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High-throughput biointerfaces for direct, label-free, and multiplexed metaplasmonic biosensing

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ABSTRACT

In recent years, metaplasmonic biosensors have emerged as a novel counterpart of well-established plasmonic biosensors based on thin metallic layers. Metaplasmonic biosensors offer high potential for sensor miniaturization, extreme sensitivity biosensing, and high multiplexing capabilities with detection methods free of coupling optical elements. These capabilities make metaplasmonic biosensors highly attractive for Point-of-Care and handled/portable devices or novel On-Chip devices; as a result, it has increased the number of prototypes and potential applications that emerged during the last years. One of the main challenges to achieving fully operative devices is the achievement of high-throughput biointerfaces for sensitive and selective biodetection in complex media. Despite the superior surface sensitivity achieved by metaplasmonic sensors compared to conventional plasmonic sensors based on metallic thin films, the main limitations to achieving high-throughput and multiplexed biosensing usually are associated with the sensitivity and selectivity of the biointerface and, as a consequence, their application to the direct analysis of real complex samples. This graphical review discusses the potential challenges and capabilities of different biofunctionalization strategies, biorecognition elements, and antifouling strategies to achieve scalable and high-throughput metaplasmonic biosensing for Point-of-Care devices and bioengineering applications like Organs-On-Chip.

Contents

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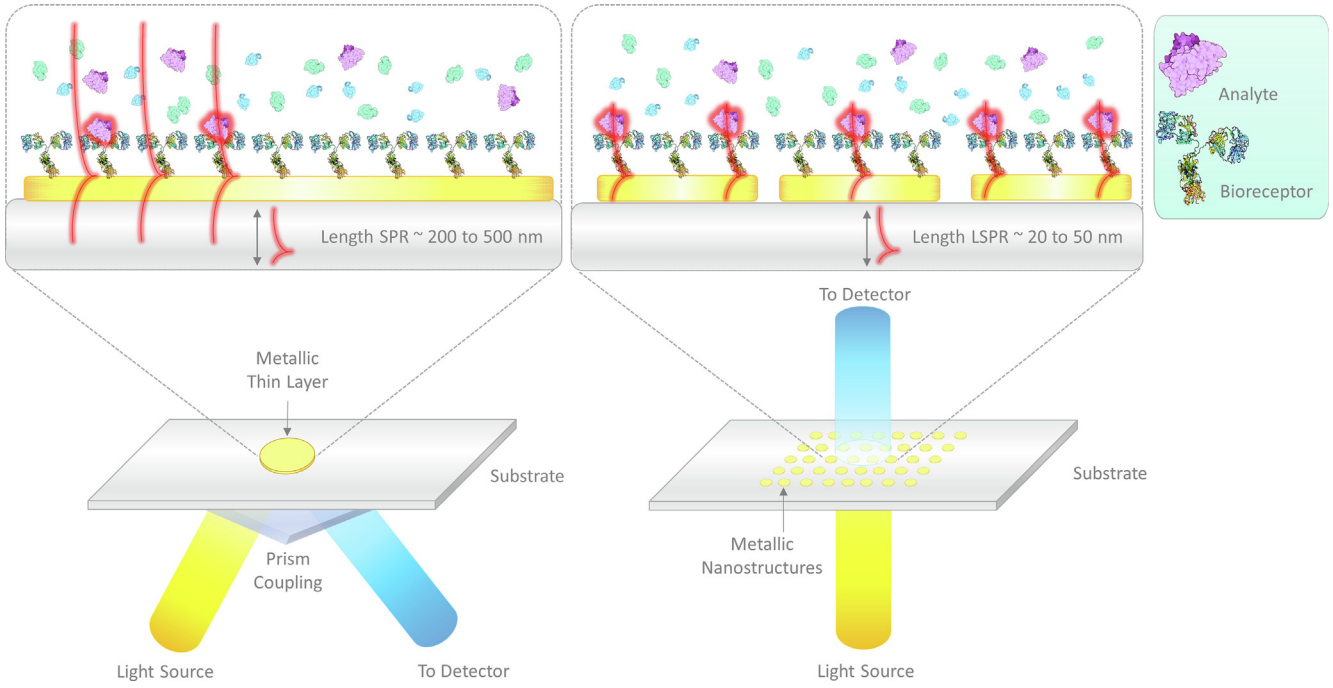

Fig. 1. Conventional plasmonic biosensors based on thin metallic layers (left) require coupling methods (i.e., prism-coupling, also called Kretschmann) and have a long evanescent field decay length (usually hundreds of nm), making them highly attractive to detecting high molecular weight or dimension analytes, i.e., proteins, exosomes, viruses, and cells in the pM-nM range. On the other hand, metaplasmonic biosensors are based on metallic nanostructures which can be distributed mainly in quasi-ordered or highly ordered 2D arrays. Compared to conventional plasmonic sensors, nanoplasmons arise from the light scattering of the metallic nanostructures, and the characteristics of the plasmonic spectral bands depend mainly on the geometry and materials of the nanostructure (Lopez et al., 2017). Metaplasmonic biosensors present a short evanescent field decay length, usually up to one order of magnitude below, compared to conventional plasmonic sensors. The last makes metaplasmonic biosensors (right) more sensitive to surface changes in comparison to plasmonic biosensors (López-Muñoz et al., 2022) and, consequently, suitable for detecting low-size/molecular-weight analytes, i.e., drug molecules, DNA chains, lipid bilayers, or low-dimension proteins in the fM-pM range (Altug et al., 2022). Metaplasmonic sensors usually allow the detection in transmission configuration, enhancing their potential integration with standard measurement platforms, i.e., microplate readers or conventional spectrophotometers, increasing their potential applications.

1. Introduction

Among the different optical biosensors, plasmonic biosensors have become the most widely commercialized optical sensors over the last few years (www.coherentmarketinsights.com, 2020). The main features of plasmonic biosensing are the potential for direct, label-free, multiplexed, and real-time monitoring of biomolecular interactions without amplification or sample pretreatment, usually in the nM-pM range. These advantageous features and the last advances in the development of lab-on-a-chip devices have widespread potential applications for plasmonic biosensing, especially in clinical diagnosis with the development of Point-of-Care (POC) devices and Organs-On-Chip (OOC) (Mughal et al., 2022; Tokel et al., 2014).

Plasmonic biosensing fundamentals have been extensively described over the last decade. Briefly, plasmonic biosensing is based on the evanescent field sensing principle. The evanescent field represents an electromagnetic field generated by the collective oscillation of surface electrons (plasmons) excited by a light beam with particular characteristics (momentum, polarization, and wavelength) that decay exponentially at a thin metallic film/dielectric interface. The evanescent field is highly sensitive to surface refractive index changes such as those caused by changes in mass on the surface of the metallic layer (Lopez et al., 2017). These refractive index changes influence the light propagation parameters (i.e., intensity, phase, or spectral variations, among others), which can be used to monitor biomolecular interactions. Conventional plasmonic biosensors based on thin metallic films generate plasmons by the extensively described prism, grating, and waveguide coupling methods (Lopez et al., 2017); however, these conventional plasmonic coupling methods can be overcome using metallic nanostructures (Fig. 1).

Over the last few years, the development of metaplasmonic biosensors has been mainly focused on the design and development of novel plasmonic metasurfaces, trying to maximize their theoretical biosensing performance to later incorporate into novel biosensing platforms for POC devices and bioengineering applications (i.e., *in situ* cell culture monitoring and OOC). However, the final performance of metaplasmonic sensors involves the deep synergy between the metaplasmonic sensor and the biointerface (López-Muñoz et al., 2022; Mughal et al., 2022), and multiple characteristics of the biointerfaces are involved (Fig. 2) like the selected bioreceptor, its immobilization strategy, and antifouling properties.

2. Bioreceptor immobilization strategies

The immobilization strategy mainly provides the accessibility for the biorecognition events (i.e., the distribution and density of the biorecognition element and orientation of the bioaffinity binding sites) and the physicochemical stability of the biointerface. In general terms, the immobilization strategy must ensure: i) uniform distribution, packing density, and proper biorecognition element orientation and ii) physicochemical stability and robustness. Various approaches to immobilizing these bioreceptors onto plasmonic sensors have been developed for many years. They aim to provide the best analytical performance considering the type of biorecognition element (i.e., antibody, aptamer, nucleic acid) and the target analyte (i.e., concentration, dimensions, carrier fluid/biofluid) (Oliverio et al., 2017). These approaches can be mainly summarized as those based on i) physical adsorption immobilization, ii) covalent immobilization using functional self-assembled monolayers (SAMs), and iii) bioaffinity-based immobilization (Fig. 3).

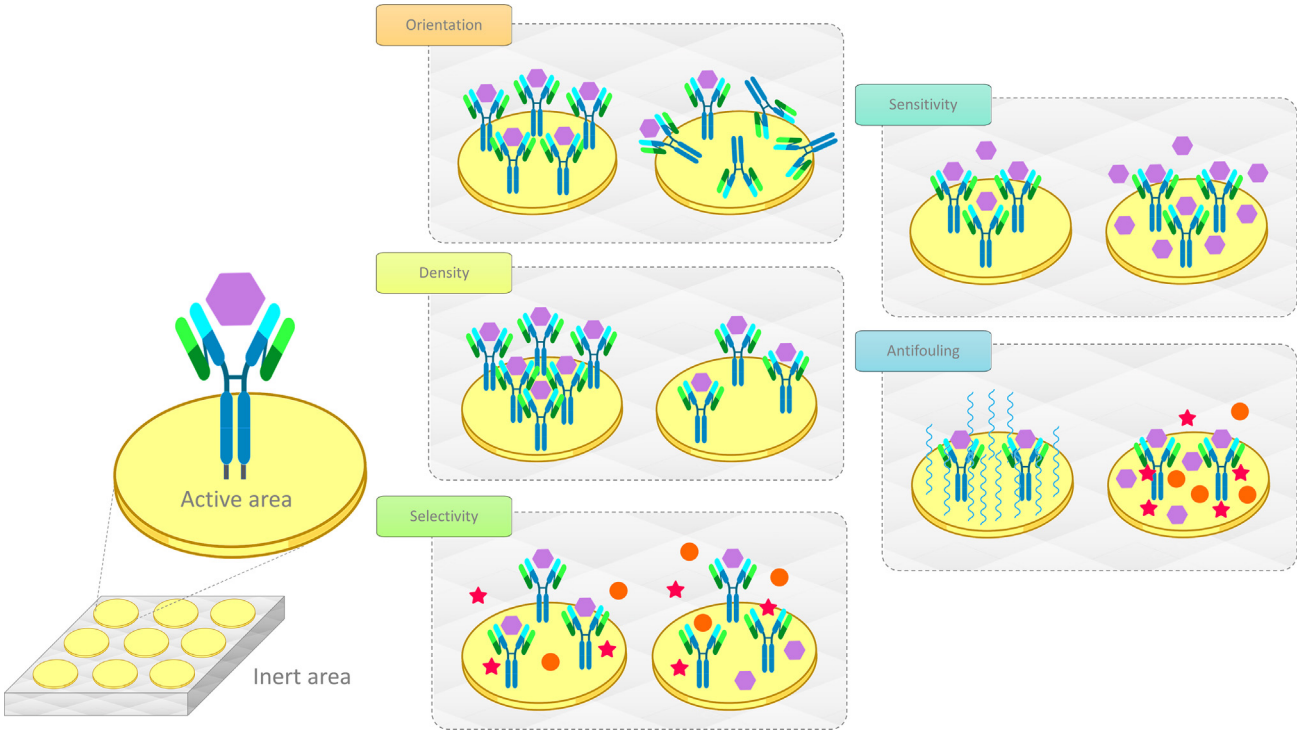

Fig. 2. Bioreceptor orientation, density, sensitivity, selectivity, and surface antifouling properties are the most relevant variables in biointerface design and engineering for high-throughput metaplasmonic biosensing. The orientation and density of the bioreceptor affect the access and detection of the target analyte. Biorecognition element orientation can complicate the analyte to achieve the bioaffinity regions; meanwhile, a low density of the biorecognition elements decreases the possible detection of the analyte. Besides the sensitivity issues often being the limiting factor, especially in clinical diagnosis applications, the specificity and selectivity of the biointerfaces are still challenging to surpass, especially when multiplexing and the biodetection in whole complex samples are required. The selectivity and sensitivity of the biointerfaces are mainly correlated to the bioreceptor. Selectivity is related to the ability of the bioreceptor to bind its intended target biomolecule within a complex mixture; meanwhile, the sensitivity is considered the ability to detect lower abundance antigens (in general terms, the affinity between the bioreceptor and the analyte). Finally, real clinical and bioengineering applications involve complex media like blood, urine, and cell culture media that require superior antifouling properties to avoid and minimize undesired non-specific adsorptions and the potential of false-positive results (López-Muñoz et al., 2022; Mughal et al., 2022).

Physical adsorption. Is the most straightforward approach to attaching the bioreceptor to the sensor surface in which the biomolecules are attached to the surface through van Der Waals forces, hydrogen bonding, and hydrophobic interactions. It is usually done by immersing the electrode surface into the biomolecule solution, followed by a fixed incubation period (Sandhyarani, 2019). This scheme is used in solid-based assays, such as enzyme-linked immunoassay (ELISA). However, despite being a simple and cost-effective method with high scalability and multiplexed potential, it suffers from important drawbacks. Changes in the pH or buffer composition can lead to reproducibility and stability problems, causing denaturation, unfolding, or loss, affecting the recognition activity of the bioreceptor molecules (Sandhyarani, 2019).

Covalent binding. SAMs are the most widely used method for biomolecule immobilization in plasmonic sensors thanks to their ability to control surface properties such as surface charge, morphology, and grafting density (Soler and Lechuga, 2022). SAMs generate a densely packed and highly ordered hydrophilic layer on the sensor surface, displaying reactive functional groups in the scaffold, which can be later used to covalently bound the bioreceptor (but randomly oriented) by cross-linking, i.e., by amine–amine binding (Soler and Lechuga, 2022). The disadvantages of using self-assembled monolayers are the complexity of fixing the optimal cross-linking parameters (each bioreceptor has optimal attachment conditions) and the alkanethiol chain's density, composition, and length can highly affect cross-linking (mainly by potential steric hindrance effects) (Peláez Gutiérrez, 2021). The last makes SAMs not scalable for multiplexed biosensing.

Bioaffinity-based immobilization. It can be used as an alternative when the covalent method results in a damaged or unsuitable ligand activity. A capture molecule with high affinity for the ligand is covalently immobilized on the sensor surface, which subsequently contributes to ligand immobilization, i.e., protein A/G-antibody, steptavidin-biotin, and poly(histidine) tagged molecules are some examples (Hamming and Huskens, 2021; Soler and Lechuga, 2022). The bioaffinity-based immobilization is a highly scalable process for multiplexed biosensing. I.e., protein G has well-known antibody attachment conditions, and protein G with thiol groups is commercially available, which allows direct attachment to the metallic surface through the specific interaction between thiol groups of cysteine residues and bare gold (Jeong et al., 2007). The last forms a self-assembled protein G layer, avoiding the time-consuming steps of SAM formation and cross-linking and producing a highly oriented protein-antibody biolayers. However, the main drawback is that the interaction between protein G and antibodies is not covalent and can be disrupted by changes in pH.

3. The bioreceptor

It represents the biosensing interface's core, considering it provides the bioaffinity, selectivity, and specificity of the bioassay. As previously described, biorecognition elements have been used differently over the last few years (Fig. 4). Still, antibodies are the most widely used for this purpose due to their high specific affinity and selectivity,

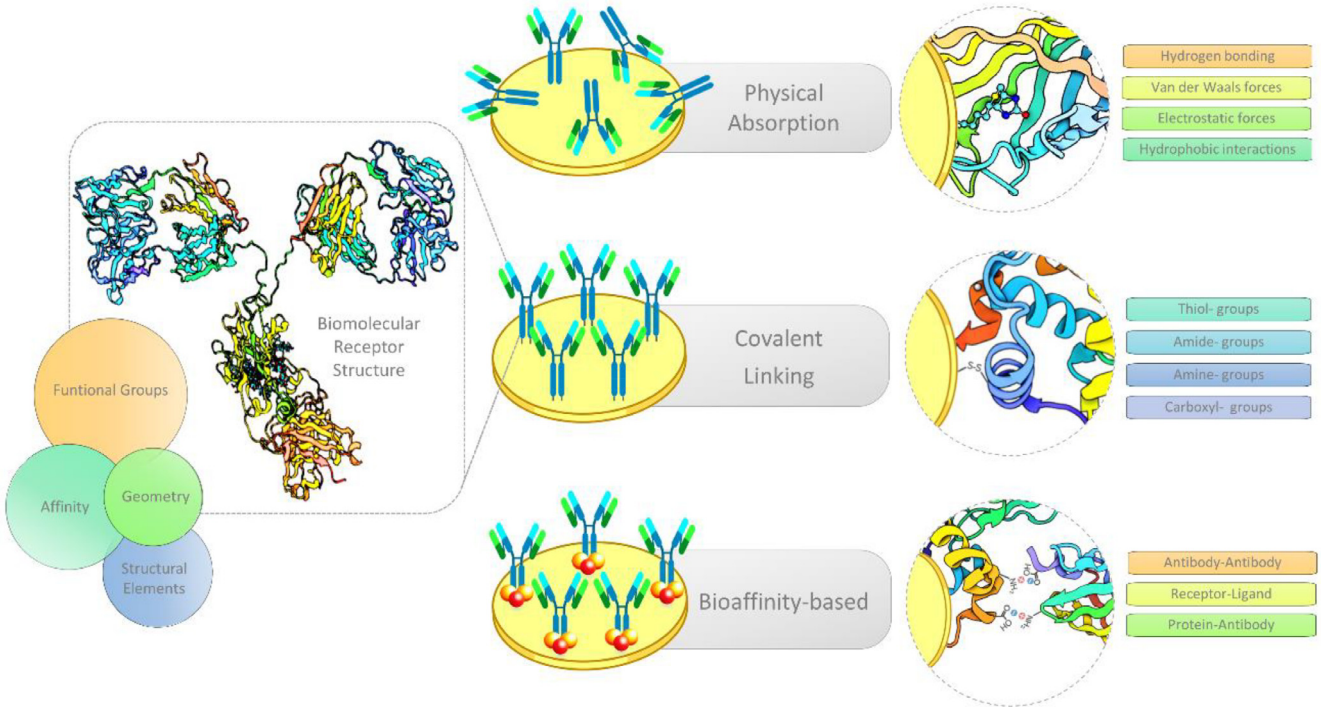

Fig. 3. Immobilization strategies fin plasmonic and metaplasmonic biosensing, the selection of the immobilization strategy must consider the physicochemical characteristics and structure of the bioreceptor. Physical adsorption attaches the bioreceptor to the sensor through van Der Waals forces, hydrogen bonding, and hydrophobic interactions. It only requires physical contact between the biomolecule solution and the sensors' surface. It presents severe drawbacks due to limited reproducibility and stability; pH or sample composition changes can affect the bioassays. Covalent binding usually is performed by SAMs and has the potential to control the surface properties such as surface charge, morphology, and grafting density (Soler and Lechuga, 2022). SAMs allow using different reactive functional groups to create covalent bonds with the bioreceptor by cross-linking strategies. Bioaffinity-based immobilization is based on the natural biochemical interaction between different biomolecules, and one of the biomolecules is used as a ligand or anchor for the bioreceptor. Engineered proteins with specific residues can allow the direct attachment of the ligand or anchor to the sensors' surface. However, the bioreceptor can be detached from the ligand by changes in pH.

together with well-established cross-linking methods based mainly on the reactivity of carboxyl-to-amine reactive groups. On the other hand, other bioreceptors, such as cell receptors, and aptamers, represent other biorecognition candidates with attractive characteristics (Soler and Lechuga, 2022). These new bioreceptors should have superior physicochemical stability, large-scale production, and the potential for direct immobilization in the sensor surface, avoiding cross-linking processes.

Antibodies. They have a well-established production process and represent the most commonly employed bioreceptors, which can be produced towards any analyte at low concentrations with high specificity and selectivity. The antibody-antigen interaction is highly specific; however, the use of antibodies presents limitations. The limitations may include poor solubility, limited thermal stability, and aggregation, which can lose their recognition activity under aggressive conditions (Bhattarai and Hameed, 2020). Antibodies have antigen binding sites exclusively located on the Fab regions; a proper orientation is essential for exposing the binding sites toward the analyte to maximize capture efficiency and sensitivity (Soler et al., 2019).

Bioengineered antibodies. They can have well-defined attachment points with biotin or thiol points for linkage compared to conventional antibodies. They can also be engineered with positively charged amino acids (i.e., arginine) in the peptide linker; or a 6-histidine amino acid sequence on the C-terminus for immobilization via electrostatic and non-covalent interactions, respectively. These engineering modifications make bioengineered antibodies an excellent substitute for naturally generated antibodies within biosensing systems. They present several desirable characteristics, like low molecular weight, increased flexibility, high physicochemical stability, and easy access to the antigen (Sharma et al., 2016).

DNA strands. They have the potential to detect direct hybridization between synthetic DNA probes with a complementary sequence. DNA strands can be engineered to incorporate specific functionalities like fluorophores or other molecules that can allow multiple detection schemes and be large-scale synthesized. DNA strand-based biosensors present advantages like high thermal tolerance, easy modification, and efficient surface regeneration due to their stable chemistry. Functional DNA strand-based biosensors mainly consist of DNAzyme biosensors and DNA aptamer biosensors, resulting in a powerful alternative to traditional bioprobes due to their high stability, adjustable affinity, and selectivity to various targets (Hua et al., 2022).

Aptamers. They are defined as a stretch of single-stranded DNA (ssDNA) or RNA (ssRNA) of 25 to 90 bases in length. They can be chemically synthesized by the Systematic Evolution Of Ligands by Exponential Enrichment (SELEX) to bind to a specific target (including ions, small molecules, proteins, and whole cells) (Seo and Gu, 2017). Thanks to their tendency to form helices and loops, they are highly versatile and bind targets with high selectivity and specificity. Aptamers have a small size, high stability, and outstanding performance in complex media. Aptamers have several advantages over antibodies as they have a lower molecular weight and size (<10 kDa), are easier to generate in the laboratory, are very cost-effective, and have long-term stability, high binding affinity, specificity, and reliability (Luka et al., 2015).

Peptide and Peptide Aptamers. Peptides are amino acid sequences which are linked via peptide bonds with shorter lengths than those of proteins. Depending on the peptide sequence, the structure and interaction capacity of peptides can be manipulated and modulated for biosensing. They present advantages such as well stablished synthesis protocols, accessibility, easy modification, and

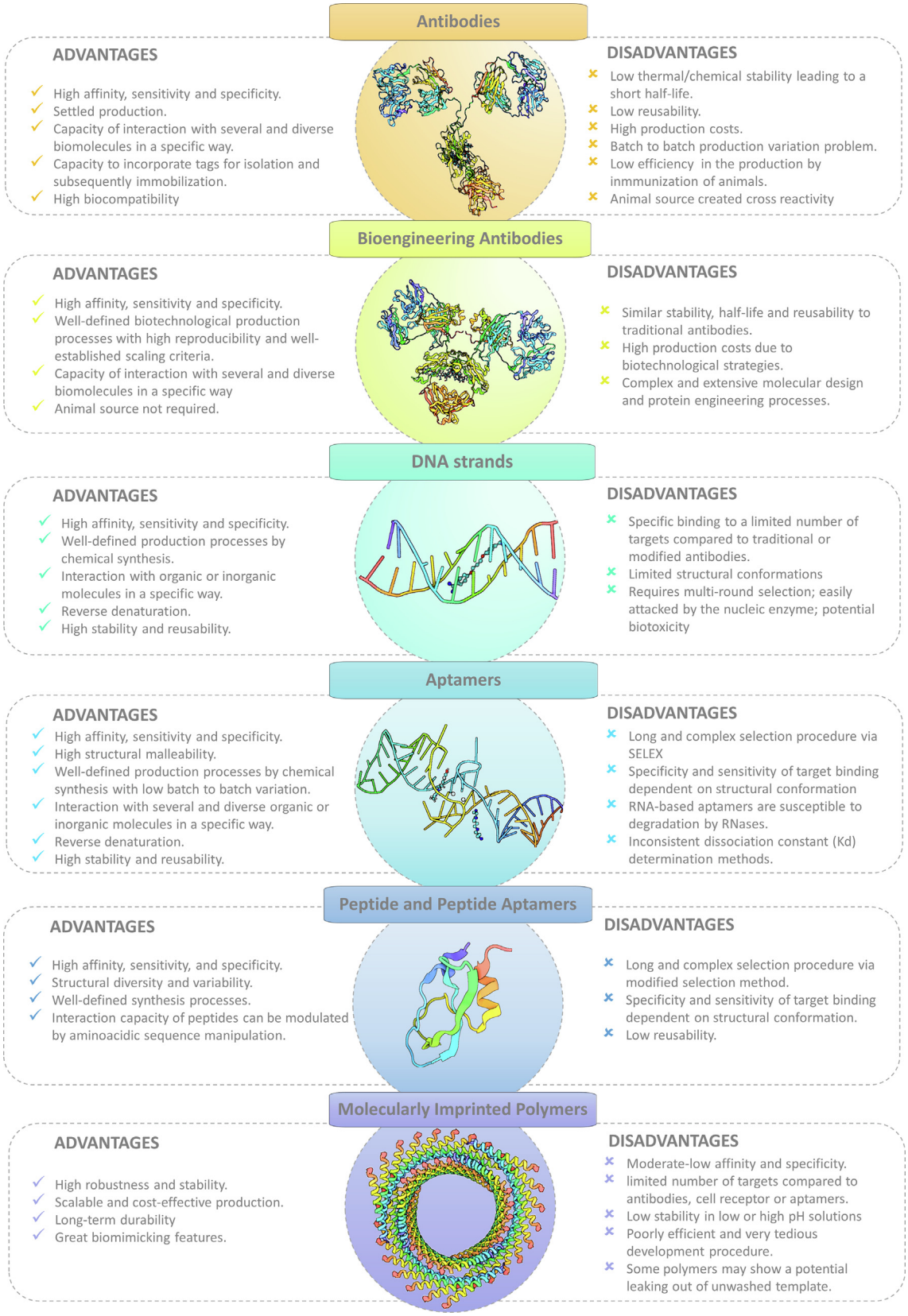

Fig. 4. Advantages and disadvantages of different reported bioreceptors for plasmonic and metaplasmonic biosensing.

high selectivity (Karimzadeh et al., 2018). There is a group of peptides called peptide aptamers. Specifically, it refers to small, artificial polypeptide sequences extending between 5 and 20 amino acids with specific bind affinity to given target biomolecule. The typical structure of peptide aptamers is a short loop inserted within a scaffold protein (Acquah et al., 2020). The short peptide region is responsible for binding with its target molecule to be detected and the scaffold protein helps to improve the binding affinity and specificity by maintaining

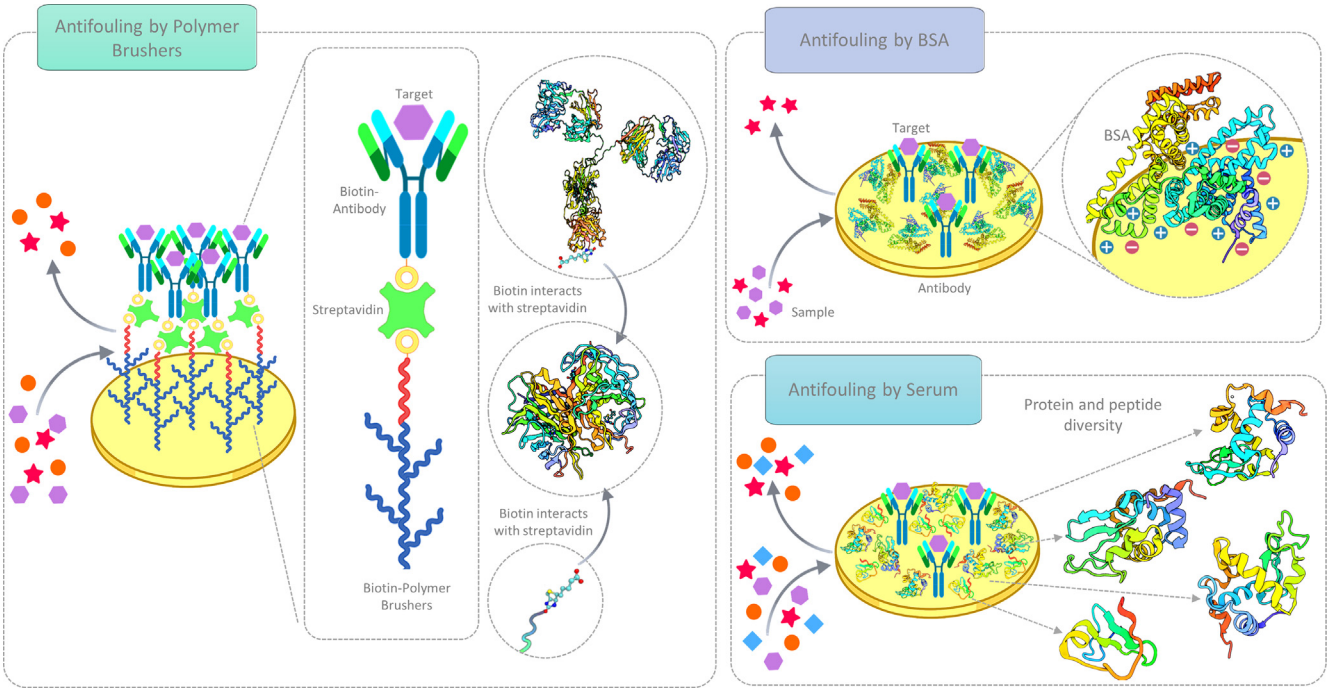

Fig. 5. Main surface antifouling strategies used in plasmonic and metaplasmonic biosensing. Polymer brushes are a highly attractive solution with superior antifouling properties and the potential to add multiple functional groups or other molecules. However, the approaches based on creating polymer brushes-based SAM have drawbacks that must be considered. I.e., the decrease of biosensing performance with the height of the final biointerfaces due to the inherent exponential decay of the evanescent field and the identical drawback present in SAMs in the complexity of fixing the optimal cross-linking parameters is present (Kotlarek et al., 2019). Proteins represent a fast and straightforward antifouling strategy. Proteins like BSA or casein have been widely used in ELISA and plasmonic and metaplasmonic materials to minimize non-specific adsorptions in complex samples by filling unreacted sites after a cross-linking process or by blocking hydrophobic and electrostatic interactions with the sensor surface. However, whole serum is an effective antifouling strategy considering its high molecular diversity. It can effectively block hydrophilic, hydrophobic, and electrostatic non-specific adsorptions while minimizing cross-reactivity with mammalian bioreceptors when using fish or chicken serum.

and conserving the structural conformation of the binding peptide. This association allows peptide aptamers to bind to their target proteins with high affinity and high specificity (Acquah et al., 2020).

Molecularly imprinted polymers (MIPs). They are templated synthetic polymers designed to selectively bind the target biomolecule using a "lock-key" mechanism (Soler and Lechuga, 2022). The polymerization strategies allow the imprinting of various biomolecules ranging from aminoacids to whole proteins. Considering their synthesis is based on a polymerization strategy (which involves a careful selection of solvents, monomers, cross-linkers, and initiators), they are considered "plastic antibodies" with high-throughput fabrication processes, high stability, and reproducibility (Parisi et al., 2021). Considering their high robustness, they are highly attractive for remote biosensing and biosensing under harsh conditions (Soler and Lechuga, 2022). However, there are still challenges in terms of bioaffinity and specificity in comparison to conventional antibodies.

4. Antifouling strategies

Several biosensing applications (i.e., POC devices, OOC and cell monitoring) require using a complex matrix with several components (i.e., aminoacids, proteins, glucose, and cells). Consequently, the reduction of non-specific bindings is necessary to avoid false-positive results and cross-reactivity in the bioassay. Complex matrices present different types of potential non-specific bindings (i.e., electrostatic, hydrophobic, hydrophilic). As a consequence, it is desirable a biointerface with board antifouling properties (Mughal et al., 2022; Soler and Lechuga, 2022). Between the different antifouling strategies used in metaplasmonic biosensing, there have been described two main strategies the use of i) hydrophilic compounds (also called polymer brushes) and ii) proteins: single proteins like bovine serum albumin (BSA), casein or gelatin, or whole serum to have molecularly diverse passivation. Whole serum from other species, like chicken and fish, minimizes cross-reactivity with mammalian-based bioreceptors (Fig. 5).

Polymer brushes. They are macromolecular structures with polymer chains densely tethered to another or a surface; these chains change the surface's properties and present antifouling properties. Pegylated-based polymer brushes have been widely described in plasmonic biosensing (Peláez Gutiérrez, 2021). Poly(L-lysine)-grafted-poly (ethylene glycol) (PLL-g-PEG) is a well-known pegylated polymer brush with high hydrophilicity and protein absorption resistance (Feng and Huang, 2018). PLL-g-PEG represents a highly scalable antifouling strategy, considering it can be incorporated later without interfering with the biorecognition element attachment process. Moreover, PLL-g-PEG does not affect the density and height of the biorecognition layer compared to a polymer brush self-assembled monolayer (Peláez Gutiérrez, 2021). Consequently, it provides antifouling properties to the plasmonic metasurfaces while maintaining biorecognition performance.

Proteins. BSA and other proteins like casein have been widely used for surface passivation coatings on bulk and nanostructure surfaces by minimizing any hydrophobic and electrostatic attractions between the complex surface and the functionalized surface (Peláez Gutiérrez, 2021). BSA molecules noncovalently adsorb and form a protein monolayer coating. The coating performance is sensitive to environmental parameters such as pH and ionic strength. On the other hand, the whole serum has a high molecular diversity. Consequently, it effectively blocks different non-specific biomolecule-surface/covalent and protein–protein interactions. The last makes it an excellent antifouling choice; however, the potential for cross-reactivity with protein A and anti-Immunoglobulin G (anti-IgG) antibodies exists. Consequently,

using whole serum from different species (fish or chicken serum) is recommended to avoid cross-reactivity while retaining the blocking properties with mixed characteristics (Frutiger et al., 2021).

5. Conclusion and perspective

Metaplasmonic biosensors represent a highly attractive class of optical biosensors for direct, label-free, sensitive, and multiplexed biosensing. As recently proposed, glancing angle deposition and thermal dewetting are two lithography-free fabrication strategies based on the nano-patterning/sculpting of thin films, which can allow the development of high-throughput and scalable quasi-ordered metaplasmonic materials for biosensing (López-Muñoz et al., 2022). The last by surpassing the main limitation of conventional top-down nanofabrication strategies (i.e., nanostencil, nanoimprint, and electron beam lithography): a master nano-mold/pattern is required to transfer metasurfaces with an associated high cost (López-Muñoz et al., 2022). Although the main associated cost in developing metaplasmonic biosensors is related to the nanofabrication processes, the cost associated with the bioreceptors development and the biointerfaces and microfluidic costs has to be considered. A deep synergy between all the elements must be performed to balance development cost and performance in view of potential market applications.

Regarding the biointerfaces, we consider that using engineered, modified biorecognition elements with the potential for direct attachment to gold surfaces by thiol chemistry can drastically reduce the developing time and efforts (which finally involves associated human resources and materials costs) to find the optimal binding conditions. The last can maximize the biosensing performance and allow "modular" biointerfaces with a direct attachment of biorecognition elements to the sensor surface to achieve multiplexed biosensing. Finally, considering the antifouling surfaces, a combination of pegylated polymer brushes (PLL-g-PEG) with a mixture of proteins different from the host specie (i.e., chicken serum) is the most simple, practical, and scalable approach to achieve antifouling properties. The last will cover a wide diversity of non-specific absorptions while avoiding cross-reactivity problems. As we can observe, there is a broad and highly potential field of research in biointerfaces, requiring interdisciplinary work between physics, materials science, and biotechnology.

CRediT authorship contribution statement

María J. Ugarte-Orozco: Writing – original draft, Visualization. **Gerardo A. López-Muñoz:** Conceptualization, Writing – original draft, Writing – review & editing, Supervision, Funding acquisition. **Aurora Antonio-Pérez:** Writing – original draft, Visualization. **Karla M. Esquivel-Ortiz:** Writing – original draft, Visualization. **Javier Ramón-Azcón:** Writing – review & editing, Supervision, Funding acquisition.

Data availability

No data was used for the research described in the article.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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