A Review of Emerging Nanophotonic Biosensors and Their Expanding Applications

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Abstract
Over this time, biomedicine has benefited greatly from the penetration of nanotechnology, which has solved several issues and improved illness diagnosis and treatment. Early, quick, and accurate disease identification is an essential need in the field of biomedicine, as it is the first step in effectively addressing different ailments. Nanophotonics is the study of how light and matter interacts at the nanoscale. Nanomaterials have greatly enhanced the techniques used to identify and analyze biomolecules. The examples cited above include plasmonic nanomaterials, waveguides, substrates used for surface-enhanced Raman spectroscopy (SERS), and bright materials, among other things. Multiple strategies can be used together to enable multimodal sensing. Enhancing the specificity of biosensors can be achieved by modifying the surface of nanoparticles with chemicals that are specific to the analyte. High sensitivity, high precision, multiplexing power, and portability will be achieved in the detecting sector by the application of nanophotonic techniques. Förster resonance energy transfer (FRET), usually referred to as fluorescence resonance energy transfer, and is a widely used technique in the field of molecular sensing. Evanescent wave biosensors facilitate the identification of biomolecules without the necessity of labeling. Evanescent-field biosensors may detect biomolecules on the sensor surface in real-time by measuring changes in refractive index. The aforementioned treatment offers a rapid, non-intrusive, and straightforward method for identifying illnesses. Fluorescent nanoparticles provide a practical method for detecting biomolecules. Various materials have been generated in connection with this issue. Surface-enhanced Raman scattering (SERS) techniques can also be used for disease diagnostics.
Keywords-Nanophotonics, plasmonic nanomaterials, biomolecules, biosensors, biomedicine.

Introduction

Biosensors play a pivotal role in a multitude of sectors, spanning from healthcare to food safety, offering indispensable contributions to various facets of modern life. Among these, diagnostic technologies stand out as the cornerstone of the biosensor market, significantly influencing approximately 70% of medical decisions[1]. Despite the sensitivity of conventional methods such as labelled immunoassays, their cumbersome nature involving high costs and time-consuming procedures poses substantial challenges. On the other hand, lateral-flow assays (LFAs), reminiscent of ubiquitous home pregnancy tests, provide rapid results but often sacrifice sensitivity, limiting their utility in certain diagnostic contexts[2-3].The advent of rapid, user-friendly biosensor technologies holds the promise of revolutionizing disease management paradigms, particularly by enabling early diagnosis, a critical determinant in conditions like cancer where timely intervention profoundly impacts outcomes[5-8]. Envisioned applications extend beyond individual healthcare settings to encompass wearable biosensors seamlessly integrated into everyday life and public infrastructure, fostering both personal and public safety. However, the envisioned ubiquity of biosensors also entails the generation of vast datasets, necessitating advanced artificial intelligence (AI)

algorithms for efficient processing and interpretation[9-13].In this landscape of innovation, nanophotonic biosensors emerge as a beacon of promise, particularly in their label-free optical configurations. These cutting-edge technologies, leveraging the principles of nanophotonics, hold the potential to overcome existing limitations and usher in a new era of biosensing capabilities. Yet, they are not without their challenges, as the development and widespread adoption of nanophotonic biosensors necessitate addressing various technical hurdles and ensuring seamless integration into real-world applications. Despite these obstacles, the transformative potential of nanophotonic biosensors in revolutionizing healthcare, safety, and beyond underscores their significance as a frontier of scientific exploration and technological advancement[14-15].

- **Evanescent – field-based nanophotonic biosensors**

Optical affinity biosensors represent a sophisticated class of analytical tools designed to interact with specific target molecules, or analytes, using biomolecular receptors. By exploiting the intricate molecular recognition mechanisms of these receptors, these biosensors translate such interactions into measurable outputs via optical means. Evanescent-field-based photonic biosensors, typified by technologies like surface plasmon resonance (SPR), navigate the intricacies of probing analytes with light while preserving a crucial separation from the sample under examination[16-17]. This separation ensures that the optical interrogation does not interfere with the integrity of the sample, maintaining its pristine condition for further analysis. In stark contrast to conventional sensor designs, nanophotonic structures offer a revolutionary approach by confining light tightly in close proximity to their surface[18-20]. This tight confinement creates an environment where the interactions between light and analyte become significantly intensified, leading to enhanced sensitivity and a marked reduction in background interference. Functioning akin to miniature optical 'nanoantennas,' [21]these structures elevate the intensities of localized fields, amplifying the signals generated by analyte interactions. Furthermore, the resonance properties of nanophotonic structures can be finely tuned through meticulous control over nanostructure design parameters. This precision engineering empowers researchers to tailor the sensor's response characteristics with unparalleled accuracy, thus offering a pathway towards the realization of highly customizable and versatile biosensing platforms[22-25].

- **Affinity biosensors based on plasmonic nanostructures**

In the early 2000s, nanoplasmonic biosensors emerged as an alternative to conventional SPR biosensors. These biosensors utilize surface plasmons supported by metal nanostructures, with the first generation based on localized surface plasmons (LSPs) excited on metal nanoparticles (NPs)[26]. LSPs have a decay length typically ranging from 5 to 25nm, significantly shorter than conventional plasmons. Plasmonic NPs absorb and scatter incident light, with sensitivity increasing with NP size and resonance wavelength[27-29]. Various NP shapes have been explored to enhance sensitivity[30-35].Detection methods include total internal reflection microscopy and dark-field microscopy. Ordered groups of NPs, such as arrays of nanodisks or nanoholes, exhibit Fano resonances, dramatically reducing linewidths. Nanohole arrays, for instance, demonstrate extraordinary optical transmission[36-39]. Arrays combined with spectroscopic imaging enable real-time analysis, including affinity measurements and cell therapy applications. Plasmonic surface lattice resonances, observed with gold NPs on glass substrates, offer high sensitivity for biomolecule detection. For instance, gold-capped mushroom-shaped structures achieved detection of cytochrome c and alpha-fetoprotein at low concentrations[40-44].Nanoplasmonic biosensorshave seen limited use in studying biomolecular interactions, but they have been extensively explored for bioanalytical purposes, particularly in medical applications for detecting protein and nucleic acid disease biomarkers. These biosensors typically achieve limits of detection ranging from 1 pg/ml to 100 ng/ml for proteins and from 100 fM to 10 nM for nucleic acids. However, most studies focus on analyte detection in simple solutions rather than complex biofluid matrices due to several challenges.Firstly, there's a lack of straightforward and robust functionalization methods to resist non-specific binding from interfering substances in complex matrices. Secondly, cost-effective fabrication of large batches of nanostructures is needed to optimize surface functionalization and detection assays. Finally, there's a limited level of device integration, with most studies focusing on individual biosensor elements rather than the system as a whole[45-48].Side-by-side comparisons of different nanophotonic biosensors or different types of biosensors are rare in studies. One such comparison was conducted by Špačková et al., who investigated plasmonic biosensors based on randomly distributed gold nanorods with varying fill fractions compared to conventional SPR biosensors[49]. They found that biosensor performance relies on both optical and mass transport characteristics of plasmonic nanostructures, with optimized

nanostructures enabling detection of analytes at concentrations an order of magnitude lower than conventional SPR biosensors. However, indirect comparisons of nanoplasmonic affinity biosensors should be approached cautiously due to diverse experimental conditions and methodologies for determining limits of detection[50,51].Despite these challenges, the number of studies focusing on clinical applications of plasmonic biosensors has increased[52,53]. For instance, Yuan et al. utilized an LSP biosensor based on silver NPs to detect human epididymis secretory protein 4 in blood samples from ovarian cancer patients with a LOD of 4pM[54]. Chen et al. developed an integrated LSP-based biosensor platform combining a gold nanorod microarray with microfluidics, achieving parallel multiplex immunoassays detecting six cytokines in serum with a LOD <20pg/ml[55]. They observed strong correlation with commercial enzyme-linked immunosorbent assays and demonstrated measurement of elevated cytokine levels, particularly interleukin-6 (IL-6) and IL-10, in samples from neonates who underwent cardiopulmonary bypass surgery for congenital heart disease.It's important to note that the limit of detection is a complex metric influenced by various factors such as nanostructure, optical reader, microfluidics, biofunctionalization layer, and assay configuration. Assessing the contribution of each element to analytical performance can be challenging, as improvements in sensing characteristics of plasmonic nanostructures may be offset by low affinity of immobilized receptors, for instance.

1. Affinity biosensors based on resonant dielectric nanostructures

Plasmonic nanostructures based on coinage metals have limitations, including a narrow spectral range and issues like loss[56], instability at high temperatures, and poor compatibility with CMOS processes. Transition metal nitrides, transparent conductive oxides, metal sulfides, and doped oxides are being explored as alternatives for refractometric biosensing and surface-enhanced spectroscopy. Another approach uses high-index dielectric nanostructures, offering low optical absorption, high quality factor resonances, and reduced heat generation. While dielectric resonators exhibit lower field enhancement than plasmonics[57,58], they show minimal quenching and have been used for refractometric sensing for decades. Whispering-gallery modes in microstructures like silica or silicon exhibit very high Q values, while nanometric slots offer additional field enhancement[59]. Dielectric nanostructures offer more modest Q values but allow broadband operation under low-loss conditions. Various parameters like Q and near-field enhancement influence sensitivity, requiring careful consideration of trade-offs. Despite smaller wavelength shifts compared to plasmonics, dielectric resonators have shown promise in detecting analytes, achieving low limits of detection in experimental setups[60,61]. However, their application to clinical samples remains to be demonstrated.To enhance the refractive index sensitivity of nanoscale dielectric resonators, researchers have developed methods to reduce radiative coupling, resulting in narrower resonance linewidths. However, this often leads to a narrower operating bandwidth[62-65]. For instance, Yang et al. achieved a low-loss silicon metasurface with a high Q value of ~500[66] using Fano-type resonances, comparable to plasmonic values. By utilizing coherent coupling among numerous unit cells, they achieved sharper resonances. Another approach involved using a silicon oligomer to achieve lower Q values (~35) with enhanced sensitivity parameters. While high-Q metasurfaces can be achieved through coherent coupling, they may sacrifice spatial resolution. Studies on arrays of silicon nanoresonators showed contributions of lowest-order electric and magnetic Mie modes to detection sensitivity. Breaking the in-plane symmetry of unit cells in dielectric metasurfaces can generate quasi-BIC modes with very high Q values. These metasurfaces have been optimized for hyperspectral imaging, achieving high sensitivity and enabling multiplexed detection at the diffraction limit. Additionally, diatomic meta-units in dielectric metasurfaces have been utilized for real-time detection of extracellular vesicle-binding events at very low concentrations[67-71].

2. Nanophotonic biosensors based on surface-enhanced spectroscopies

Affinity biosensors based on nanostructured metals or dielectrics rely solely on the characteristics of receptors, which may not be universally available for all analytes. Vibrational spectroscopies, such as infrared absorption and Raman scattering, can complement refractometric biosensors by offering selectivity without requiring analyte-specific receptors, while also providing insights into molecular structure. These methods probe molecular vibrations, revealing unique 'fingerprints' and conformational details without the need for external labels. However, applying vibrational spectroscopies to small-volume biological samples faces challenges due to their relatively low sensitivity. Molecular absorption cross-sections for infrared spectra are typically around 10–20 cm2 per molecule, while non-resonant Raman scattering cross-sections range from about 10–31 to 10–29 cm2 per molecule, limiting signal levels for accurate analysis. Additionally, the strong absorption of mid-infrared

radiation in water can obscure analyte signals, posing an extra challenge for biosensing in aqueous environments.Nanophotonic structures enhance analyte signals through surface-enhancement mechanisms like SEIRA[72,73] and SERS[74-76]. SERS, for instance, can boost Raman signals by up to ten orders of magnitude, sparking significant interest in understanding this enhancement, especially with the observation of single-molecule SERS from plasmonic hot spots[77,78]. Researchers have developed various SERS substrates using both top-down and bottom-up approaches[79-81], with noble metals being predominant. However, resonant dielectric nanostructures and metasurfaces are emerging as promising alternatives due to lower absorption losses, CMOS compatibility, and higher robustness. Studies have demonstrated SERS with resonant dielectric structures like silicon disk dimers, which generate less heat compared to metals, and have been utilized for detecting molecules like β-carotenal[82]. These structures offer advantages such as reduced heat generation, enabling easier surface functionalization and potentially serving as valuable complements to metallic SERS substrates for affinity biosensing and bioanalytical applications.

SEIRA signals can be enhanced by optimizing near fields using plasmonic antennas with nanoscale gaps, leveraging the 'lightning rod effect'[83]. For instance, Dong et al. designed a bowtie-shaped gold structure with a <3nm gap, achieving nearly seven orders of magnitude SEIRA signal enhancement[84]. They demonstrated detection sensitivity down to ~500 molecules with a commercial Fourier transform infrared spectrometer. John-Herpin et al. utilized grating-order-coupled plasmonic nanogap antenna arrays to detect proteins at very low concentrations, down to 100pg/ml for chemically specific detection[85]. Etezadi et al. applied SEIRA for real-time secondary structure analysis of proteins, showing potential for disease-related protein studies[86]. Alternative SEIRA substrate materials, including dielectric nanostructures and van der Waals materials[87-90], have also been explored, promising broader applicability. Continual advancements in mid-infrared laser sources[91], detectors, and low-loss waveguides[92] show promise for building hybrid waveguide–integrated SEIRA platforms[93].

While vibrational spectroscopy covers a wide spectral range, many nanophotonic substrates rely on single-resonant antennas with narrow bandwidths. To address this, broadband metasurfaces based on multiresonant antennas have been developed. Aouani et al. demonstrated multispectral SEIRA spectroscopy using a log-periodic trapezoidal nanoantenna, achieving high enhancement factors over a spectral window of 3μm[94]. Rodrigo et al. showed a self-similar multiperiodic nanorod antenna array supporting four independently controlled resonances over an ultrawide spectral range from 1.5 to 10μm[95]. These designs enable spectroscopic resolution of biomimetic interactions and cargo release dynamics. Challenges remain in simultaneously detecting various analytes with overlapping vibrational bands. Chemometric analysis, particularly using machine learning algorithms, is anticipated to play a crucial role in exploiting spectral information for discriminating individual analytes in complex biological samples[96-100].

Future perspectives and challenges

The continued development of nanophotonic biosensors for clinical applications necessitates a comprehensive multidisciplinary approach addressing various technical challenges and opportunities in platform development.

a. Optoelectronic integration and miniaturization

Integrated photonic circuits are driving advancements in nanophotonic biosensors, enhancing miniaturization, portability, and throughput. Integration can be vertical or planar. In the vertical scheme, nanostructures simplify light-coupling requirements compared to conventional SPR, enabling miniaturization and multiplexing. Each nanostructure can act as a transducer, expanding throughput capabilities to nanoscale dimensions. However, issues arise with highly absorptive or turbid solutions due to optical loss, interference, and scattering. Planar integration utilizes optical waveguides arranged in a 1D array for multiplexed detection. This configuration allows for higher miniaturization by integrating active and passive optoelectronic components onto a single sensor chip. While most planar sensors still rely on external light sources and detectors, research has shown success in silicon-based integrated sensors utilizing conventional waveguides and optical microresonators. Incorporating subwavelength nanostructures and nanopatterns onto low-loss waveguides shows promise in enhancing sensor performance and leveraging the light-guiding function of waveguides. Recent advancements include the fabrication of nanoplasmonic structures onto waveguides to control spectra and increase sensitivity for various applications such as refractometric methods, SERS, and SEIRA[101-108].

b. Cost-effectiveness

To mitigate cross-contamination and complex cleaning procedures, inexpensive disposable biosensor chips are favored. Integration schemes allowing single-use cartridges and stand-alone readers are practical

solutions. For instance, the nanophotonic biochip can be housed in a cartridge, separated from the light source and detector, enabling customized consumables for detecting various analytes with the same reader. This approach optimizes reader costs by utilizing off-the-shelf optoelectronic components and avoids performance degradation associated with multiuse biosensor formats.However, it requires careful consideration of biomaterial costs for producing inexpensive single-use cartridges. There's a trend toward merging nanophotonic biosensors with smartphones to reduce costs and enable large-scale distribution. Such sensors can measure signals from patient samples, analyze data with personalized apps, and transmit results wirelessly to clinicians[101, 102, 109].

Although biosensors with planar integration offer smaller footprints and portability, their cost may be higher for single-use scenarios due to elaborate fabrication processes. Current nanophotonic biochips rely on repeated patterning of engineered nanostructures, often achieved through electron-beam or focused-ion-beam lithography. However, these methods are costly and low throughput, prompting interest in alternative manufacturing approaches for commercialization. Leveraging silicon-compatible manufacturing methods and infrastructure, such as nanoimprinting and interference lithography, holds promise, although challenges remain regarding materials compatibility with front-end CMOS processing. Large-scale and low-cost top-down lithography approaches are expected to gain more attention as alternative manufacturing strategies[110-113].

c. Sample handling.

Microfluidic systems integrate well with biosensors, facilitating sample treatment, concentration, and analyte delivery while minimizing sample volume and reagent consumption. However, slow analyte transport to subwavelength hot spots in nanophotonic biosensors can lead to longer detection times. Efforts to address this challenge include microfluidic components enabling analyte concentration and improved transportation to sensor surfaces, as well as the integration of external lasers and electrical fields. Capillary microfluidics, leveraging surface-tension effects, and digital microfluidics, utilizing electric forces to manipulate microdroplets, offer promising alternatives to bulky external microfluidic components. Metallic nanostructures can serve as electrodes, facilitating the integration of digital microfluidics without pumps or valves[114-120].

Sample collection and processing are critical for on-site biosensing, especially considering the diverse analytes and matrix compositions. While blood is commonly used for biomarker detection, its collection requires separating components and suppressing matrix effects. Sample dilution with a buffer can reduce matrix effects, but concentration may be necessary for detecting scarce analytes. Simpler biofluids like saliva, sweat, tears, or urine, collected non-invasively, are gaining attention for bioanalysis due to their simpler composition[120-124].

d. Surface functionalization

In complex clinical samples like blood plasma and serum, non-specific binding to biosensor surfaces poses a major challenge, as analyte concentrations are typically lower than in buffer solutions. Functionalization methods resistant to non-specific binding while ensuring robust receptor immobilization are urgently needed. Traditional approaches, such as surface treatment with protein blockers or detergents, offer limited resistance in clinical samples. Alternative methods involving polymers like zwitterionic polymers are being explored, but a universal strategy to prevent fouling from complex biological media is lacking. Antifouling coatings in nanophotonic biosensors typically require a minimum thickness, potentially placing immobilized receptors outside hot spots. Small receptors like aptamers and nanobodies are increasingly used to ensure analyte-receptor binding within hot spots. Immobilization is commonly achieved through covalent or streptavidin-biotin binding. While high-affinity receptors are preferred, reversible molecular switches have shown promise for continuous biosensing[125-131].

Nanostructured biochips, unlike conventional biochips with flat surfaces, exhibit uneven sensitivity, demanding new functionalization approaches like material or site-specific methods. For example, Zijlstra et al. reported a site-specific procedure enabling preferential functionalization of gold nanorod tips. Galloway et al. employed a light-assisted functionalization approach using a three-photon absorption process to immobilize proteins in plasmonic dimer hotspots. Tijunelyte et al. described a localized click reaction near gold nanoparticles, with plasmonic tuning of the click chemistry[132-135].

e. Emerging directions

Materials science and fundamental optics advancements drive nanophotonic biosensor progress. 2D quantum materials, hybrid optical materials, and phase-change materials enable active, tunable biochips. For instance, graphene's optoelectronic properties offer dynamic plasmonic resonance control, as seen in Rodrigo et al.'s electrically tunable mid-infrared plasmonic biochemical sensors. The atomic-layer thickness of 2D materials and acoustic graphene

plasmons achieve tight near-field confinements for small-molecule detection. Light generation from graphene, metals, or hybrid nanomaterials with active components like quantum dots could lead to ultracompact, electrically/optically addressable biosensors. Combining optical and non-optical detection techniques on a single platform enables multifunctional biosensors, extracting more information from samples. Nanophotonic biochips can perform refractometric sensing, SERS, SEIRA, and chiral sensing simultaneously. Surface-enhanced luminescence mechanisms with plasmonic and dielectric nanostructures offer promising avenues. Leveraging spectral, temporal, spatial, and polarization degrees of freedom in optics will enhance artificial intelligence utilization. Intelligent biosensors embedded in future digital healthcare systems align with the Internet of things[136-139].

Nanophotonic biosensors demonstrate sensitivity for observing individual molecular binding events, but translating scientific advances into everyday devices requires further multidisciplinary efforts. Exploring nanoscale optical physics for new sensing mechanisms, integrating photonics/optoelectronics, and collaborating with commercial foundries pave the way for miniaturized, inexpensive biosensors. Advanced functional coatings and coupling with microfluidics for sample collection/treatment are essential for reliable analysis in complex biological environments. Mobile, affordable biosensors address modern healthcare, food safety, and environmental monitoring needs, enhancing overall quality of life[140-144].

Conclusion

In conclusion, the exploration of emerging nanophotonic biosensors presents a frontier of innovation with vast potential across diverse applications. Through advancements in materials science and fundamental optics, researchers are pushing the boundaries of sensitivity, miniaturization, and functionality. From 2D quantum materials to hybrid optical structures and phase-change materials, the toolbox for creating active, tunable biochips is expanding rapidly.

These nanophotonic biosensors offer a myriad of applications, from healthcare diagnostics to environmental monitoring and beyond. Their ability to achieve highly sensitive, label-free detection of molecular binding events opens new avenues for early disease diagnosis, drug discovery, and personalized medicine. Furthermore, the integration of optical and non-optical detection techniques enables multifunctionality, empowering researchers to extract rich information from complex samples.

The convergence of nanophotonic biosensors with other technologies, such as microfluidics and artificial intelligence, promises even greater strides in the future. By marrying advanced functional coatings with microfluidic systems, researchers can enhance sample collection and treatment, paving the way for mobile and affordable biosensing solutions. Additionally, leveraging the spectral, temporal, spatial, and polarization degrees of freedom in optics enables intelligent biosensors that can seamlessly integrate into the Internet of Things for real-time monitoring and analysis.As we continue to explore the rich landscape of nanophotonic biosensors, collaborative efforts across disciplines will be essential for translating scientific advances into practical devices for everyday use. By addressing challenges such as non-specific binding, sample handling, and cost-effectiveness, we can unlock the full potential of these remarkable technologies to improve human health, enhance food safety, and safeguard our environment.

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