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REVIEW

Nanoplasmonic Biosensors: A Comprehensive Overview and Future Prospects

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Abstract: Recent nanotechnological advancements have resulted in a paradigm shift in biosensing applications through the advent of nanoplasmonic biosensors. These devices integrate nanomaterials with phenomena like surface plasmon resonance (SPR) and localized SPR (LSPR) to address the critical diagnostic and analytical needs across medicine, food safety, and drug discovery. Leveraging metals like gold and silver, these sensors exhibit enhanced optical and electronic properties, enabling the detection of biomolecules at ultralow concentrations. However, despite their transformative potential, challenges concerning stability, reproducibility, cost-efficiency, and scalability impede widespread implementation. This review offers a rigorous analysis of nanoplasmonic biosensors, emphasizing their underlying operational mechanisms and diverse applications. It also delves into design paradigms, fabrication protocols, and optimization strategies while concurrently examining prevailing challenges and prospective advancements. Furthermore, it highlights emerging trends, such as hybrid plasmonic nanostructures, conferring advantages in miniaturization, automation, and high-throughput analysis, thereby establishing a robust foundation for future innovation in the field.

Keywords: SPR, nanoplasmonic, optical biosensor, device, nanomaterial

Introduction

Biosensors are analytical devices that integrate a biological sensing element with a transducer to detect and quantify specific biological targets. These targets can range from molecules such as proteins, DNA, and antibodies to whole cells and tissues. Biosensors have become increasingly important in various fields including healthcare, environmental monitoring, and food safety. One recent advance in biosensing technology is the use of optical methods. Optical biosensors use light to detect and measure the presence of a target molecule. This can be achieved through diverse mechanisms including fluorescence, absorbance, or surface plasmon resonance (SPR).[1–9] In recent years, there has been notable progress in the realm of optical biosensors, marked by the integration of nanomaterials and advancements in SPR technology.[10–16] This progress has resulted in the emergence of label-free biosensors characterized by high sensitivity and efficiency. These biosensors have found widespread applications in professional sectors such as medical diagnostics, food safety, environmental monitoring, and drug screening.[17–21]

Nanomaterials, particularly inorganic-organic hybrid materials, have played crucial roles in constructing improved biosensors. These materials demonstrate outstanding electronic, optical, mechanical, and thermal properties, making them particularly well-suited for enhancing the overall performance of biosensors.[22] Nanomaterials have exhibited significant potential across a broad spectrum of applications, owing to their distinctive properties.[23–29] One of the key advancements in optical biosensors is the incorporation of SPR technology. SPR is a phenomenon in which light interacts with the collective oscillation of conduction electrons on the surface of a nanomaterial, such as gold (Au), silver (Ag), or

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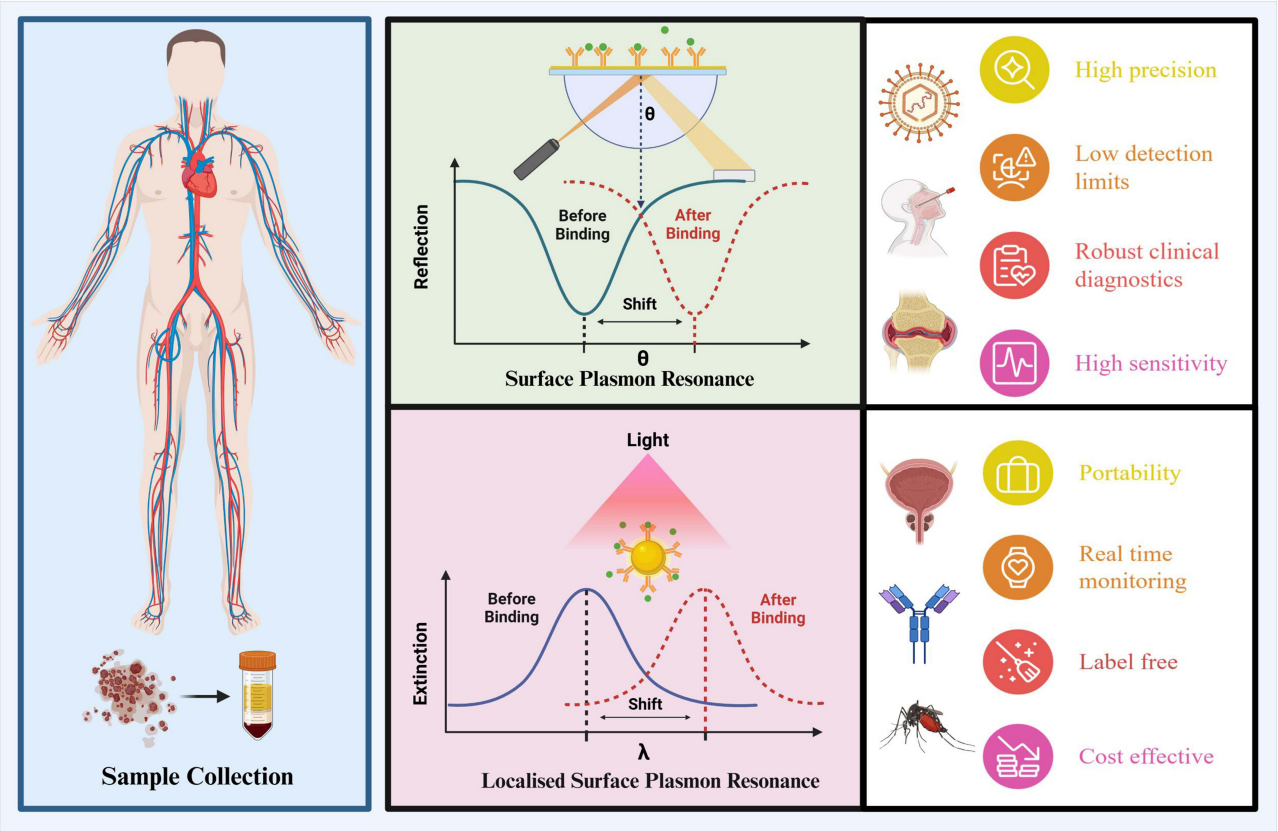
Graphical Abstract



hybrid nanoparticles (NPs).[30–32] Such interactions allow for the absorption and scattering of light with high efficiency, making it a powerful tool in biosensing.[33] Furthermore, by combining nanomaterials with SPR, researchers have developed a new type of optical biosensors known as nanoplasmonic biosensors. These nanoplasmonic biosensors utilize the unique properties of nanomaterials to enhance the sensitivity and detection capabilities of SPR-based biosensing. The substantial surface-to-volume ratios inherent in nanomaterials facilitate a more-extensive surface area for molecular interactions. This characteristic enables the detection of extremely low concentrations of small molecules with high sensitivity. Nanomaterial-facilitated enhanced performances in sensing systems are achieved by providing more active regions for molecular binding. This improves the overall sensitivity of the biosensors, making them highly efficient for analyzing and detecting target molecules.[34]

Moreover, such biosensors offer real-time detection, allowing for immediate monitoring of biological processes. This real-time capability is essential for applications such as monitoring reactions in drug development or tracking disease progression in a patient. Furthermore, localized SPR (LSPR) biosensors are label-free, eliminating the need for fluorescent or radioactive tags on target molecules. The fabrication process of nanomaterial-based LSPR biosensors is also relatively simple, which is essential for achieving suitable and affordable industrial applications. This simplicity allows the mass production of these biosensors, making them more accessible for widespread use in various fields. Applications of nanomaterial-based LSPR biosensors are extensive.[35] They can be used to detect and analyze biomarkers in bodily fluids, providing crucial information for early disease detection and personalized medicine.

Furthermore, nanoplasmonic biosensors exhibit considerable potential in drug delivery systems. By virtue of their capacity to selectively target and bind to specific molecules or cells, these biosensors offer a means to deliver therapeutic agents precisely to the intended location within the body. This targeted approach minimizes side effects and enhances

treatment efficiency. In the field of food safety, nanomaterial-based LSPR biosensors offer a rapid and sensitive method for detecting contaminants and toxins in food products. These biosensors are adept at detecting even minute traces of harmful substances, thereby ensuring the safety and quality of food prior to it reaching consumers. Overall, nanomaterial-based LSPR biosensors are powerful and versatile tools for various applications. Nanomaterial-based LSPR biosensors represent cutting-edge technology in the field of optical biosensors. Nanoplasmonic biosensors stand out for their label-free detection and analysis of target molecules, coupled with their straightforward fabrication and scalability for mass production. This makes them particularly attractive in various sectors, including medicine, food safety, and environmental monitoring. In essence, nanoplasmonic biosensors offer a practical and cost-effective solution for diverse industrial applications. This review aims to articulate the significance of nanoplasmonic biosensors across a spectrum of fields such as medicine, food safety, and environmental monitoring.[36,37]

Surface Plasmon Resonance (SPR)

The SPR phenomenon, initially discovered in 1902, has undergone progressive comprehension, leading to an intricate understanding of surface plasmon physics. In 1983, a pivotal advancement occurred with the successful application of SPR in developing a biosensor aimed at detecting biomolecular interactions (Figure 1a). The inaugural commercial SPR-based biosensor instrument emerged from Pharmacia Biosensor AB, later rebranded as Biacore.[38] Presently, various companies manufacture SPR instruments, with SPR-based biosensors as the predominant optical biosensing method. The SPR phenomenon materializes at the interface of two media (typically glass and liquid) on the surface of a metal or other conducting material when illuminated by polarized light at a specific angle. This process generates surface plasmons, resulting in a reduction in the intensity of reflected light at a particular angle, referred to as the resonance angle. The magnitude of this effect is directly proportional to the mass present on the surface. A sensorgram can be acquired, which illustrates the shift of reflectivity, angle, or wavelengths over time. Irrespective of the configuration, SPR allows real-time monitoring of changes in the refractive index at the sensor surface, which are directly correlated with biomolecule concentrations, thereby offering a label-free approach. To assess ligand-analyte interactions, one of the interacting molecules must be immobilized on the sensor surface. A practical SPR instrument integrates an optical detector, typically measuring an intensity shift, a sensor chip featuring a Au surface and a layer facilitating ligand immobilization, and a fluidics system for seamless flow-through operation. An SPR system and working principle are illustrated in Figure 1a.[39]

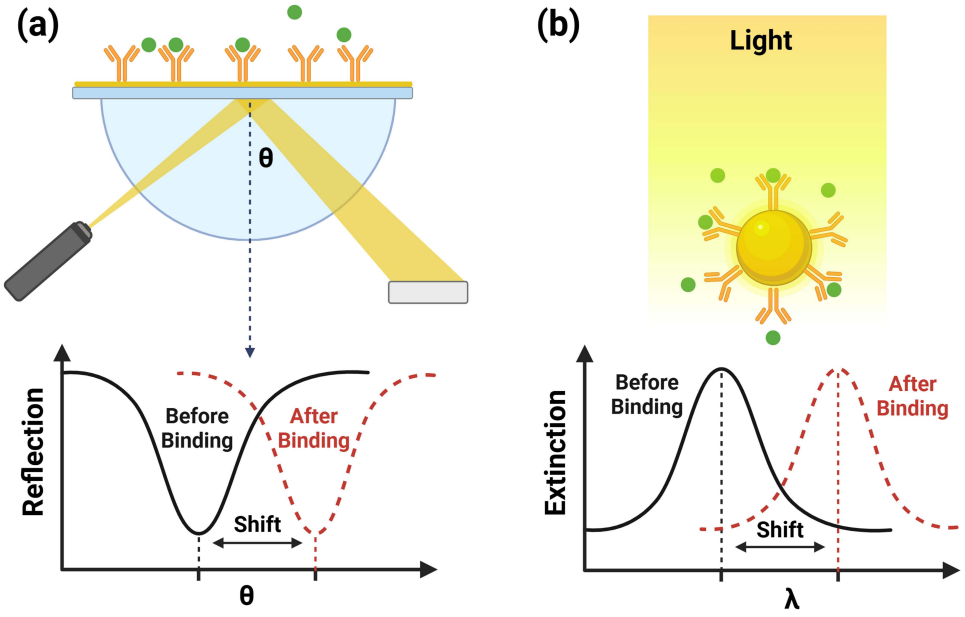


Figure 1 Schematic illustration of the application of (**a**) surface plasmon resonance (SPR) and (**b**) localized surface plasmon resonance (LSPR) for detection.

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Localized Surface Plasmon Resonance (LSPR)

Localized SPR (LSPR) is a phenomenon that occurs when localized electromagnetic fields are enhanced by interactions of light with metal nanostructures. This enhancement leads to the generation of a strong electric field around the surface of the nanostructures, resulting in intense light absorption.[40] The principle behind LSPR is that when incident light interacts with metal nanostructures, it induces coherent oscillations of the conduction band electrons, leading to resonant absorption and the scattering of light at specific wavelengths (Figure 1b). Utilizing the unique optical properties of the plasmonic nanostructures in which coherent excitation of conduction electrons at metal nanoparticle surfaces such as Au and Ag is coupled to incident light and leads to resonance effects.[41] The local refractive index fluctuations make the resonance condition extremely sensitive and LSPR is therefore in high demand in biosensing applications. These biosensors have emerged as the most promising due to their label-free nature, ultra-sensitivity, and capacity to analyze biological and chemical interactions in real-time.[42] The significance of LSPR lies in its ability to detect and measure the nanoscale adsorption of materials onto metal surfaces. This principle has been harnessed for developing biosensors, which are devices used to detect and analyze biological molecules. For example, LSPR biosensor assays have played a pivotal role in diagnosing various stages of Epstein-Barr virus (EBV) infections in clinical serum samples and determining levels of soluble vascular endothelial growth factor receptors. Additionally, these biosensors have been employed for the rapid screening of antibiotics in milk samples and the high-sensitivity detection of the patulin mycotoxin. Notably, an SPR biosensor was utilized for the sensitive and anion-selective detection of As(III) with an impressive detection limit of 1.0 nM.[43–48] Depending on the detection mechanism utilized, LSPR based biosensing can be classified into colorimetric, fluorometric, and exciton energy transfer-based plasmonic biosensors with respective merits around biomedical diagnostics, environmental monitoring, and food security applications.[41,42]

Colorimetric LSPR biosensors take advantage of the varied optical properties of plasmonic NPs in the accomplishment of visible color change via aggregation or binding to the analyte. AuNPs and AgNPs have unique colors depending on their localized surface plasmon resonance; any change in their plasmonic environment, eg, aggregation or change in the dielectric medium, causes red shifting of the LSPR peak, visible color change. On the other hand, the fluorometric LSPR biosensors take advantage of the coupling between fluorophores and plasmonic nanostructures to enhance fluorescence signals and thus significantly enhance sensitivity and specificity in biosensing.[49] Two underlying mechanisms for such an enhancement include metal-enhanced fluorescence (MEF) and plasmon-enhanced fluorescence (PEF), where fluorophore excitation and emission processes are both amplified by the local electromagnetic field around plasmonic NPs.[50,51] In addition, exciton energy transfer (EET) plasmonic biosensors capitalize on the coupling between the excitonic material, ie, quantum dots, dye molecules, and semiconducting nanocrystals, and the plasmonic nanostructure to deliver sensitive optical detection through mechanisms such as Förster resonance energy transfer (FRET) and plasmon-exciton coupling.[41,52–54]

AuNPs and AgNPs possess intrinsic colors as a result of their local surface plasmon resonance; any disturbance of their plasmonic surroundings, ie, aggregation or change of the surrounding dielectric environment, induces a shift of the LSPR peak that is expressed as a visible color change.[49,55,56] On the other hand, fluorometric LSPR biosensors exploit the synergetic increase effect of the plasmonic nanostructures on fluorophores, and the result is the magnification of the fluorescence, which increases the sensitivity and specificity for biosensing. This enhancement is through two most pervasive mechanisms: plasmon-enhanced fluorescence (PEF due to localized electromagnetic fields generated around plasmonic NPs that enhance fluorophore excitation and emission) and metal-enhanced fluorescence (MEF).[50–52] Quantum dot-plasmonic nanostructure coupling and semiconductor nanocrystal-dye molecule couple excitonic material-plasmonic nanostructure EET form the foundation for EET-based plasmonic biosensors in a bid to enable specific, ultrasensitive optical detection via mechanisms such as Förster resonance energy transfer (FRET) and plasmon-exciton coupling.[51]

The various LSPR-based biosensors, viz., colorimetric, fluorometric, and exciton energy transfer-based biosensors, possess varied strengths and weaknesses and thus are applicable for different purposes. Colorimetric biosensors are best suited for real-time and instrument-independent sensing but might have compromised interference and sensitivity for complex samples.[54] Fluorometric biosensors are more sensitive due to plasmon-enhanced fluorescence but are instrument intensive. Energy transfer-excited exciton plasmonic biosensors are more sensitive with increased signal-to-noise ratio but require acceptor-donor system design skillfully.[57,58] The future will be dictated by the advances in hybrid plasmonic nanostructures, machine learning-based data analysis, and microfluidic integration for the LSPR-based biosensing modalities. Biosensors

must be rendered more stable, reproducible, and inexpensive in the future work so that they can be applied to other medical and environmental applications.

Nanoplasmonic Biosensors

Nanoplasmonic biosensors are an innovative combination of nanomaterials, LSPR or SPR and optical biosensors that have garnered significant attention in recent years.[59] These biosensors utilize the unique properties of NPs, particularly AgNPs and AuNPs, which exhibit LSPR. This phenomenon occurs when incident light excites the conduction band electrons in metallic surfaces, resulting in tightly confined optical fields. Nanoplasmonic biosensors have emerged as promising platforms for a wide range of medical and biological applications due to their high sensitivity and selectivity, and label-free detection capabilities. Their high sensitivity and selectivity make them valuable tools in medical diagnostics, environmental monitoring, and drug discovery. Nanoplasmonic biosensors offer several advantages, including label-free detection without the need for fluorescent or radioactive labels. This not only increases convenience and reduces costs but also allows the detection of small molecules and low concentrations with high accuracy. Moreover, nanoplasmonic biosensors facilitate swift and precise detection of targets, characterized by high sensitivity and specificity. This renders them particularly well-suited for identifying disease biomarkers in proteins and nucleic acids.[60]

Additionally, nanoplasmonic biosensors are being actively investigated for next-generation sensing applications that require system miniaturization, simpler optical geometries, increased spatial resolutions, and high-throughput multiplexing detection. As shown in Figure 2, it can be seen that the reflective index changes as the sample binds, allowing the recognition of molecules immobilized on the LSPR sensor. The size, shape, composition of structures, and dielectric

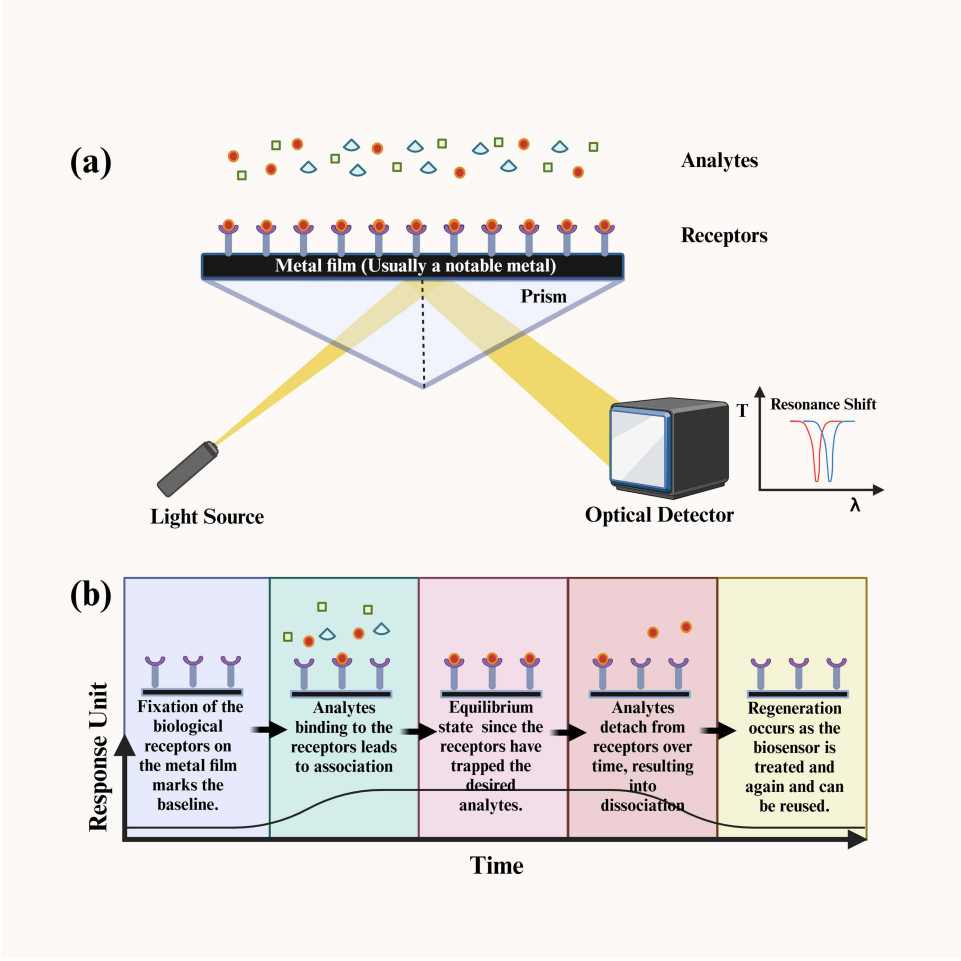

Figure 2 Schematic illustration of (a) an optical biosensor and detection and (b) measurement arrangement of the biosensor..

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properties of the surroundings all play crucial roles in determining the intensity and position of the LSPR. These factors collectively contribute to the creation of an optical sensor. Importantly, even small alterations in the reflective index of the sensing medium can cause shifts in the LSPR, impacting its role in detecting specific analytes or chemicals.[61–64]

Gold-Based Nanoplasmonic Biosensors

SPR and LSPR based Au nanoplasmonic biosensors have been used as sensitive and selective probes of biomolecules with unparalleled versatility. SPR- and LSPR-based biosensors have been widely used for the detection of cancer, autoimmune disease, and infection biomarkers of disease. Advances in nanofabrication techniques such as nanoimprinting, electrochemical deposition, and self-assembly have allowed one to engineer highly reproducible and scalable biosensors that improve their diagnostic performance. Researchers have explored different sensor architectures by incorporating nanomaterials such as Au nanowires, polydopamine (PDA), molybdenum selenide ($MoSe_2$), and AgNPs to enhance detection sensitivity and selectivity.

As a noble metal, Au plays a crucial role in enhancing SPR and LSPR biosensors due to its excellent optical and plasmonic properties. Their chemical stability, satisfactory conductivity, and biocompatibility have rendered Au films a suitable material for the biosensing function to enable firm biomolecular interaction with satisfactory sensitivity. Au films used in SPR sensors are responsible for being the dominant plasmonic layer in facilitating the effect of resonance to allow refractive index change sensing caused by biomolecular binding. Thickness and uniformity of Au film are most important to sensor performance via a bearing on resonance wavelength shift and detection sensitivity. LSPR sensors, in contrast, capitalize Au nanostructures such as NPs, nanowires, and nanospheres to create localized plasmonic resonance to facilitate electromagnetic field confinement and label-free biosensing of biomolecules with specificity.

The size, shape, and surface functionalization of Au nanostructures significantly affect their resonant properties, and therefore there is a potential to tune them at the molecular level for specific biosensing applications. Stability and biofunctionalization are further enhanced with the incorporation of Au with other nanomaterials such as $MoSe_2$ and polydopamine and also improved sensor performance. These developments emphasize the pivotal importance of Au in plasmonic biosensors and provide the technology of highly sensitive real-time and reproducible diagnosis to modern medicine. Various researches utilizing Au based nanoplasmonic biosensors have been summarized in Table 1.

Liu et al introduced an economical and reliable biosensing platform for real-time protein detection based on capillary LSPR sensors and AuNPs functionalized in the capillary.[65] Coupled with a complementary metal-oxide-semiconductor (CMOS) image sensor, the platform allows instant and accurate quantification of protein interactions. The device can detect changes in the frequency of scattered light by AuNPs, which are altered upon protein binding, for protein identification and quantitation of proteins like transferrin and immunoglobulin G (IgG).[73] Augmented by the extinction effect of AuNPs, the portable device possesses high-throughput screening and disposable sensor potential. Its convenience, portability, and inexpensiveness make it suitable for many applications including disease diagnosis, environmental monitoring, and field-portable diagnostics, bringing protein detection outside the traditional lab setting.[74–79]

Hsieh et al designed a novel device for rapid EBV detection by integrating microfluidic PCR with a Au nanoslit-based SPR sensor.[80] The sensor, fabricated through laser scribing and nanoimprinting, enhances LMP1 DNA sequence within a microchannel and detects it using a DNA probe on the SPR sensor. The sensor, which facilitates simplified PCR process, reduces analysis time to 36 minutes from 105 minutes in traditional methods with good sensitivity at a 10□[11] g/mL detection limit. The sensor was shown to distinguish between EBV-positive and -negative samples, demonstrating its usability for real specimen application. The platform is integrated to enable on-chip amplification and detection, with potential for rapid and efficient detection of various viruses, including COVID-19. Cost-effective fabrication and usability of the device demonstrate huge implications in public health and disease control.[80–86]

Another research provides a synchronous detection apparatus for SARS-CoV-2 and HHV-4 DNA that reduces PCR time by 55%. Integrating microfluidic PCR with SPR sensor on a nanoslit, the apparatus performs duplex PCR with 30 thermal cycles and detects unlabeled artificially infected cell genes. Laser scribing and nanoimprinting provide fast and sensitive detection. The apparatus uses controlled temperatures for denaturation, annealing/extension, and detection, with instantaneous amplicon detection via SPR. This technology enables quick clinical decision-making, significantly due to

Table 1 Summary of Different Research of Au Based Nanoplasmonic Biosensor

Study	Synthesis Technique	Material Used	Sensitivity	Response Time	Specificity	Novelty	Reference
Capillary LSPR sensor	Functionalization of AuNPs in capillary	AuNPs	Changes in scattered light frequency	Instant	Protein binding specificity	Portable, cost-effective, real-time protein detection	[65]
SARS-CoV-2 and HHV-4 duplex PCR SPR sensor	Laser scribing and nanoimprinting	Au nanoslit-based SPR sensor	PCR time reduced by 55%	30 thermal cycles	Detects unlabeled genes of co-infections	Rapid, sensitive co-infection detection	[66]
LSPR sensor on polymer substrate	Co-hot embossing, lithography, DC sputtering	Au on COP film	423 nm/RIU	Instantaneous	LMP1 protein quantification (R^2=0.98)	One-step printing, mass production capability	[67]
Au nanowire array-based SPR sensor	PDMS microfluidic chip fabrication	Capped Au nanowire array	Wavelength shift-based detection	Real-time	LMP1 DNA binding specificity	Fano resonances, enhanced sensitivity	[66]
Solar-powered RA diagnostic device	Nanoplasmonic chip with solar centrifuge	Peptide-functionalized nanoplasmonic chip	Color intensity change-based	Rapid	RA autoantibody specificity	Solar-powered, low-cost alternative for remote settings	[68]
Optical fiber SPR biosensor	PDA-MoSe2@AuNPs-PDA multilayer structure	$MoSe_2$@AuNP nanocomposite	1.8-fold lower detection limit than conventional SPR	Real-time	High IgG specificity	Enhanced binding efficiency and stability	[69]
Dengue NS1 LSPR immunosensor	Au nanospheres functionalized with cysteamine and dengue antibodies	Au nanospheres	Plasmon peak shift-based	Rapid	Dengue NS1 antigen specificity	Label-free, low-cost, adaptable to other biomolecules	[70]
3D ZnO nanowire LSPR sensor	ZnO nanowire growth on optical fibers	ZnO nanowires with AuNPs	404% higher PSA sensitivity than 2D sensors	Real-time	PSA detection (0.51 pg/mL)	3D structure for enhanced sensitivity	[71]
LSPR multiplex detection system	Nanoimprinting, e-beam lithography	Au-coated nanoslit array on polycarbonate	Resonant spectrum red-shift-based	Instantaneous	IgG, IgA, IgM multiplex detection	Label-free, low-cost, high specificity	[72]

the increased severity of co-infections. The ability of the device to detect co-infected patients assists in the development of effective treatment protocols.[87–92]

Another study fabricated an LSPR sensor integrated in a microfluidic channel using a co-hot embossing technique on a silicon substrate. Nanostructure and microfluidic molds, which were prepared via two-time lithography, were used to emboss a COP film, and Au was sputtered by a DC sputter and shadow mask.[93,94] The sensor had a 423 nm/RIU sensitivity that was calibrated with glycerol solutions and effectively quantified LMP1 protein with high correlation (R^2=0.98). This one-step printing technique enables rapid and mass production of SPR sensors on polymer substrates, with an easy-to-use biosensing device for biomolecule quantification under working conditions.[67,95,96]

Furthermore, a novel SPR sensor was fabricated based on a capped Au nanowire array in a PDMS microfluidic chip for LMP1 gene detection.[97] The sensor utilizes Fano resonances, generated by polarized light transmitted through the nanowire array, which are sensitive to LMP1 DNA binding. DNA is ready in PCR amplification and the sensor measures the resonance wavelength shift upon contact between gene sequences and the Au nanowire surface. The suggested design has potential for portable, low-cost, and real-time gene detection with proposed improvements such as sandwich assays and DNA methylation for enhanced specificity and sensitivity.[66,98–101]

In addition, another study developed a point-of-care diagnostic device for RA that combines solar-powered centrifugation with a smartphone nanoplasmonic sensor. It is critically important that RA, a widespread chronic autoimmune disease marked by joint inflammation, is early diagnosed to improve patient prognoses.[102,103] Whole blood is centrifuged to separate plasma, and RA-indicative autoantibodies are detected by color intensity changes on a peptide-functionalized nanoplasmonic chip. This system provides low-cost, rapid RA diagnosis, particularly in resource-limited settings, and demonstrates an environmentally friendly and low-cost alternative. The solar-powered centrifuge can be utilized where there is no conventional electricity, making it more relevant to global health.[68,104,105]

Simultaneously another work developed a very sensitive optical fiber SPR biosensor, with a PDA-$MoSe_2$@AuNPs-PDA multilayer structure, for IgG detection. The $MoSe_2$@AuNP nanocomposite increases SPR signals, and PDA layers enhance binding efficiency, resulting in an 1.8-fold lower detection limit compared to conventional SPR biosensors.[106] The sensor exhibits high selectivity for IgG, good regeneration performance, and stability, offering a label-free, real-time, and miniaturized sensing platform with potential for simple and cost-effective disease diagnosis.[69,107–111]

Mahmood et al developed a label-free LSPR immunosensor to detect the dengue NS1 antigen with Au nanospheres. The sensor tracks plasmon peak shifts due to refractive index changes with analyte binding at the surface of Au nanospheres. A glass slide is coated with Au nanospheres and functionalized with cysteamine and dengue antibodies. After antigen exposure, LSPR changes detect the presence of dengue NS1. This technique offers rapid, low-cost detection of dengue and can be adapted to other biomolecules for early diagnosis and improved treatment.[70,112–116]

Furthermore, a fiberoptic LSPR sensor for the detection of PSA was built from a 3D structure of ZnO nanowires decorated with AuNP. The sensor employs LSPR, which is sensitive to changes in the environment of AuNP, for the detection of biomolecules. By creating a 3D ZnO nanowire forest on optical fibers, the sensor was 171% more sensitive than 2D sensors in sensing bulk refractive index changes and 404% more sensitive in sensing PSA with a detection limit of 0.51 pg/mL. The 3D structure is sensitive, portable, and compact and can be utilized for real-time label-free biosensing with potential for further optimization through AuNP and ZnO nanowire property tuning.[117–119]

Another work reported a label-free multiplex detection system integrating an LSPR sensing array and PDMS microfluidic channels for synchronous measurement of human IgG, IgA, and IgM. Surface activation induces individual regions of sensing with specific antibodies. Analyte-antibody conjugation results in a red-shift of the resonant spectrum, quantitatively measuring the analytes. The device integrates a Au-coated nanoslit array on a polycarbonate substrate, nanoimprinted and e-beam lithographed, with a PDMS microfluidic channel. This platform offers higher sensitivity and specificity for multiplex detection, easier diagnostics with its label-free character, and low-cost mass production.[72,120–122]

Silver-Based Nanoplasmonic Biosensors

Pandey et al's article provides insights into the use of AgNPs embedded in polymer composites for the purpose of improving plasmonic biosensing applications (Figure 3a). AgNPs have unique properties such as LSPR. The resonance frequency of this plasmon can be manipulated based on the size and shape of the NPs and the nature of the surrounding

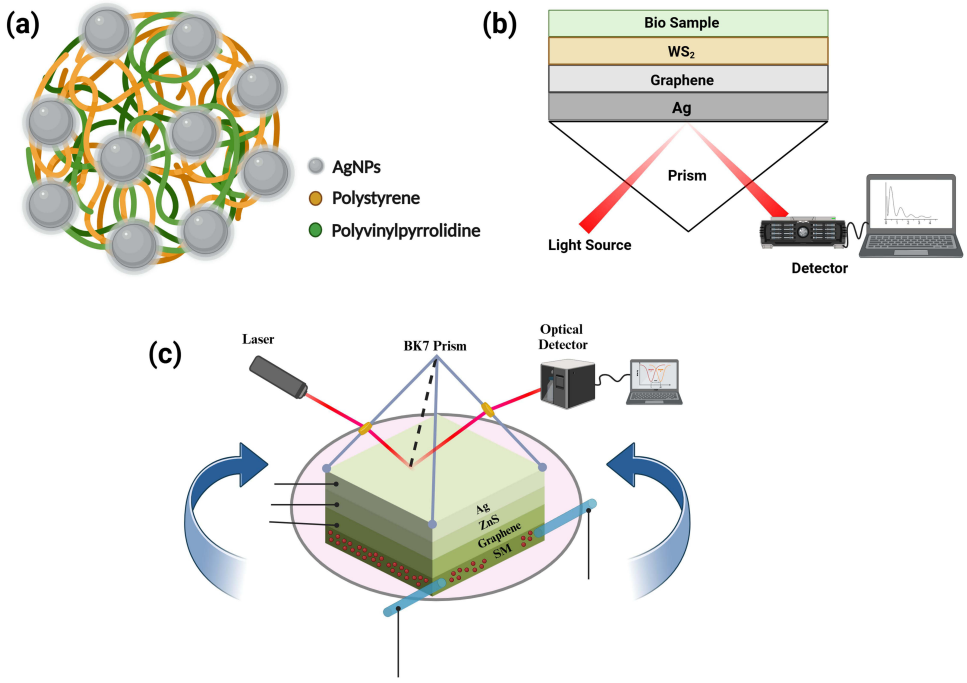

Figure 3 (**a**) Schematic illustration of structure and design of a silver nanoparticle (AgNP)-based polymer optical biosensor. (**b**) Illustration depicting the conceptualized five-layer surface plasmon resonance (SPR) biosensor architecture utilizing graphene-WS for the specific purpose of detecting glucose in urine. (**c**) Illustration of the configuration of a stratified SPR biosensor.

environment. The mechanism discussed in the paper involves embedding AgNPs in two types of polymer composites, polystyrene/poly (4-vinylpyridine) (PS/PVP) (50:50) and PS/PVP (75:25), through a process called vacuum evaporation. Three important equations were used to calculate the scattering efficiencies, absorption efficiencies, and extension efficiency for these embedded NPs, which are key parameters to assess their sensitivity as sensors. Furthermore, by examining their refractive index sensor performance evaluated by metrics such as the full width at half maximum frequency, quality factor, sensitivity, and figure of merit, the researchers were able to determine the sensing capability of different NP-embedded polymer composites.

Moreover, AgNPs exhibit unique properties, which are effective in biosensing applications. However, they have significant limitations, including instability, proneness to agglomeration, and toxicity. Embedding these NPs in polymer composites helps to overcome those issues. First, polymer composites help stabilize the NPs, improving their practical application. Second, due to the toxicity of AgNPs, embedding them in polymer matrices reduces their adverse effects, paving the way for safer use in biosensors. Finally, inserting AgNPs into polymer matrices allows for homogeneous NP dispersion, minimizes agglomeration, and thus enhances the performance of these NPs as resources for highly sensitive biosensing. As to applications, AgNPs and associated technologies are crucial for developing medical diagnostics, environmental monitoring tools, and other biosensing devices. This research highlighted the importance and promising future of AgNPs embedded in polymer composites, which offer multiple benefits in the fabrication of ultrasensitive and efficient plasmonic biosensors. In conclusion, the research conducted in this article sets the groundwork for future exploration and optimization in the domain of AgNPs within polymer composites for plasmonic biosensing applications.[123–128]

Authors in a recent research article presented an Ag-based SPR biosensor with graphene and tungsten disulfide layers, designed for urine-glucose detection (Figure 3b). Simulations showcased an optimized layer configuration of Ag (56 nm), graphene (1.36 nm), and tungsten disulfide (WS_2) (3.2 nm). This design exhibited higher sensitivity and field enhancement than conventional Au-based SPR biosensors. The optimized structure achieved a sensitivity of 288.86°/RIU and a figure of merit of 88.89°/RIU, making the proposed design suitable not only for glucose concentration detection, but potentially other biomarker and heavy metal detections, promising to provide a wide range of applications.

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The proposed biosensor is based on SPR, a resonance condition occurring when light hits a metal surface at a specific incidence angle, exciting free electrons and creating oscillating surface plasmon polaritons. The sensor design incorporates an Ag layer to support these plasmons, graphene layers for oxidation protection, and WS_2 to improve performance and sensitivity. The configuration was optimized to maximize the sensitivity, which is defined by the shift in the resonance angle concerning a change in the refractive index of a biosample. This research addressed the cost and efficiency challenges of SPR-based biosensors by deriving an Ag-based design to replace traditional Au usage, which significantly reduced costs. The sensor also showed improved sensitivity and field enhancement, making it more efficient in detecting minute changes in glucose concentrations in urine samples. With the alarming rise of diabetes, enabling low-cost, efficient urine-glucose detection can aid early diabetes detection. Furthermore, the design bears potential for optimizing the sensing of other biomarkers or heavy metals, expanding its use in diverse applications such as chemical or gas detection, thus enhancing its value in biosensing technologies.[129,130]

Another study by Karki et al presents an enhanced approach to SPR-based biosensing by utilizing distinct properties of graphene and zinc sulfide (ZnS). To begin with, the authors proposed an addition to the conventional prism-based SPR sensor by depositing layers of ZnS and graphene over Ag metal. These material choices are entirely based on the unique properties that these materials exhibit. ZnS is a compound semiconductor, which has unique optoelectronic properties, such as a wide energy bandgap, offers excellent chemical and thermal stability, and provides good adsorption efficiency. Meanwhile, graphene, a 2D material, is electroactive and transparent with a large cross-sectional area allowing for significant adsorption, making it an ideal candidate for enhancing the surface area of SPR sensors (Figure 3c).

Moreover, a key aspect of the investigation was the optimization of the thickness of the Ag metal layer. The authors determined the optimal Ag thickness to be 50 nm, as this yields the minimum reflectance. This optimization is integral to enhancing the overall sensitivity of the sensor. The study specifically used four layers of ZnS along with one graphene layer to attain the maximum sensitivity, which was reported to be 292.8°/RIU. This sensitivity enhancement outperformed several previous works. It is important to note that SPR sensor sensitivity is a critical performance metric, as it determines the lowest detectable change in the RIU. Increased sensitivity allows detection of smaller changes in the RIU, which corresponds to the ability to detect lower concentrations of analytes or target molecules. The technological significance of this research lies in its potential applications in biochemical and biological analyte detection realms, where enhanced SPR sensor sensitivity translates into improved detection capabilities. Furthermore, this paper signifies a substantial contribution towards improvements in SPR sensor design, by careful optimization of material layers, demonstrating its potential for enhanced sensing applications. Therefore, the research is significant and has the potential to substantially contribute to biosensing technology.[131]

Other Hybrid Nanoplasmonic Biosensors

A research article by Hsieh et al outlined the development of a nanofluidic preconcentrator integrated with an aluminum-based nanoplasmonic sensor for EBV detection. The team embarked on crafting a device that can detect low abundances of the LMP1 protein biomarker, a critical component for EBV diagnoses. The authors used nanoslit sensing chips manufactured via nanoimprinting on a COP substrate, and aluminum was deposited on the nanostructure. The surface of the sensing region was further modified using (3-aminopropyl) triethoxysilane (APTES), which in turn allowed the conjugation of LMP1 antibodies. The developed device demonstrated a capacity for enriching samples up to 1000-fold, offering a valuable pathway for early diagnosis of viruses, including EBV (Figure 4a–g).

The developed device operates based on preconcentration processes where voltage-induced forces generate a concentrated protein plug in the main microfluidic channel. Specifically, voltages applied to the device cause ions in the main channel to flow to a buffer channel, developing ion concentration polarization. This process results in an ion-depleted region which traps proteins leading to efficient preconcentration. Following this, an APTES-treated aluminum-capped nanoslit system, modified with anti-LMP1 IgG, was used to detect the LMP1 protein. Detection was performed through analyzing spectral shifts in the resonant spectrum produced when broadband light is subjected to transverse magnetic polarization and passes through the nanoslit Fano sensing region. EBV is a common herpesvirus linked to various diseases, and as such, the early detection of the virus is crucial. With the developed device, a lower detection limit for the LMP1 protein, one of the key biomarkers for EBV, can be achieved due to the preconcentration process,

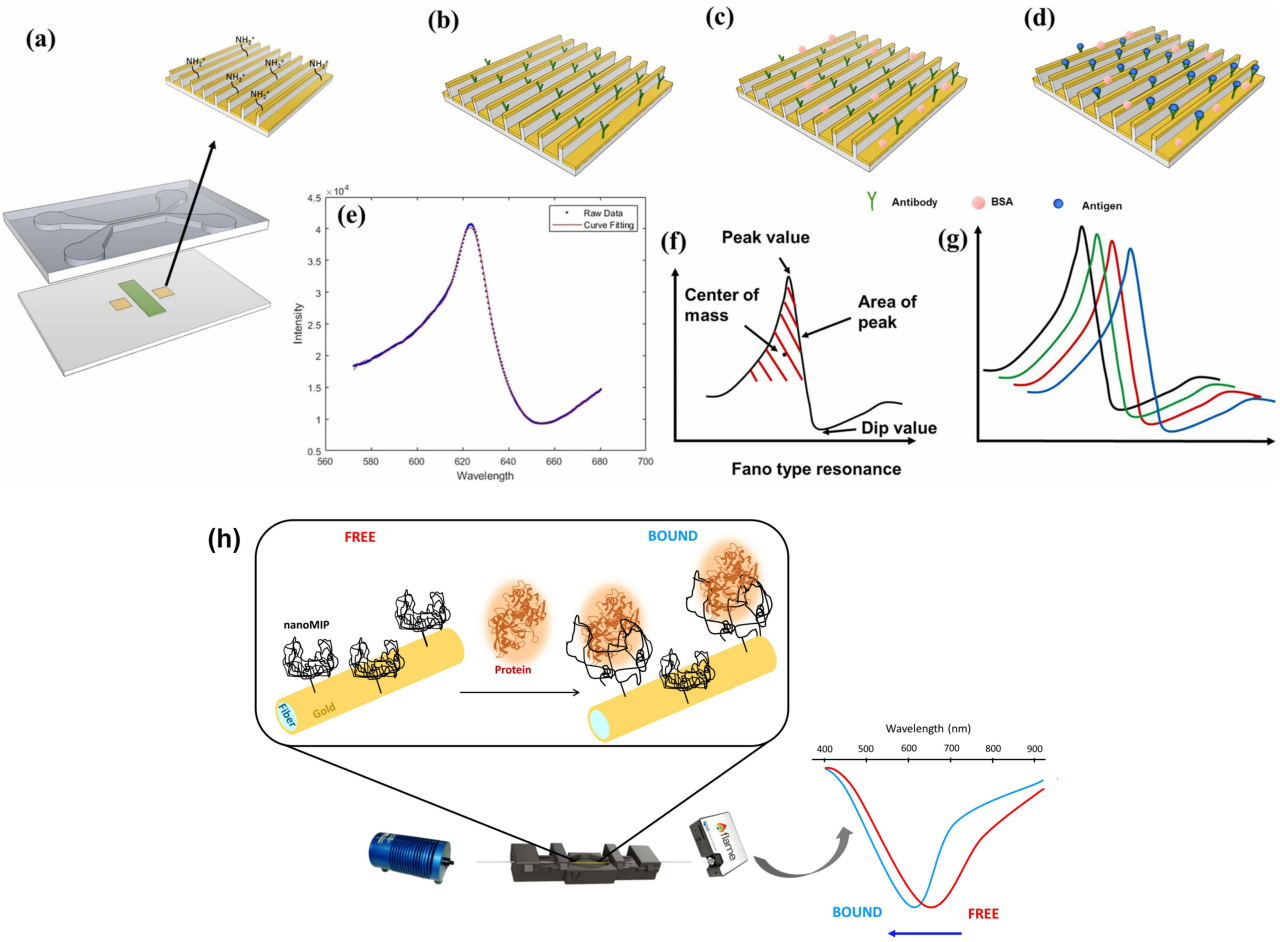

Figure 4 Procedural steps for modifying antibodies and implementation of analytical techniques are outlined as follows. (**a**) The sensing region surface is characterized by an abundance of amino groups. (**b**) Conjugation of anti-latent membrane protein-1 (LMP1) IgG to amino groups within the sensing region is achieved through carboxy-amine conjugation. (**c**) Following anti-LMP1 IgG modification, bovine serum albumin (BSA) is employed to obstruct unreacted sites. (**d**) The sensing chip is then utilized to detect the LMP1 protein. (**e**) The nanoslit surface plasmon resonance (SPR) sensing chip captures a standard Fano-type resonant spectrum when broadband light, oriented in the transverse magnetic (TM) direction, is introduced. (**f**) Four distinct analytical methods are employed, encompassing the area, center of mass, peak value, and dip value methodologies. (**g**) The underlying mechanism involves a progressive redshift in the resonant spectrum as targets progressively adhere to the surface. (a-g)Reproduced from Hsieh H-Y, Luo J-X, Shen Y-H, et al. A nanofluidic preconcentrator integrated with an aluminum-based nanoplasmonic sensor for Epstein-Barr virus detection. Sens Actuators B Chem. 2022;355:131327. Copyright (2022), with permission from Elsevier.[132] (**h**) Schematic illustration of the SPR-light diffusing fiber (SPR-LDF) sensor system. Reprinted from Arcadio F, Seggio M, Del Prete D, et al. A plasmonic biosensor based on light-diffusing fibers functionalized with molecularly imprinted nanoparticles for ultralow sensing of proteins. *Nanomaterials*. 2022;12 (9):1400.[133]

allowing for better diagnostic sensitivity. Furthermore, this research suggests an effective direction for creating rapid, sensitive, and cost-effective diagnostic tools for EBV and also for other diseases, including COVID-19. It provides a potential pathway for the efficient diagnosis and management of disease outbreaks in laboratories.[132,134–136]

Other research discusses the development of a SPR sensor in silica light-diffusing fibers (LDFs) functionalized with a specific nanosized molecularly imprinted polymer (nanoMIP) receptor for recognizing the human serum transferring protein, a biomarker of iron metabolism. The sensor was fashioned by removing the cladding from a section of LDFs using a mechanical stripper. The exposed core was then sputter-coated with a 60-nm Au film. The Au film was essential for enabling SPR, a sensing mechanism that detects small refractive index variations at the interface between a thin metal film and a dielectric medium. The SPR-LDFs were then functionalized with nanoMIPs. These nanoMIPs served as synthetic receptors that bind to the target analyte, causing a change in the refractive indices and thus, triggering SPR. The combination of an SPR-LDF platform and nanoMIPs produced a highly sensitive and selective biosensor with an ultra-low detection limit of about 4 femtomoles (Figure 4h). In addition, the researchers designed a 3D-printed holder to secure the SPR-LDF sensor during the tests and established a measurement cell for efficient setup and potential scaling up of measurements. Significantly, this novel combination of SPR-LDFs and nanoMIPs led to an extremely sensitive sensor

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and owing to the production simplicity of an SPR-LDF platform (which requires only a metal deposition step), it also opens the door to economical large-scale production of such sensors. This work represents a significant step forward in plasmonic biosensor technology and offers a practical solution for ultra-low detection of specific proteins and other analytes.[133,137–142]

Key Considerations for Selection and Optimization of Nanoplasmonic Biosensors

The evolution of SPR and LSPR biosensors have led to significant advancements in disease diagnostics, drug discovery, and personalized medicine. The various applications of these nanoplasmonic biosensors have been highlighted in Table 2. These biosensors rely on nanomaterials and plasmonic effects to detect biomolecules, pathogens, and chemical interactions with high specificity and real-time monitoring. The key differentiator between SPR and LSPR lies in their operating principles: SPR sensors measure bulk refractive index changes over a metal film, making them highly sensitive to biomolecular interactions, whereas LSPR sensors use localized surface plasmons in metal NPs, enabling miniaturization and cost-effective fabrication for point-of-care (POC) applications.

The fabrication techniques significantly influence the sensitivity, reproducibility, and cost of biosensors. SPR biosensors, requiring electron beam lithography, nanoimprinting, and DC sputtering, achieve precise nanostructures, improving optical response stability and detection limits. However, these methods demand high-end instrumentation, cleanroom facilities, and complex processing, increasing fabrication costs. This is ideal for critical biomedical applications like cancer biomarker detection and viral diagnostics like Epstein-Barr virus and dengue.[80] On the other hand, LSPR biosensors, produced via hydrothermal synthesis, drop casting, and self-assembly, enable scalable, cost-effective, and simpler fabrication, making them more accessible in resource-limited settings. While these methods lower manufacturing complexity, they sometimes compromise precision and batch-to-batch reproducibility, which can affect sensor consistency in clinical diagnostics. However, LSPR's real-time, label-free nature makes it highly effective for rapid disease screening.

Material choice is pivotal in defining the biosensor's sensitivity, stability, and specificity. Au remains the standard for SPR sensors due to its high conductivity, chemical inertness, and strong plasmonic resonance, facilitating biomolecular detection with high signal-to-noise ratios. However, Au's cost and limited tunability have driven the use of hybrid materials, such as MoS_2, graphene, and perovskites, which enhance surface area, binding efficiency, and optical response.[143] For LSPR biosensors, AgNPs provide stronger plasmonic resonance than Au, resulting in higher sensitivity. However, Ag's tendency to oxidize over time reduces its long-term stability, making it less suitable for long-term biomedical applications unless surface passivation techniques are applied. ZnO nanowires and polymer coatings[71] (eg, PDMS, polydopamine) further extend sensing areas, increase detection stability, and improve biocompatibility, enhancing sensor performance in complex biological environments.

While SPR sensors are favored in clinical laboratories for their high precision and stability, they require bulk optical setups (eg, BK7 prism configurations), complex readout systems, and controlled environmental conditions.[145] This makes them less adaptable for decentralized healthcare. In contrast, LSPR's miniaturization and compatibility with portable devices allow for POC diagnostics, enabling early disease detection in field settings. For instance, LSPR sensors using Au nanospheres for dengue detection achieve rapid real-time results, whereas SPR biosensors integrated with multilayered perovskite-graphene structures provide highly specific glucose monitoring for diabetes patients.[146]

The integration of nanomaterials, innovative fabrication techniques, and advanced synthesis methods has propelled biosensors into next-generation platforms for early disease detection, therapeutic monitoring, and drug screening. SPR sensors, with their highly controlled nanostructures and low detection limits, are becoming instrumental in pharmaceutical research, where real-time binding kinetics of drug candidates with target proteins must be analyzed. Meanwhile, LSPR sensors, due to their low-cost, field-deployable nature, enable rapid screening of infectious diseases and personalized diagnostics. The future lies in hybrid approaches merging SPR's precision with LSPR's portability to develop multifunctional, high throughput. The key comparison between SPR and LSPR based biosensors is listed in Table 3.

Table 2 Summary of Nanoplasmonic Biosensors and Their Key Properties

Optical Technology	Components	Fabrication Techniques	Materials Used	Application	Advantages	Reference
SPR	PCR microchannel, Au-capped nanoslit	Laser scribing technique, hot embossing nanoprint lithography, DC sputtering	Polycarbonate, Au	Epstein-Barr virus detection	Higher specificity, less analytical time, low costs, decreased sample volumes	[80]
SPR	Centrifuge, Au-capped nanoslit	Stereolithography (3D printer), injection molding, DC sputtering	Polycarbonate, Au	Rheumatoid arthritis detection	High specificity, low costs, high accessibility in remote areas	[68]
SPR	Nanoplasmic sensing array, microfluidic channels	E-beam lithography, nanoimprinting, DC sputtering.	PDMS, Au	Label-free multiplex detection	Acceptable sensitivities, parallel microfluidic assessments available	[72]
SPR	Nanofluidic preconcentrator, Al-based nanoslits	E-beam lithography, nanoimprinting, DC sputtering	COP, Al	Epstein-Barr virus detection	Larger sensing area, better spectral resolution, signal stability	[132]
SPR	Nanostructure, Au-based nanoslit	Co-hot embossing, e-beam lithography, DC sputtering	COP, PDMS, Au	LMP1 detection (nasopharyngeal carcinoma)	Label-free immunoassays, easy fabrication (one-time printing)	[67]
SPR	Nanoslit, microfluidic PCR	Hot embossing nanoimprinting lithography, thiol-Au reaction, and electrostatic adsorption	Polycarbonate, Au	LMP1 detection (nasopharyngeal carcinoma)	Label-free detection, compact, and portable	[87]
SPR	Refractive prism, multilayered biosensor	Vacuum thermal evaporation, electrospinning	Si, titanium carbide, Ag	Detection of low-index chemicals and biomolecules	High sensitivity, biocompatibility, fast response time	[143]
SPR	Nanosphere, optical source	Hydroxylation, salination, drop casting	Au nanospheres	Early detection of dengue fever	High sensitivity, label-free, real-time detection, simple, portable	[70]
SPR	Au nanowire, microfluidic chip	Hot-embossing nanoimprinting, e-beam lithography, DC sputtering	Au, polycarbonate	Detection of the *LMP1* gene, diagnosis of Epstein-Barr virus	High sensitivity, label-free detection, real-time detection, specificity, miniaturization	[66]
SPR	SPR sensing platform, metal-molybdenum diselenide ($MoSe_2$) multilayer	Electrostatic interaction, hydrothermal method	Polydopamine (PDA), $MoSe_2$, AuNPs	Detection of specific immunoreactions	High sensitivity, large surface area, miniaturized, rapid-response, label-free	[69]

(*Continued*)

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Table 2 (Continued).

Optical Technology	Components	Fabrication Techniques	Materials Used	Application	Advantages	Reference
LSPR	Capillary LSPR sensor, CMOS image sensor	Polyelectrolyte modifications, electrostatic interactions	AuNPs, capillaries, diallyl dimethylammonium chloride, sodium-p styrene sulfonate, allylamine hydrochloride	Detection of transferring and IgG	Higher sensitivity, multiplex detection, low cost, miniaturized	[65]
SPR	LDFs, molecularly imprinted NPs	Sol-gel polymerization, layer-by-layer deposition	Silica, nanoMIPs (methacrylic acid, ethylene glycol dimethacrylate, azo initiator), Au	Protein detection, food safety	Ultralow detection limit, high selectivity, reusability, simple, portable	[133]
LSPR	Au NP-based sensing platform, SAM	Computational modeling, Campbell's modeling, layer-by-layer deposition, drop casting	AuNPs	Early detection and point of care in dengue	High sensitivity, label-free detection, real-time monitoring, simple, portable	[144]
SPR	BK7 prism, multilayer sensor	Thermal evaporation, chemical vapor deposition	Graphene, Ag, ZnS	Detection of various analytes, including proteins and DNA	High sensitivity, wide detection range, simple, portable	[131]
SPR	MoS_2-graphene hybrid nanostructure, SF10 prism	Layer-by-layer deposition	MoS_2, graphene, Ag	Detection of various biomolecules, including proteins, DNA, and viruses	High sensitivity, wide detection range, label-free detection, real-time monitoring, compact size, low cost	[145]
SPR	$MAPbX_3$-graphene hybrid nanostructure, BK7 prism	Layer-by-layer deposition	Ag, titanium dioxide, mixed-dimensional perovskite $MAPbX_3$, graphene	Glucose level monitoring	High sensitivity, wide linear range, fast response time, simple, portable	[146]
SPR	Barium titanate ($BaTiO_3$)-graphene hybrid nanostructure, prism (BK7)	Layer-by-layer deposition	Ag, $BaTiO_3$, graphene	Detection of various biomolecules, such as proteins, DNA, and viruses	High sensitivity, wide linear range, fast response time, simple, portable	[147]
SPR	BK7 prism, temperature monitoring sensor (PDMS based), refractive Index monitoring sensor (ZnSe based)	Layer-by-layer deposition	Ag, ZnSe, PDMS	HIV-DNA hybridization detection with DNA melting temperature monitoring.	High sensitivity, simultaneous measurement of DNA hybridization and temperature, real-time monitoring, simple, portable	[148]
LSPR	ZnO nanowire mesh, AgNP-based optical fiber	Hydrothermal synthesis, NP immobilization	Optical fiber, ZnO nanowires, AuNPs	Diagnosis of prostate cancer	Extended sensing area, light trapping effect by nanowires	[71]

Abbreviations: SPR, surface plasmon resonance; LSPR, localized surface plasmon resonance; Au, gold; Al, aluminum; LDFs, light-diffusing fibers; SAM, self-assembled monolayer; Ag, silver; NPs, nanoparticles; Si, silicon; PDMS, polydimethylsiloxane; ZnO, zinc oxide; IgG, immunoglobulin G.

Table 3 Key Comparison Between SPR and LSPR Based Biosensors

Category	SPR Biosensors	LSPR Biosensors
Operating Principle	Measures bulk refractive index changes over a continuous metal film using propagating surface plasmons	Relies on localized oscillations of conduction electrons in metal nanoparticles (NPs)
Sensitivity & Detection Limits	Highly sensitive, fM-pM detection range	Moderate to high sensitivity, pM-nM detection range
Fabrication Techniques	Electron Beam Lithography (EBL), Nanoimprinting (NIL), DC Sputtering, Thermal Evaporation – Requires cleanroom facilities, high-end instrumentation	Hydrothermal Synthesis, Drop Casting, Self-Assembly, Electrostatic Adsorption – Lower-cost, scalable but may affect reproducibility
Materials Used	Gold (Au) standard due to chemical inertness and conductivity; Graphene, MoS_2, Perovskites used for hybrid structures	Silver (Ag) preferred for stronger plasmonic resonance but prone to oxidation; ZnO nanowires, polymer coatings (PDMS, polydopamine) enhance stability
Cost & Scalability	Expensive, complex fabrication, high operational cost; bulk optical setup limits portability	Lower-cost, highly scalable, ideal for resource-limited settings and POC applications
Application Areas	Cancer biomarker detection, Protein binding kinetics, Viral diagnostics (Dengue, HIV, EBV), Pharmaceutical research	Rapid infectious disease screening (Dengue, HIV, Prostate Cancer), Personalized medicine, Field diagnostics
Strengths	High precision, low detection limits, robust clinical diagnostics	Portable, real-time monitoring, label-free, cost-effective fabrication
Limitations	Requires bulk optical components, costly, complex fabrication	Lower batch-to-batch reproducibility, slightly less sensitive than SPR
Future Trends	Hybrid SPR-LSPR biosensors, AI-integrated spectral analysis, multiplexed biomarker detection, wearable plasmonic sensors	Flexible, miniaturized biosensors, smart diagnostics, integration with IoT for real-time monitoring

Current Challenges and Future Prospects

Biosensor development grapples with diverse challenges, notably detecting low-concentration analytes in complex media crucial for accurate diagnoses. Creating affordable, robust platforms that accurately identify multiple analytes remains elusive. Elevating sensor performance, particularly in near-infrared ranges, demands innovative structures to enhance sensitivity, detection accuracy, quality factor, and figure of merit across applications.[149] Expanding sensor applications for societal benefit amid rising disease rates is vital, necessitating advancements in prism-based SPR sensors. The unavailability of point-of-care testing and continuous measurements, and low sensitivity for small molecules in label-free assays are other limitations. However, limited experimental work presents challenges for new researchers. Furthermore, the complexity of biosensors adds difficulties despite potential advancements.

Addressing issues like non-specific interactions affected by temperature, moisture, and composition fluctuations is crucial. Moreover, enhancing parameters like sensitivity and refractive index accuracy is essential. Overcoming these challenges requires cost-effective accessibility, regulatory compliance, and real-time monitoring. Research emphasizes chip chemistry, miniaturization, and antifouling strategies to propel the use of SPR for routine biomedical and point-of-care diagnostics.[150] Despite strides in nanomaterial-based sensors, barriers persist, including costs and technological bottlenecks, impeding biosensor progress.

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Disclosure

The authors declare that they have no competing interests.

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