. The fluorescence enhancement was found to be distance-dependent, with the GNR array effectively overcoming quenching even at close proximity by fine-tuning the distance between the fluorophore and nanoarray surface. The enhancement correlated with the spectral overlap between the fluorophore and the plasmonic resonance of the GNR array, which is crucial for optimizing the efficiency of the process [16]. Through the utilization of the GNR array chip, fluorescence enhancement has led to the establishment of a detection limit at 10 pM, a value notably below that achieved by conventional LSPR aptasensors reliant solely on spectral shifts. These findings demonstrate the potential of the GNR array chip for practical and highly sensitive plasmonic DNA biochip applications. A further implementation of MEF was observed, specifically in the form of enhanced surface plasmon-coupled emission (SPCE), achieved by employing a hollow plasmonic structure [17]. Due to its distinctive features, including signal enhancement, distance dependence, and background suppression, SPCE holds great promise in the fields of biosensing and bioimaging [18][19]. The process involves the assembly of gold nanoshells (GNSs) onto a gold substrate via electrostatic adsorption, followed by the application of a thin layer of fluorophores (approximately 30 nm) using spin-coating. The resulting SPCE fluorescence signals exhibited enhancements of 30- and 110-fold compared to normal SPCE and free space emission, respectively. The observed enhancements were a result of several factors, including the formation of a nanostructure platform with a uniformly distributed region known as a plasmonic hotspots (where the electromagnetic field is significantly amplified) between GNSs and the gold substrate, the generation of an intense electromagnetic field by the GNSs, and the strong interactions between fluorescence and surface plasmons. This approach using hollow nanoparticles provides a convenient means to enhance the fluorescence signal, thereby improving the detection sensitivity in fluorescence-based sensing and imaging platforms [20].

The development of multifunctional and multiplexed MEF platforms in the near-infrared (NIR) range holds great value, as it offers the advantages of reduced autofluorescence and minimized photoinduced damage. The utilization of a cost-effective, nanosphere lithography-based technique for fabricating three-dimensional (3D) gold

nanohole-disc arrays (Au-NHDAs), serves as another notable illustration of MEF [21]. These arrays consist of glass pillars on top of nanoholes in a thin gold film. The pillars' top surfaces are covered with gold nanodiscs, and small gold nanoparticles (nanodots) are positioned on the pillar sidewalls. This produces uniform and reproducible Au-NHDAs with controlled structures and adjustable optical properties in the near-infrared (NIR) range. These Au-NHDAs exhibit significant NIR fluorescence enhancement (over 400 times) due to the 3D plasmonic structure, enabling strong coupling of surface plasmons through glass nanogaps. The enhancement factor varies with the nanodisc diameter while maintaining the same resonance peak and separation distance. The hotspots in [22] are created by pairs of collapsible nanofingers, allowing for adjustable gap sizes with high precision at the sub-nanometer scale. Through experimental investigations, optimal gap sizes of the hotspots are identified for different dielectric spacer materials to maximize plasmon-enhanced fluorescence [23]. Intensely amplified electromagnetic fields in hotspots can be achieved in the vicinity of plasmonic nanostructures, comprising metallic nanoparticles positioned in close proximity with sub-nanometer interparticle gaps.

MEF can improve nanoantennas by creating accessible gaps, enhancing nearby fluorophores' fluorescence. The nanofabrication technique described in [24] combines electron beam lithography, planarization, etch back, and template stripping to produce large arrays of in-plane nanoantennas. This technique results in remarkable fluorescence enhancement (up to 104104 to 105105 times) and enables detection volumes at the nanoscale in 20 zL range. The study in [25] showed that the adhesion layer between the gold film and glass substrate strongly influences the fluorescence enhancement of single molecules. They achieved a record-high enhancement factor of 25 by using a titanium dioxide (TiO_2) adhesion layer. Metallic nanoparticles can significantly impact the emission of nearby fluorescent molecules and materials. In the case of indocyanine green (ICG) dye molecules, the fluorescence enhancement can be remarkable when they are in close proximity to nanoparticles with matching plasmon resonance frequencies and large scattering cross sections [12]. To achieve optimal fluorescence enhancement, it is crucial to align the plasmon resonance frequency of the nanoparticle with the emission frequency of the molecule. By increasing the particle's scattering efficiency and tuning the plasmon resonance, the fluorescence of the molecule can be enhanced by more than 50 times. Dragan et al. have compared simulation study with empirical study for MEF sensors [26]. The simulations using finite difference time domain (FDTD) techniques reveal a significant enhancement of the excitation field attributed to resonant plasmonic modes supported by the nanoparticle aggregates. In the experimental investigations using Rhodamine 6G dispersed in polymethylmethacrylate, a remarkable 423 fold increase in fluorescence is observed. These findings highlight the potential of nanoparticle aggregates as a cost-effective and scalable platform for the development of mass-produced fluorescent biosensors that harness MEF. The 2-color DNA assay combines MEF with microwave-accelerated DNA hybridization to analyze DNA fragment sequences in solution. Using the "Catch and Signal" technology, it enables the simultaneous recognition of two target DNA sequences in one well [26]. Fluorescent labels (Alexa 488 and Alexa 594) attached to single-stranded DNA (ssDNA) fragments act as biosensor probes, enhancing MEF. It is shown that microwave irradiation for 30 s greatly speeds up selective DNA hybridization at room temperature, increasing the rate by about 1000 fold. This DNA assay platform greatly improves quantitative analysis of genome DNA sequences, offering a fast and simplified biomedical platform for nucleic acid analysis. Surface modification utilizing core/shell configurations using either inorganic or organic ligands has been

demonstrated as a highly effective approach for attaining the external enhancement of luminescence [27]. A crystal lattice match is crucial for enhancing luminescence in inorganic materials [28]. Using noble metals and Ln^{3+} doped materials in the core/shell configuration, which can be termed as an external approach, improves the emission. On the other hand, an internal approach involves modifying the crystal structure and introducing sensitizers, which involve inner adjustments to alter the local structure, local symmetry, and interaction with active ions to enhance luminescence.

The new nanoplasmonic structure, termed as disk-coupled dots-on-pillar antenna array (D2PA), and an optimized spacer achieved substantial fluorescence enhancements of 2970 fold on average and 4.5×1064.5×106 fold at hotspots [29]. It demonstrated excellent uniformity over a large sample area, various dye concentrations, and laser powers. The structure was cost-effectively fabricated on 400 wafers using nanoimprint, self-alignment, and self-assembly methods. The presence and interaction of metal components, including metal ions or metallic nanostructures, have a significant influence on the aggregation of nanocrystals (NCs) or fluorophores, leading to a phenomenon known as Aggregation-Induced Emission (AIE) [30]. In AIE, the aggregation process induced by these metal components causes a notable enhancement in the emission of fluorescence. The metal components can modify the radiative and non-radiative decay rates of the nearby fluorophores, resulting in increased fluorescence intensity, improved quantum yield, and other properties. Solvent-induced aggregation [31], assembly-induced enhancement [32], and ion-induced aggregation [33][34] can be categorized as enhancement based on properties, where the presence and interactions of metal components induce the aggregation of nanocrystals or fluorophores, leading to enhanced fluorescence signals.

3.2. Plasmonic Photonic Crystal-Induced Fluorescence Enhancement (PPCIFE)

Research indicates that combining the effects of plasmonics and photonic crystals (PCs) can lead to fluorescence enhancement. For instance, a technique to enhance the luminescence of $CsPbCl_3$ nanocrystals (NCs) by combining them with Ag plasmon and photonic crystals has been investigated [35]. Theoretical simulations and experimental analysis revealed that when the plasmon peak of the Ag film and the photonic stop band of polymethyl methacrylate opal photonic crystals (OPCs) were well matched with the emission peak of the blue $CsPbCl_3$ NCs, notable fluorescence enhancements of approximately 50 fold and 20 fold were achieved, attributed to improved excitation and emission fields. Subsequently, by synergistically utilizing surface plasmon and photonic crystal effects, the luminescent intensity of $CsPbCl_3$ nanocrystals in $CsPbCl_3$/Ag/OPCs hybrids is significantly enhanced by over 150 fold, resulting in an estimated emission efficiency of 51.5%. The fluorescence enhancement can also be achieved by combining the effects of photonic crystals and gold nanoparticles (AuNPs) with plasmonic properties. This method relies on the use of gold nanoparticles on silica photonic crystal microspheres (SPCMs) to enhance the natural fluorescence of proteins without labeling [36]. Aflatoxin B1 (AFB1) was detected as a model molecule. AFB1-bovine serum albumin and anti-AFB1 monoclonal antibodies were immobilized on SPCMs and AuNPs, respectively. AuNPs greatly enhanced the fluorescence of the antigens on SPCM using near UV excitation. Electric field simulation showed a maximum near-field enhancement of 20, resulting from the combined effects of photonic crystal and AuNP plasmon. Extensive research has investigated the strategic combination of metal and dielectric plasmonics with the interface of photonic crystals called photonic crystal-coupled emission, leading to

valuable biophysicochemical insights. It has been observed that the coupling of photonic crystals with Ag soret colloids, nanovoids, and Bloch surface waves enhances luminescence [37]. Additionally, further research on a synergistic approach that involves the use of plasmonic-silver nanoassembly and high refractive index Nd_2O_3 sources, commonly referred to as `Huygen' sources, demonstrated effective light scattering. Fluorescence enhancements exceeding 1200 fold, coupled with directional and polarized emission, were utilized to detect Rhodamine B dye at attomolar levels within integrated cavity hotspots that experienced amplified electromagnetic field intensity. Arranging finite-sized hexagonal arrays of nanoapertures in a lattice pattern within a gold film enables highly directional and enhanced emission from single fluorescent molecules placed in the central aperture [38]. This arrangement leads to a remarkable increase in brightness, with enhancements of up to 40 times per molecule in the forward direction. Another approach demonstrates that a remarkable 52-fold increase in signal intensity is achieved by combining plasmonic fluor nanoparticles and photonic crystals with a fluorescent dye [39]. The interaction between nanoparticles and light, along with improved light collection and increased emission rate, contribute to this enhancement. The method is showcased by successfully detecting a specific protein using a sandwich immunoassay. The limit of detection achieved is 10 fg mL^{-1} in buffer and 100 fg mL^{-1} in human plasma, demonstrating a sensitivity nearly three orders of magnitude higher than that of standard immunoassays. Hybrid structures of silver and hydrophobic 3D photonic crystals were created to investigate fluorescence enhancements [40]. The interaction between localized surface plasmon resonance and the 3D photonic stop band resulted in highly tunable properties. The study focused on fluorescence enhancements of conjugated polymer and quantum dot materials based on the hybrid structures, achieving a maximum enhancement of 87 times compared to glass substrates.

3.3. Photonic Crystal-Based Fluorescence Enhancement

Photonic crystals (PCs) are materials with a periodic variation in refractive index that selectively control the propagation of light, thereby significantly altering the emission properties of embedded optically active materials [41]. PCs can be categorized into one-dimensional, two-dimensional, and three-dimensional structures based on their spatial variations in refractive indexes [42]. When one-dimensional photonic crystals (1DPCs) combined with nanoscaled ZnO particles were fabricated using the spin-coating technique, a noticeable enhancement in the fluorescence of the organic dyes, compared to films of 1DPCs or ZnO alone, was observed [43]. Additionally, modifying the nanoscaled ZnO particles with Poly (sodium 4-styrene sulfonate) (PSS) and Poly (allylamine hydrochloride) (PAH) through self-assembly revealed that the degree of fluorescence enhancement was influenced by the thickness of PSS and PAH. Colloidal photonic crystals (CPCs) significantly enhance fluorescence efficiency by optimizing structure and dye arrangement [44][45]. An E-F-E double heterostructure (E denotes the monolithic CPC with a periodicity overlapping the excitation wavelength, while F represents the monolithic CPC with a periodicity overlapping the emission wavelength), made from multilayer CPCs, achieved a thousand-fold fluorescence enhancement. This heterostructure trapped both excitation and fluorescence by coupling CPCs with multiple-beam interference through overlapping periodicity for excitation and matching periodicity for fluorescence [46][47]. Fluorescence detection can also be enhanced using magnetically responsive $CoFe_2O_4$@SiO_2@Ag CPCs [48]. The fluorescence spectra of different fluorescent molecules, such as Rhodamine B (RB) and fluorescein isothiocyanate (FITC), were selectively enhanced by adjusting the magnetic field to tune the photonic band gap of

the substrates. The composites achieved high enhancement factors of 12.6 and 17.6 fold for RB and FITC, respectively, when the photonic band gap matched the fluorescence emission wavelength of fluorescent molecules. A genetic algorithm was used to design two photonic crystals using Al_2O_3 and TiO_2, with one crystal containing SiO_2. The sandwiched crystal formed a Fabry–Perot cavity, achieving 14-fold excitation enhancement [49]. By controlling electric field radiation using photonic forbidden bands, fluorescence in a 3.18 µm layer was enhanced by 60 fold. Regional differences in enhancement were due to phase changes from varying optical path lengths. A specialized two-dimensional photonic crystal array structure is used to significantly enhance the fluorescence intensity of sulfur dioxide, achieving a sensitivity of 1.224 $L \cdot mg^{-1}$ in the UV band [50]. Experimental measurements of TiO_2 used in conjunction with the photonic crystal structure demonstrate a 10-fold increase in intensity compared to samples without the photonic crystal structure at room temperature. To improve the sensitivity of the microfluidic sensor for rapid detection of Cu^{2+} content in lubricating oil, a fluorescence enhancement method is employed by incorporating SiO_2 inverse opal photonic crystals (IOPCs) into the sensor [51].

3.4. Hydrogel-Based Fluorescence Enhancement

Hydrogels are soft materials characterized by their porous structure and ability to retain a high amount of water while maintaining a distinct three-dimensional structure when swollen [52]. Due to these properties, they share similarities with biological tissues, making them suitable for various applications in the fields of biomedical and bioinspired materials [53]. Luminescent Carbon Quantum Dot hydrogels (CQDGs) can be used for direct determination of silver ions (Ag^+) [54]. Different types of Carbon Quantum Dots (CQDs) were employed, each with unique surface properties (*passive*-CQDs with carboxylic groups, *thiol*-CDQs, and *amine*-CDQs), to create hybrid gels with a low molecular weight hydrogelator (LMWG). The use of gels significantly enhances fluorescence and shows selectivity for Ag^+ ions due to their interaction with carboxylic groups on the CQDs. Among them, the CQDGs with carboxylic groups on their surface showed the highest selectivity for detecting Ag^+ ions, possibly because of Ag^+ ions' flexible coordination. The sensing platform relies on a strong Ag–O interaction, which leads to the quenching of photoluminescence of *pasivate*-CDQs (p-CQDs) through charge transfer. The method demonstrates a low detection limit (LOD) and quantification (LOQ) of 0.55 and 1.83 µg mL^{-1}, respectively, and it has been effectively employed for the analysis of river water samples. A pH and mechano-responsive coordination polymeric gel is formed by reacting Mg^{2+} with N-(7-hydroxyl-4-methyl-8-coumarinyl)-alanine [55]. The gelation process results in 3D nanostructures that trap water, leading to the formation of a freeze-dried hydrogel with uniform ribbon-shaped fibers. The hydrogel displays a distinct UV-vis absorption transition and, notably, exhibits a substantial enhancement in fluorescence intensity along with a longer lifetime compared to the original ligand. The incorporation of modified carbon nanodots into a unique hydrogel derived from a low molecular weight salt enhances the gelation properties, significantly increases fluorescence, and enables the hybrid gel to exhibit promising sensitivity towards heavy metal ions, particularly Pb^{2+}, making it suitable for sensing applications [56]. Hydrogel microbeads can act as a platform for a bacterial sensor to detect nitro compounds [57]. Green fluorescent protein-producing *Escherichia coli*, which were engineered to be sensitive to nitro compounds, were encapsulated within hydrogel beads based on poly(2-hydroxyethyl methacrylate) [poly(HEMA)]. The hydrogel acted to concentrate and enhance the fluorescent signals emitted by the bacteria. By incorporating 80 wt% MAETC into the

hydrogel beads, the fluorescence intensity of the bacterial sensors significantly increased compared to beads without MAETC. Supramolecular hydrogel serves as a unique matrix to immobilize proteins, peptides, substrates, chemosensors, and mesoporous silica particles on solid supports [58]. The gel's semi-wet conditions and 3D nanofiber network structure effectively trap these substances while maintaining their functionality, resulting in a remarkable increase in fluorescence intensity. This enhanced fluorescence provides valuable insights into molecular recognition and enzyme activity, enabling effective monitoring and study of biological events. A boronic acid-based anthracene fluorescent probe was functionalized with an acrylamide unit and incorporated into a hydrogel system for monosaccharide detection [59]. The hydrogel exhibited a significant enhancement in fluorescence intensity upon exposure to fructose, resulting in a 10-fold increase in fluorescence intensity for the detection of monosaccharides. By forming a protective "shell" on the surface of functionalized carbon nanoparticles, glucose has been shown to significantly enhance their fluorescence while limiting movement and reducing fluorescence loss [60]. This leads to a remarkable 70-fold increase in fluorescence intensity under optimal conditions and enables the detection of glucose in serum samples, demonstrating a low limit of detection (10 μM) and a linear response within the concentration range of 50 μM to 2000 μM. Protein-induced fluorescence enhancement is a powerful method that significantly enhances fluorescence intensity when a protein binds closely, allowing for high-resolution studies of molecular interactions without the need for protein labeling [61][62][63].

3.5. Other Enhancement Methods

The method of enhancing the fluorescence of green fluorescent protein (GFP) chromophore effectively detects small distances and is utilized for studying DNA and RNA interactions, providing high-resolution data and sensitivity to short distances. It serves as a valuable alternative to or combination with FRET (fluorescence resonance energy transfer). Fluorescence enhancement in synthetic GFP (green fluorescent protein) chromophore (GFPc) analogs can be achieved through two methods: physical encapsulation and chemical modification [64]. These approaches have great potential in enhancing the fluorescence of synthetic GFPc analogs, making them promising candidates for application in novel sensors or fluorescent probes. The fluorescent dye PicoGreen exhibits limited luminescence when in solution, but it forms a highly luminescent complex upon binding to dsDNA. During binding, it undergoes intercalation (insertion between DNA base pairs) and electrostatic interactions, which immobilize the dye molecule [65]. This immobilization leads to a significant fluorescence enhancement of PicoGreen, resulting in an increase of over 1000 fold compared to its free state. The fluorescence enhancement observed when selectively detecting potassium (K^+) and cesium (Cs^+) ions using bis-15-crown-5 and bis-18-crown-6 systems, respectively, has been termed as self-assembling fluorescence enhancement (SAFE) [66]. Self-assembled structures enhance fluorescence when interacting with specific targets, like barium ions. A bis-15-crown-5-naphthalenediimide compound acts as a chemosensor, inducing self-assembly and forming an intramolecular excimer, resulting in increased fluorescence. The fluorescence probes, RPd2 and RPd3, containing conjugated allylidene-hydrazone ligands, exhibit a 170-fold fluorescence enhancement and better selectivity for Pd^{2+} compared to other metal ions [67]. RPd2, with enhanced specificity and detectability, holds potential for Pd^{2+} analysis in contaminated water and soil. Adding N-phenyl substituents to 4-aminostilbenes in a study on various trans isomers of stilbene derivatives led to a more planar structure, resulting in a red shift in absorption and fluorescence spectra [68]. This enhanced fluorescence was attributed to the increased charge-transfer character in

the excited state. The N-phenyl derivatives exhibited high fluorescence quantum yields and low photoisomerization quantum yields, indicating significant fluorescence enhancement. The binding of curcumin with α- and β-cyclodextrins (CDs) leads to a remarkable increase in its fluorescence, up to 7 times stronger when combined with 30 mM HP-β-CD [69]. This enhanced fluorescence could be valuable for fluorescence-based detection methods involving this important pharmaceutical compound. A novel type of carbon dots, co-doped with fluorine and nitrogen (F, N-doped CDs), shows improved fluorescence under UV light and high pressure (0.1 GPa). At regular atmospheric pressure (1.0 atm), F, N-doped CDs' fluorescence intensity increases with UV light exposure (5 s to 30 min) and emits light of a different color (blue-shift) from 586 nm to 550 nm [70]. Another alternative method was reported by the synergic usage of dye-doped nanoparticles that encapsulated 200 dye molecules in a single 22 nm organosilicate particle [71] and high surface area porous films as biosensosing substrates. This method reported LOD to be as low as 21.3 fg/mL for detecting botulinum neurotoxin type A(BoTN/A) [72].

While plasmonic enhancements offer significant improvements in sensitivity and detection limits, several factors including quenching risks, cost and complexity, comparison with mainstream methods, reproducibility and scalability warrant careful consideration. While quenching is particularly useful in fluorescence sensors for detecting the presence of quencher molecules, plasmonic materials, particularly metal nanoparticles, can sometimes expedite the quenching process rather than enhancing fluorescence, especially when the fluorophore is too close to the metal surface. This proximity-dependent quenching can reduce the efficiency of fluorescence emission, undermining the enhancement effect and potentially leading to false negatives or less sensitive detection [6]. Implementing plasmonic materials in fluorescence-based detection systems can increase both the cost and complexity of the sensor design and fabrication. Plasmonic nanoparticles like gold and silver are more expensive than conventional fluorophores and may require sophisticated synthesis and functionalization techniques to ensure biocompatibility and stability [73]. Additionally, integrating these materials into devices necessitates precise control over nanoparticle size, shape, and spacing to achieve the desired plasmonic effect, further complicating the sensor design and increasing production costs [74]. While plasmonic enhancements can offer superior sensitivity and lower detection limits, the overall utility of these sensors must be evaluated in the context of existing technologies. Factors such as ease of use, durability, cost-effectiveness, and the ability to integrate into existing analytical workflows are crucial for determining whether plasmonic strategies offer a tangible advantage [75]. Achieving consistent and reproducible enhancements across different batches of plasmonic materials can be challenging, potentially limiting the scalability of these approaches for commercial applications. Variability in nanoparticle size, shape, and surface chemistry can lead to inconsistent fluorescence enhancement, affecting the reliability of sensor readings. The various enhancement types, the processes described, and the corresponding achieved enhancement factors are succinctly summarized in **Table 1**.

Table 1. Enhancement types, processes mentioned and achieved enhancement factor.

Enhancement Type	Process	Enhancement Factor *	References
MEF	SPCE	30 and 110 times compared to normal SPCE and free space emission	[17]

Enhancement Type	Process	Enhancement Factor *	References
		respectively	
MEF	Nanosphere lithography for 3D Au-NHDAs	Over 400 times	[21]
MEF	Plasmonic Antenna Arrays	104104–105105 times	[24]
MEF	TiO_2 adhesion layer	25 times	[25]
MEF	Metallic Nanoparticles	Over 50 times	[12]
MEF	Plasmonic Meta-surfaces	423 times	[76]
MEF	2-color DNA assay	1000 times	[15]
MEF	Plasmonic Nanodots	2970 on average and 4.5×1064.5×106 times at hotspots	[29]
PPCIFE	Combining Ag plasmon with PCs	Up to 150 times	[35]
PPCIFE	Combining AuNPs with SPCMs	20 times	[36]
PPCIFE	PCs coupled emission	1200 times	[37]
PPCIFE	Lattice Arrangement with Au film	40 times per molecule	[38]
PPCIFE	Combining plasmonic fluor NPs and PCs with a fluorescent dye	52 times	[39]
PPCIFE	Hybrid Ag and hydrophobic 3D PCs	87 times	[40]
PCs Based	CPCs coupling	1000 times	[46]
PCs Based	$CoFe_2O_4@SiO_2@Ag$ CPCs	12.6 and 17.6 times for RB and FITC, respectively	[48]
PCs Based	Sandwiched crystal using Al_2O_3 and TiO_2	Up to 60 times	[49]
PCs Based	TiO_2 in conjunction with 2D PCs	10 times	[50]
Hydrogel Based	Fructose exposure	10 times	[59]

* Enhancement Factor: a ratio of the fluorescence, which was enhanced by surface plasmons, to the fluorescence, which was measured on the surface without surface plasmon.

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