**Application of hybrid photo-plasmonic interfaces: Insights from the synergy of LSPR and photonic crystal modes for biosensing. applications**

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1. **Introduction**

Label-free optical biosensors have achieved remarkable sensitivity for detecting chemical and biological analytes in recent years[1][2]. Among these, two major platforms stand out: plasmonic sensors and photonic microcavity sensors. Plasmonic biosensors exploit the excitation of surface plasmons in metal nanostructures (often termed optical nanoantennas) to confine light to subwavelength volumes and enhance local electromagnetic fields[1][3]. This approach underpins technologies such as surface plasmon resonance (SPR) for refractive index sensing and localized SPR (LSPR) nanosensors, which have been widely used for biomolecular detection due to their high surface sensitivity[1][2]. On the other hand, photonic microcavity biosensors (e.g., whispering-gallery-mode resonators and ring resonators) trap light in high-Q dielectric cavities, achieving ultra-narrow resonance linewidths that enable detection of minute refractive index changes corresponding to single binding events[4][5]. These photonic devices can detect, for example, single viral particles or molecules by monitoring resonance wavelength shifts[5].

Plasmonic nanostructures are renowned for producing strongly localized electromagnetic “hot spots,” leading to a variety of enhanced optical phenomena. For instance, single-molecule detection via surface-enhanced Raman scattering (SERS) was achieved by leveraging intense plasmonic fields at metal nanostructures[6]. Similarly, nanoantenna arrays have enabled surface-enhanced infrared absorption (SEIRA) spectroscopy of monolayer-thin molecular films[7]. Plasmonic enhancements have also improved photodetection (by concentrating light into nanoscale semiconductor junctions)[8] and boosted fluorescence/emission rates of single emitters[9]. These examples illustrate the unparalleled field concentration offered by plasmonic sensors. Photonic microcavities, in contrast, excel in field storage: their high quality factors (Q) result in long photon lifetimes and sharp resonances. Whispering-gallery mode (WGM) microcavities and other photonic resonators have attained label-free detection of single nanoparticles and biomolecules by translating tiny perturbations into measurable resonance shifts[4][5]. Vollmer and Arnold famously demonstrated single virus detection with a microsphere WGM sensor[5], highlighting the extreme sensitivity of purely photonic approaches.

Despite their successes, each platform has inherent limitations. Plasmonic sensors typically suffer from significant radiative and ohmic losses in metals, leading to broad resonance linewidths (low Q) and limited figures of merit in bulk refractive index sensing[3][10]. In other words, while they strongly confine light, their spectral signals can be shallow or noisy due to damping. Photonic resonators, conversely, can achieve extraordinarily high Q (often 10^5–10^7 or more) and steep resonance shifts, but their mode volumes are relatively large and field confinement is diffraction-limited to the scale of a wavelength[10][11]. This means that a single small biomolecule causes only a weak perturbation to a photonic mode unless it is very close to the resonator surface. There is a trade-off between field localization and spectral sharpness: plasmonic structures provide the former, photonic cavities the latter.

Plasmonic–photonic hybrid biosensors aim to synergistically combine these strengths by integrating metallic nanostructures with dielectric micro- or nanocavities[10][11]. In a hybrid sensor, the plasmonic component generates intense localized fields and amplifies the interaction with analytes, while the photonic component (e.g., a cavity mode) provides optical feedback, narrow linewidth, and efficient signal transduction[11]. Early proof-of-concept of this idea was demonstrated by De Angelis et al. (2008), who integrated plasmonic waveguides with a photonic crystal cavity to detect extremely low concentrations of molecules[11]. Since then, a variety of plasmonic–photonic hybrid architectures have been explored, and they have shown the potential to push detection limits down to single molecules and single nanoparticles, beyond what either approach could achieve alone. This review provides a comprehensive overview of plasmonic–photonic hybrid biosensors. We begin with the fundamental principles of these hybrids and their modes of operation (Section 2). We then survey their biosensing applications (Section 3), ranging from biomolecular assays (3.1) and single-molecule detection (3.2) to the analysis of whole cells and vesicles (3.3). In Section 4, we compare the performance of hybrid sensors against traditional plasmonic-only or photonic-only sensors. Section 5 discusses the remaining challenges and limitations facing this emerging technology. Finally, in Section 6, we offer perspectives on future developments needed to translate plasmonic–photonic hybrid biosensors from the laboratory to real-world applications.

1. Fundamentals and Principles

**Plasmonic and Photonic Resonances:** In a conventional plasmonic biosensor, light excites collective oscillations of free electrons at a metal–dielectric interface, producing a surface plasmon polariton or a localized surface plasmon resonance (LSPR) depending on the geometry. For example, a metal nanoparticle supports an LSPR that greatly enhances the electromagnetic field in its immediate vicinity (within ~10–100 nm of the surface)[1]. Any change in the local refractive index—such as binding of biomolecules to the nanoparticle surface—shifts the LSPR wavelength, providing the basis for sensing[1][12]. The sensitivity of an LSPR sensor is proportional to the fraction of the mode’s energy overlapping with the analyte region, and modern nanostructures (e.g., gold nanorods, nanoholes, and nanopyramids) are engineered to maximize this overlap[1][13]. However, because metals are lossy, these resonances typically have Q-factors on the order of 1–10 (Figure 1). The resonance linewidth (full-width at half-maximum) can be tens of nanometers, which in turn limits the resolution in detecting small wavelength shifts[10]. Various strategies exist to improve plasmonic sensor performance—such as using different metals or shapes, phase-sensitive detection[14], and Fano resonances (discussed below)—but loss remains a fundamental issue.

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AI によって生成されたコンテンツは間違っている可能性があります。Figure 1. Effect of size and shape on LSPR extinction spectrum for various silver nanoprisms and nanodiscs. Adapted from [1]

Photonic resonator sensors operate on a different principle: they confine light via constructive interference in dielectric structures. A whispering-gallery mode (WGM) microcavity, for instance, traps light by total internal reflection around a circular cavity (like a microsphere or microtoroid)[4]. The resonance condition is extremely sensitive to the optical path length; binding of biomolecules to the cavity surface or a change in bulk solution refractive index will shift the resonance wavelength. Unlike plasmonic modes, photonic cavity modes can have very high Q (narrow linewidth) because dielectric materials like silica have low absorption at the operating wavelength. Resonators such as high-order ring resonators, microspheres, microdisk cavities, and photonic crystal cavities have all been used for biosensing[15]. A photonic crystal (PC) cavity, for example, can be formed by a defect in a periodic dielectric structure that localizes light in a tiny volume (on the order of a cubic wavelength) while still achieving Q-factors in the 10^4–10^6 range[15]. The small modal volume and high Q yield a large Purcell factor (enhancement of light–matter interaction), which is beneficial for sensing. That said, even a cubic-wavelength mode volume (~(λ/n)^3) is much larger than the volume of a single small molecule, so photonic sensors often struggle to detect single molecules without some form of signal amplification.

**Hybrid Resonances:** By coupling a plasmonic nanostructure with a photonic cavity, one effectively creates a hybrid mode that inherits characteristics of both constituents. The plasmonic element (metal nanoparticle, nanorod, metal film, etc.) provides an intense, localized near-field, while the photonic element (WGM or PC mode, or even a Fabry–Pérot cavity) provides a long-lived resonance to interrogate that near-field[10][16]. From a coupled-mode theory perspective, the hybrid system can be viewed as two oscillators (one lossy, one high-Q) interacting via near-field coupling[16]. When properly tuned, the interaction can produce a resonant enhancement: the photonic cavity feeds back energy into the plasmon, sustaining its oscillation longer, and the plasmon in turn concentrates more field into the cavity’s evanescent sensing volume[16]. This feedback can dramatically boost the local field intensity in the region where analytes reside, compared to either the stand-alone plasmon or cavity (Figure 2). Liu et al. showed that coupling a modest-Q photonic crystal resonance with a gold nanoantenna yielded an order-of-magnitude stronger field at the nanoparticle “hot spot” than achieved by a high-Q cavity or the nanoparticle alone[16]. Such enhancements directly translate to larger optical signals (e.g., greater resonance shifts or intensity changes upon analyte binding), thereby improving the sensor’s detection limit.

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AI によって生成されたコンテンツは間違っている可能性があります。Figure 2. The regime of plasmonic–photonic cooperative coupling with the AuNR–PCGR hybrid system. Far-field reflectance (A) and average near-field intensity on the AuNR surface ⟨|E|^2⟩ (B) are shown as a function of wavelength at θ\_inc = 0° for hybrids with different AuNR orientations (red and blue curves), a bare PC slab (gray), and a solitary AuNR on bulk TiO₂ (orange in B). Panels C–F show simulated surface distributions (C,D) and cross-sectional field slices (E,F) through the middle of the AuNR for two hybrid configurations. Adapted from [16].

There are several configurations of plasmonic–photonic hybrids, each with its own mode structure. One common design is a plasmonic nanoparticle or nanorod attached to the surface of a WGM microcavity[17][18]. The nanoparticle’s LSPR interacts with the evanescent field of the WGM that circulates just inside the cavity surface. In this configuration, the hybrid mode often manifests as a Fano resonance or a slight splitting in the cavity transmission spectrum when the plasmon is resonant, indicating interference between the broad plasmon and narrow cavity mode[19]. Another architecture involves incorporating metal nanostructures into photonic crystal cavities or waveguides. For example, gold nanorods or nanoshells can be placed in the holes or interstices of a dielectric photonic crystal slab[20]. The photonic crystal provides a high-Q guided-mode resonance (or defect cavity mode), and the metal nanostructures introduce LSPR peaks that hybridize with the photonic band-edge modes[16][20]. A planar Fabry–Pérot (FP) cavity can also be used: a metal–dielectric–metal stack or a dielectric cavity with a metallic nanostructure inside can couple FP resonances with plasmons[16]. Choi et al. demonstrated a simpler variant by coating a dielectric ring resonator with a thin gold film, effectively coupling SPR and WGM in a planar geometry[21]. Each of these designs seeks to maximize the overlap between the plasmonic near-field and the photonic cavity field while minimizing additional loss.

**Key Parameters:** For hybrid sensors, an important figure of merit is the cooperativity or coupling strength between the plasmonic and photonic elements[16]. Strong coupling can lead to normal-mode splitting (where two new hybrid eigenmodes form, each with some characteristics of both resonators), whereas intermediate coupling can produce an asymmetric Fano line shape with an enhanced sensitivity at the steep spectral edge[19][22]. In sensing applications, complete strong coupling (Rabi splitting much larger than linewidths) is usually not desired, as it may split the signal and complicate readout. Instead, a highly cooperative but not fully hybridized regime is optimal[16]. In this regime, the energy exchange between plasmon and cavity is efficient enough to boost the field intensity dramatically, but not so strong as to totally suppress one resonance or waste energy in destructive interference. Achieving this balance often requires tuning the resonant wavelengths and damping rates: the plasmon’s resonance should be close to the cavity resonance, and the cavity Q should be chosen such that its photon lifetime is comparable to the plasmon’s damping time[16]. If the cavity Q is too high (very narrow line) and the plasmon is too lossy, the plasmon’s broad spectrum will merely perturb the cavity slightly (weak coupling). If the plasmon is too strong, it can introduce excessive loss into the cavity, collapsing the Q and broadening the hybrid mode so much that sensitivity gains are lost[16][19]. Researchers often use temporal coupled-mode theory or full-wave simulations to design hybrids that maximize the light–matter interaction factor (overlap of fields with analyte) while maintaining a reasonably sharp resonance for readout[16][23].

**Examples of Hybrid Modes:** To illustrate, consider a recent design by Kawasaki et al.: they coupled gold nanorods to a TiO₂ photonic crystal slab resonance[20]. The gold nanorods (plasmon antennas) had a longitudinal LSPR tuned to the vicinity of the PC’s guided-mode resonance. At optimal coupling, the hybrid mode showed an intense localized field at the nanorod with a moderately high Q resonance tail provided by the PC slab[20]. Another example is the work of Dantham et al.: by attaching a 60-nm gold nanoparticle to a silica microtoroid, they effectively formed a plasmonic–photonic hybrid microcavity[18]. The hybridization was evidenced by an increase in the WGM’s sensitivity to nanoscale perturbations—enabling detection of single proteins (as discussed later)—while the microcavity still provided a narrow resonance to track those perturbations[18]. In summary, the fundamental operating principle of all these hybrids is the enhanced interaction strength: the localized plasmon concentrates the optical field where the analyte is, and the photonic cavity amplifies and interrogates the effect of the analyte on that field. This principle allows hybrid sensors to achieve sensitivities or detection limits unattainable by purely plasmonic or purely photonic devices alone.

Before moving on, it is worth noting that theoretical limits and design trade-offs for hybrid sensors are an active research area. Some studies suggest there are universal scaling laws governing the sensitivity of resonant sensors, relating effective mode volume and Q to detection limit[23]. Hybrids push toward extremely small mode volumes (thanks to the plasmonic part) while trying to keep losses low enough (thanks to the photonic part) to leverage high Q. The continuing development of new materials (e.g., low-loss plasmonic materials, graphene and other 2D materials, etc.) and nanofabrication techniques is expected to further improve hybrid sensor designs. Comprehensive reviews on the design of such hybrid nanophotonic sensors and their theoretical underpinnings can be found in the literature[13][24].

1. **Biosensing Applications**

3.1 Biomolecular Sensing

One of the primary objectives for developing plasmonic–photonic hybrid sensors is to improve the detection of biomolecules such as DNA, RNA, proteins, and peptides in solution. In traditional label-free assays (e.g., SPR or ring resonator sensors), the limit of detection might be on the order of nanomolar to picomolar for small molecules, limited by the sensor response and noise. Hybrid sensors aim to lower these detection limits by offering larger signal shifts per molecule and sharper resonance features. Significant progress has been made in applying hybrid sensors to biomolecular sensing in both diagnostics and fundamental biomolecular interaction studies.

**DNA Detection:** A notable example is the work by Kawasaki et al. on DNA sensing using a plasmonic–photonic crystal hybrid[20]. In their 2022 study, a photonic crystal slab (supporting a guided-mode resonance) was coupled with gold nanorods to create a hybrid sensor. This device was used for label-free detection of specific DNA sequences, including the identification of single-nucleotide polymorphisms (SNPs) related to Alzheimer’s disease[20]. The hybrid sensor exhibited extremely high sensitivity: it could detect DNA at concentrations down to ~5.9 aM (approximately a few thousand molecules in the sample) and distinguish single-base mismatches via the difference in perturbations on the hybrid resonance caused by adsorbed DNA molecules[20]. Such performance greatly exceeds that of conventional SPR sensors for DNA (which typically detect in the fM to pM range). The improvement is attributed to the strong plasmonic field at the gold nanorods enhancing the effect of DNA binding on the local refractive index, while the photonic crystal resonance provides a high-Q readout of that change. This demonstrates the power of hybrids in applications like genotyping and early disease diagnosis, where detecting extremely low levels of nucleic acids is crucial.

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Figure 3. Label-free DNA detection by AuNR–TiO₂ photonic crystal slab (PCS) plasmonic–photonic hybrid sensor. (A)The SEM image of hybrid structure surface. (B) Far field reflectance of bare- (black line) and AuNR coupled PCS. (C) The electric field distribution around AuNR in the hole of PCS at resonant peak wavelength A and B. (D) Far-field reflectance intensity changes observed by loading probe-DNA–modified AuNRs onto a photonic crystal slab and by perturbations due to target DNA hybridization. (E) The calibration curve for label-free DNA detection. Adapted from [20]

In another approach, photonic crystal biosensors have been integrated with plasmonic nanostructures to amplify signals in immunoassays and DNA hybridization assays. Inan et al. reviewed various photonic crystal–based biosensors and noted that their sensitivity can be significantly increased by incorporating plasmonic effects[15]. One could, for instance, embed metal nanoparticles in a 1D photonic crystal to create coupled resonances that yield larger wavelength shifts upon biomolecule binding than the photonic crystal alone[15]. Similarly, hybrid 2D photonic crystals with metallic components have achieved lower detection limits for DNA. Zhu et al. (2018) reported a 3D nanostructured plasmonic–photonic crystal that was capable of detecting DNA hybridization at very low concentrations[25]. In their device, the hybrid structure provided a clear optical signal (a shift in a photonic bandgap resonance) in response to DNA binding, with enhanced magnitude due to plasmonic field confinement. They demonstrated label-free detection of specific DNA sequences relevant to cancer biomarkers, underscoring potential applications in medical diagnostics[25].

**Protein and Biomarker Detection:** Proteins are another important class of targets. Hybrid sensors have been employed to detect antibodies, enzymes, and other protein biomarkers with improved sensitivity. Choi et al. showed that coating a high-Q microring resonator with a thin gold film (thereby combining WGM and SPR) enhanced the device’s response to protein binding events[21]. In their experiments, the hybrid WGM–SPR sensor had a larger resonance shift upon binding of biomolecules (such as biotin–streptavidin) compared to an uncoated ring resonator[21]. The SPR excitation in the metal film effectively amplified the interaction of the evanescent field with the bound protein, leading to a stronger perturbation of the optical mode. This study highlighted that even a relatively simple hybridization—adding a plasmonic layer to an existing photonic sensor—can improve detection of biomolecular interactions.

Another illustrative example is by Shopova et al. (2010), who functionalized the surface of a WGM microbubble resonator with gold nanospheres to create a hybrid sensor[26]. The presence of these plasmonic nanospheres significantly increased the sensor’s response to the refractive index changes caused by biomolecules near the surface. This approach was sensitive enough to detect low concentrations of an analyte in a flow stream, benefiting from both the resonance shift of the WGM and the intensity change due to localized SPR extinction[26]. While that work was initially aimed at nanoparticle detection, the same setup can be adapted for proteins or other macromolecules by attaching receptors to the gold particles.

In general, hybrid sensors are finding use in label-free immunoassays, where an antibody or aptamer is immobilized on the sensor to capture a target antigen. The hybrid resonance will shift when the target binds. Because of the amplified field, hybrids can often detect much lower antigen concentrations than a conventional optical biosensor. For instance, recent studies (as reviewed by Singh et al.) have shown that plasmonic enhancement in ring resonators or photonic crystal sensors can bring detection limits of protein biomarkers from the pM range down to the fM or even aM range[13]. The exact performance depends on the sensor design and the affinity of the biomolecular interaction, but the trend is clear: hybrid designs offer a path to ultrasensitive biosensors that could rival or exceed the detection limits of fluorescent immunoassays, without the need for any labels.

**Real-Time and Multiplexed Detection:** Another advantage of hybrid sensors in biomolecular detection is their potential for real-time kinetic monitoring. Because the signals (wavelength shifts) are large compared to noise, one can observe binding and unbinding events in real time. For example, a hybrid WGM sensor with a plasmonic nanoparticle can track the adsorption of proteins to the nanoparticle surface as discrete step changes in resonance frequency[17]. This capability is valuable for studying kinetics of antigen–antibody interactions, DNA hybridization rates, etc., directly in solution. Moreover, by using arrays of hybrid sensors (for instance, multiple photonic crystal microcavities each coupled to plasmons and each functionalized for a different target), multiplexed detection of several biomarkers simultaneously is feasible[27]. Recent reviews have pointed out that hybrid plasmonic–photonic biosensors are strong candidates for point-of-care devices precisely because they can combine high sensitivity with the possibility of integration into compact arrays or fiber-optic formats[27]. In summary, for biomolecular sensing, plasmonic–photonic hybrids have demonstrated superior sensitivity in detecting DNA and protein targets, offering improvements in limits of detection and real-time monitoring that are pushing the boundaries of label-free analytic techniques.

3.2 Single-Molecular Detection

Perhaps the most demanding level of sensor performance is the detection of individual molecules – the ability to observe a single binding event or a single molecular interaction without any labels. Achieving true single-molecule detection in a label-free manner is extremely challenging because the optical effect of one molecule is minuscule. Pure photonic microcavity sensors have come close to this regime: for example, Armani et al. achieved detection of single bovine serum albumin (BSA) protein molecules by using an ultrahigh-Q microsphere cavity (with Q > 10^8) to monitor tiny wavelength shifts[4]. Vollmer’s group also detected single small molecules (down to 6–8 base DNA oligonucleotides) using a microsphere WGM sensor with plasmonic enhancement, though in that case the enhancement was provided by intentional adsorption of a few gold nanorods onto the sphere[17]. Plasmonic–photonic hybrids have proven especially valuable in this single-molecule regime, as they can amplify the interaction of a lone molecule to a detectable level.

**Hybrid WGM Sensors for Single Molecules:** An important milestone was the work of Dantham et al. (2013), who demonstrated label-free single protein detection using a nanoplasmonic–photonic hybrid microcavity[18]. In their experiment, a high-Q microtoroid WGM resonator was coupled with a small gold nanoparticle attached to its surface. This gold nanoparticle acted as a localized enhancer; when a protein molecule (BSA, ~66 kDa) bound to the gold nanoparticle, it induced a measurable shift in the WGM resonance frequency[18]. Essentially, the gold nanoparticle and the protein formed a composite perturbation that the microcavity could sense with sufficient signal-to-noise. Without the gold nanoparticle, the microtoroid by itself would not have been sensitive enough to detect a single BSA molecule (because the molecule’s volume was far too small relative to the mode volume). The hybrid approach increased the effective interaction by concentrating the optical field right at the binding site. This experiment clearly validated that hybrids can reach single-molecule detection levels for proteins. Notably, the resonance shifts observed were on the order of a few tens of femtometers – small but consistently above the noise floor, allowing statistical analysis of single-molecule binding events[18].

In a similar vein, Baaske et al. integrated a few gold nanorods onto the surface of a microsphere resonator and achieved detection of single short DNA strands (8-mer oligonucleotides, which are only a few kDa in molecular weight)[17]. In their Nature Nanotechnology 2014 report, the authors monitored real-time binding and unbinding of these tiny DNA strands by observing discrete step changes in the resonance wavelength of the hybrid sensor[17]. The gold nanorods provided a plasmonic enhancement that was crucial for boosting the signal of such a small molecule. The hybrid sensor was able to not only detect single binding events, but also differentiate matched vs. mismatched DNA strands by their different kinetic signatures and slightly different shift magnitudes[17]. This level of sensitivity and specificity at the single-molecule level is something conventional SPR could not achieve (SPR typically needs billions of molecules to produce a signal) and even a bare WGM cavity would have difficulty with such short DNA. Thus, hybridization was key to reaching this performance.

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自動的に生成された説明**Antenna-in-Cavity Nanosensors:** A particularly elegant implementation of a hybrid single-molecule sensor was demonstrated by Liang et al. (2017), who developed what they called an “antenna-in-a-nanocavity” system (Figure 4)[28]. In their design, a plasmonic nanoparticle was incorporated inside a photonic crystal waveguide (PCWG). This structure, published in Science Advances, allowed them to monitor single DNA–protein interactions without any fluorescent labels[28]. The hybrid sensor was so sensitive that it could detect the binding of a single DNA repair protein (XPA) to a single DNA strand immobilized in the nanogap of the antenna. By observing the shifts in the photonic cavity resonance (modified by the antenna’s presence), they measured how the protein’s binding dynamics were altered by the presence of fluorescent tags versus when the DNA was unlabeled[28]. Intriguingly, the study found that the fluorescent labels commonly used in single-molecule assays actually perturb the interaction – the labeled DNA had weaker binding to the protein – a discovery made possible only by a label-free technique with single-molecule resolution. This example illustrates the power of hybrid sensors in fundamental biophysics: they provide a means to study biomolecular processes in their native, unlabeled state, one molecule at a time.

Figure 4. AuNP–photonic crystal waveguide (PCWG) hybrid sensor for label-free analysis of single-molecule dynamics (DNA–XPA interaction). (A) SEM image of the hybrid sensor and schematic of the DNA–XPA interaction on the AuNP surface. (B) Transmission spectra of the bare PCWG (black) and hybrid structure (red). (C) Normalized electric field distributions corresponding to the bare-PCWG and AuNP-coupled PCWG at the resonant wavelength. Adapted from [28].

**Other Approaches and Observations:** Hybrid sensors have also been used to detect single nanoparticles (as a proxy for single molecules or viruses). For instance, pure photonic microcavities can detect single nanoparticles around 20–30 nm in size by mode splitting or scattering-induced shifts[5]. With a plasmonic enhancement, even smaller objects or molecules can be detected. Some hybrid systems intentionally operate in a regime where each binding or arrival of a nanoparticle causes a sudden jump in transmitted intensity due to Fano interference, providing a binary single-particle signal[19]. These have been explored for sensing individual viral pathogens or molecular aggregates. In general, achieving single-molecule detection requires not just an ultra-sensitive sensor design but also careful noise control and often low concentrations so that events are sparse and distinguishable. Hybrids help by maximizing the per-molecule signal. As reported by various groups, the use of plasmonic nanostructures can enhance the WGM resonance shift per molecule by up to an order of magnitude[17][18], effectively converting an undetectable event into a detectable one.

In summary, plasmonic–photonic hybrid biosensors have firmly entered the domain of single-molecule analytics. They bridge the gap between nanophotonic sensor technology and the single-molecule detection achievements that were once exclusive to techniques like fluorescence microscopy. The ability to observe single biomolecular interactions in real time without labels can provide deep insights into kinetic rate constants, molecular conformational changes, and interaction forces. Hybrids such as nanoparticle-loaded microcavities and antenna-in-cavity devices represent a new class of single-molecule biosensors with unique capabilities[28]. As these technologies mature, we can expect even more refined control (for example, detecting single post-translational modifications on proteins or sequencing DNA by reading single bases via nanocavity perturbations) to become feasible.

3.3 Cell and Vesicle Analysis

Moving up in scale, plasmonic–photonic hybrid sensors have also been applied to the detection and analysis of larger biological entities, such as extracellular vesicles (including exosomes) and whole cells. These analytes are typically micron- or sub-micron-sized, which means they present a large refractive index perturbation—often easy to detect by optical means if captured on a sensor. However, the challenge lies in detecting extremely low concentrations or very small numbers of such entities (for example, rare cells in a sample, or exosomes in early-stage disease patient plasma), and in distinguishing specific targets amid background. Hybrid sensors, with their enhanced sensitivity, can improve the limit of detection for these cases and potentially allow analysis of individual vesicles or cells.

**Exosome Detection:** Exosomes are nanoscale vesicles (30–150 nm diameter) released by cells, carrying molecular cargos that can serve as disease biomarkers. They are much smaller than typical optical wavelengths, so detecting them in a label-free manner often relies on capturing them on a surface and sensing the resultant refractive index change. Zhu et al. (2018) addressed this with a 3D plasmonic photonic crystal (PPC) biosensor designed for exosome detection[29]. The sensor was essentially a multilayered nanohole array (plasmonic) integrated with a photonic crystal cavity. By functionalizing the surface with antibodies against exosome markers, they could selectively capture exosomes from solution. The hybrid 3D PPC exhibited a large resonance shift upon binding of exosomes, with a sensitivity high enough to detect concentrations on the order of 10^4 exosomes per mL (~10^–5 nM)[29]. In practical terms, this meant a few tens of exosomes in the sensing area produced a measurable optical signal. The authors reported a peak wavelength shift of about 9 nm at 10^4 particles/mL, which increased to over 100 nm at 10^11 particles/mL (Figure 5)[29]. These substantial shifts indicate a strong interaction between the hybrid mode and the presence of the exosomes, facilitated by the plasmonic field enhancement around the nanostructured cavity. Notably, the figure of merit (sensitivity divided by linewidth) of the device was improved by the hybrid design, allowing clear discrimination of exosome binding events. This kind of sensor could be useful for early cancer diagnostics, where exosome concentrations in bodily fluids are very low and hard to detect with グラフィカル ユーザー インターフェイス が含まれている画像

自動的に生成された説明conventional SPR or ELISA methods.

Figure 5. 3D plasmonic photonic hybrid crystals for label-free exosome detection. (A) SEM image of the hybrid crystals; (B) SEM images of exosomes on a flat Au surface (left) and on 3D hybrid crystals (right); (C) extinction spectra of the 3D plasmonic photonic crystal biosensor without exosomes and with 1 × 10^5 and 1 × 10^11 particles/mL exosomes (left), and resonance peak shift as a function of exosome concentration (right). Adapted from [29].

It’s worth mentioning that purely plasmonic sensors have also achieved impressive results in exosome detection (for example, an array of plasmonic nanoholes known as the nPLEX platform was able to detect exosomes down to 10^2–10^3 particles/µL)[30]. However, hybrids can provide additional advantages such as narrower resonance features for potentially multiplexed or more precise readouts. Im et al. (2014) developed the nPLEX (nanoplasmonic exosome) sensor using LSPR nanohole arrays and successfully identified tumor-derived exosomes in plasma[30]. In comparison, a hybrid sensor could incorporate a photonic resonator to sharpen the LSPR signal and possibly provide spectral encoding of different exosome sizes or origins by multiple resonances. While the Im et al. study was not a hybrid, it underscores the need for high sensitivity in vesicle detection which hybrids are poised to deliver.

**Whole Cell Sensing:** Whole cell detection (for cells ~5–20 µm, like circulating tumor cells or bacteria) is generally easier from a purely optical standpoint because a cell landing on a sensor will cause a large shift or scattering loss. The challenge with cells is more about specificity (distinguishing target cells from others) and viability (keeping the cell alive or unperturbed if needed for analysis). Plasmonic–photonic hybrids have been explored as a means to monitor cell attachment and identify cells with high sensitivity. Zhu et al. (2018, Nanotechnology) reported using their multilayered plasmonic biosensor to capture live cancer cells and detect their presence label-free[25]. They functionalized the sensor surface with epithelial cell adhesion molecule (EpCAM) antibodies to capture circulating tumor cells. When a target cell bound to the surface, the hybrid sensor produced a detectable optical transmission change, which could be correlated to the cell’s presence and even its approximate size or index[25]. The hybrid nature ensured that even a single cell landing on the sensor produced a pronounced signal. In principle, this could be developed into a high-throughput cell sensor for applications like circulating tumor cell (CTC) enumeration from blood.

Moreover, hybrid sensors can be integrated with microfluidic devices to continuously monitor cells. For example, one can envision a microfluidic channel where cells flow over a photonic crystal slab that has plasmonic nanostructures on it. As each cell passes or adheres, the hybrid resonance shifts, and this could be detected in real time to count cells or assess their properties. Kumela et al. discuss prospects of hybrid biosensors for early cancer diagnosis, noting that such sensors could be made portable and combined with microfluidics for analyzing rare cells in clinical samples[27]. The enhanced sensitivity helps in cases where only a few cells (e.g., CTCs in a large volume of blood) are available and need to be captured and detected.

Another interesting application is monitoring cellular processes via hybrid sensors. Because hybrids are so sensitive to refractive index at surfaces, they can potentially detect when a cell adhered on the sensor undergoes morphological changes (like apoptosis or spreading) that alter its contact area or membrane proximity to the sensor. This was demonstrated in some photonic crystal biosensor studies (pure photonic) where cell attachment and spreading caused measurable shifts[15]. Adding plasmonic elements could amplify such signals—for instance, plasmonic hotspots at the cell–sensor interface might detect local membrane secretions or motions. While research in this direction is still emerging, it suggests that hybrid sensors could not only identify the presence of a cell but also report on its state or behavior.

**Extracellular Vesicles and Virus Sensing:** Besides exosomes, other extracellular vesicles (microvesicles, apoptotic bodies) and even viruses (which are essentially biological nanoparticles) fall into the size range that hybrid sensors excel at. As mentioned earlier, WGM sensors have detected single viruses[5], and hybrid WGM–SPR systems have been proposed to improve virus detection limits (for instance, via combining the long range of photonic sensing with the intensity of plasmonic sensing). In practice, a hybrid sensor could be coated with virus-specific ligands (like antibodies) to capture viruses, with the hybrid resonance providing an optical signature for each binding event. Given that a virus (~100 nm) is similar in scale to an exosome, the demonstrated sensitivity of hybrid PPC sensors[29] bodes well for virus detection applications such as rapid diagnostics for infections.

In summary, plasmonic–photonic hybrid biosensors have proven their utility in detecting and analyzing larger biological assemblies, from nanoscale vesicles to whole cells. They offer high sensitivity which translates to low detection limits (important for rare analytes like circulating tumor cells or low-abundance exosomes) and the possibility to monitor individual entities. This capability opens doors to liquid biopsy applications, where one might detect trace amounts of disease indicators in a minimally invasive manner. Additionally, by capturing and sensing single cells or vesicles, one can perform subsequent analysis on those entities (genomic/proteomic analysis off-chip, for example). The hybrid sensor serves as a highly sensitive front-end to identify and isolate targets. Overall, hybrids extend label-free optical biosensing across a wide size spectrum—from single molecules (Section 3.2) to whole cells (this section)—with a unified goal of maximizing sensitivity and maintaining specificity through surface functionalization.

1. **Performance Comparisons**

A critical question when evaluating plasmonic–photonic hybrid biosensors is how their performance compares to traditional sensors based on only plasmonics or only photonics. The key performance metrics typically considered are: sensitivity (wavelength shift or signal change per refractive index unit or per analyte concentration), limit of detection (the lowest quantity of analyte that can be reliably detected, often related to noise levels), and figure of merit (FOM) for refractive index sensing (usually defined as sensitivity divided by resonance linewidth). Additional metrics include response time, dynamic range, and specificity, but here we focus on sensitivity and detection limits.

In general, hybrid sensors have shown improved sensitivity and lower detection limits than their single-component counterparts. For example, in bulk refractive index sensing, a recent study by Hajshahvaladi et al. designed a hybrid plasmonic–photonic crystal sensor that achieved a simulated sensitivity of 1672 nm/RIU (nanometers shift per refractive index unit) with an exceptionally high FOM of 2388 RIU^−1[31]. These values are markedly higher than what is typically reported for pure plasmonic sensors (conventional LSPR sensors might have sensitivities on the order of a few hundred nm/RIU and FOM in the tens) and also above many pure photonic sensors. The hybrid in that study consisted of metallic rods in a photonic crystal waveguide, and the authors noted that the hybrid mode’s tight field confinement and enhanced light–matter interaction led to the superior performance[31]. By comparison, a standard photonic crystal cavity sensor might have a sensitivity of a few hundred nm/RIU (depending on design) and a high Q that gives a decent FOM, whereas a standard SPR (Kretschmann configuration) might have ~10,000 nm/RIU sensitivity in angle units but a very broad linewidth, yielding FOM ~20–30 in wavelength units. Thus, in that case the hybrid clearly outperforms the alternatives.

In the domain of detecting biomolecules and particles, performance is often evaluated by limit of detection (LOD) rather than raw sensitivity. Hybrids tend to achieve lower LODs (meaning they can detect smaller amounts). For instance, in DNA sensing, the hybrid sensor by Kawasaki et al. could detect ~5.9 aM of DNA[20], whereas a typical SPR sensor would struggle beyond pM levels (i.e., 6 orders of magnitude higher concentration). In protein detection, if a hybrid can detect single molecules (Section 3.2), its LOD in concentration terms can be extremely low (effectively limited by the sample volume and non-specific binding rather than sensor ability). Bozzola et al. systematically compared hybrid WGM sensors (WGM microresonators coupled with plasmonic nanoparticles) to pure WGM sensors for bulk refractive index changes and found that the hybrid could achieve larger resonance shifts per unit index change[10]. They pointed out that the real advantage of adding plasmonic nanoparticles is observed in the detection of very small perturbations (like single molecules or viruses), whereas for larger, bulk changes a high-Q photonic sensor was already quite sensitive[10]. In other words, the hybrid’s benefit is most pronounced in the low-limit regime (when signals are near the noise floor of the non-hybrid sensor). This is consistent with later single-molecule demonstrations[17][28][18].

One must also consider noise and stability aspects. Because hybrid sensors involve multiple resonant elements, one might worry they could introduce more noise (for example, thermal fluctuations from the metal, or additional drift channels). However, studies like Baaske et al.[17] have shown that the noise floor of a hybrid WGM sensor was limited by the readout instrumentation and environment rather than any fundamental instability introduced by the plasmonic particle. In fact, by switching from a fragile fiber-taper coupling to a more stable prism coupling, Baaske et al. improved the stability of their hybrid microsphere sensor and could observe single 8-mer DNA events reliably[17]. This suggests that with careful engineering, the hybrid does not compromise stability and can even be made robust.

In terms of resolution (the smallest detectable shift), hybrids often inherit the narrow linewidth of the photonic cavity. For example, a microsphere WGM might have a linewidth of a few tens of MHz (picometers in wavelength). Adding a plasmonic nanoparticle will broaden it somewhat, but it can still be quite narrow (perhaps only 2–3× broader). If the hybrid mode’s linewidth remains much smaller than that of a typical SPR (~nanometers), the ability to detect tiny shifts is enhanced. Offermans et al. argued that while plasmonic and photonic sensors follow a similar scaling law, the photonic sensor’s narrow linewidth generally gives it better resolution for small shifts[23]. The hybrid effectively attempts to marry the large shift (sensitivity) of a plasmonic sensor with the narrow linewidth of a photonic sensor. In practice, a well-designed hybrid can indeed produce a larger absolute wavelength shift for a given analyte while still keeping the resonance sharp enough to resolve that shift clearly[16]. The net result is an improvement in the smallest detectable refractive index change or molecular mass. For instance, in one comparison, a photonic microcavity could detect a minimum mass of ~10 attograms of analyte, whereas the hybrid version detected ~1 attogram[17]—about an order of magnitude improvement, aligning with the field enhancement factor.

**Comparing with Pure Plasmonic Sensors:** Traditional LSPR sensors (e.g., a single gold nanoparticle used as a sensor) have the advantage of simplicity and often a linear response, but they are fundamentally limited by their broad resonances. Techniques like phase interrogation or photothermal measurements can improve their resolution[14], but those add complexity. Hybrid sensors offer an alternative way to sharpen the response. Yesilkoy et al. (2018) demonstrated a phase-sensitive SPR sensor that achieved a very low LOD for cytokine detection (~a few fg/mL) by interferometric means[14]. A hybrid sensor, by contrast, might achieve a similarly low LOD by virtue of its resonance enhancement rather than external interferometry. In some cases, then, hybrids and advanced SPR techniques are complementary paths to improving performance. The hybrid approach keeps everything within the optical sensor structure itself.

**Comparing with Pure Photonic Sensors:** On the photonic side, one might compare hybrids with devices like microtoroid cavities or photonic crystal cavities alone. Microtoroids have detected single nanoparticles by mode splitting[5], and photonic crystal cavities have detected down to extremely low concentrations of biomarkers by virtue of high Q[15]. However, these pure photonic sensors can be limited by the need for ultra-high Q to see small shifts, which often requires very stable conditions and careful thermal control (because high-Q resonances can drift with temperature, etc.). A hybrid with a slightly lower Q (due to plasmonic loss) might actually be easier to work with while still giving a big signal. In Bozzola’s critical review, it was noted that hybrid WGM sensors could outperform pure WGM sensors in practical detection limits, despite the latter’s higher Q, because the hybrid gave larger absolute shifts (improving signal-to-noise)[10]. Essentially, trading a bit of Q for more coupling can be beneficial so long as noise doesn’t increase commensurately. This is borne out by experiments like Dantham’s, where the toroid’s Q dropped when the gold nanoparticle was attached, but the ability to detect single proteins emerged[18].

Quantitative Example: Suppose a certain protein at 1 pM produces a 1 pm wavelength shift in a pure photonic microcavity sensor with a linewidth of 50 pm; that shift might be barely detectable (signal is 1/50 of the linewidth). In a hybrid sensor, that same protein might produce, say, a 10 pm shift (due to field enhancement) while the linewidth might broaden to 100 pm. In that case, the signal is 1/10 of the linewidth – relatively larger and easier to detect with spectral or phase interrogation. Thus, even though Q was reduced (wider line), the sensitivity increased more, yielding a net gain in detection performance. This simplified scenario reflects what has been observed in several studies[16][17].

Finally, an important practical aspect is the dynamic range and saturation behavior. Pure plasmonic sensors can saturate when their surface is fully covered with analyte (no further shift possible), and pure photonic sensors can have a limited dynamic range due to nonlinear response at large bulk index changes (because eventually the mode profile changes significantly). Hybrids do not fundamentally change those limits, but their higher sensitivity means they might reach the saturation or non-linear regime at lower analyte concentrations. This can be managed by calibration or by operating in dilute regimes. It’s a reasonable trade-off when pursuing ultra-low LOD.

In conclusion, across numerous comparisons in the literature, plasmonic–photonic hybrids show equal or better performance than the best conventional sensors in their respective scenarios, often vastly superior for low-concentration detection. A 2017 study in Scientific Reports explicitly noted that their hybrid outperformed “either the purely plasmonic or purely photonic crystal sensors reported in the literature” in both sensitivity and FOM[31]. Likewise, reviews highlight that the real advantages of adding plasmonics are seen in the hybrid architectures, validating the effort of combining the two technologies[10]. The main point is that by carefully balancing the merits of plasmonic and photonic resonances, one can design a biosensor that is extremely sensitive, with a very low limit of detection, while maintaining a manageable signal readout. These performance benefits are driving the continued interest in hybrid biosensors for applications that demand the utmost sensitivity.

1. Challenges and Limitations

While plasmonic–photonic hybrid biosensors are promising, there remain several challenges and limitations that researchers are actively working to address. These challenges span fabrication, integration, stability, and fundamental physical trade-offs:

* **Fabrication Complexity:** By their nature, hybrids require combining two different types of nanoscale components (metallic and dielectric resonators) in a precise geometry. Techniques such as electron-beam lithography, focused ion beam milling, or advanced self-assembly are often needed to create, for example, a photonic crystal cavity with embedded metal nanostructures or a microcavity with attached nanoparticles[20]. This can be time-consuming and costly. Ensuring reproducibility is also difficult – small variations in nanoparticle size or placement can lead to device-to-device variability in coupling strength and resonance condition. For instance, in the hybrid PC slab sensor by Kawasaki et al.[20], the gold nanorods had to be positioned on or in the photonic crystal with good control of their quantity and distribution to tune the plasmon–photonic coupling. Any batch fabrication method (like nanoimprint lithography for the PC) must then be followed by accurate placement or growth of plasmonic particles. This multi-step process can introduce yield issues. Researchers are exploring methods like colloidal self-assembly (to place nanoparticles in cavities) and even DNA-origami–mediated assembly to precisely arrange nanoparticles, but these are still being perfected. Until fabrication is streamlined, large-scale production of hybrid sensors (such as chips with hundreds of identical hybrid cavities) remains challenging.
* **Alignment and Tuning of Resonances:** The hybrid effect is strongest when the plasmon resonance and photonic cavity resonance overlap spectrally[16]. In practice, slight fabrication errors can detune them. Photonic cavity resonances can sometimes be tuned post-fabrication by methods like gas condensation, thermal annealing, or refractive index trimming, and plasmon resonances can be tuned by adjusting nanoparticle size/shape or the surrounding medium. However, achieving perfect alignment often requires careful design or even active tuning mechanisms. If the resonances are misaligned, the hybrid sensor may perform sub-optimally or just behave like two separate sensors on the same chip (one plasmonic, one photonic, but not strongly coupled). For example, a hybrid WGM sensor needs the right nanoparticle (with an LSPR at the WGM wavelength) – using a gold nanorod whose aspect ratio peaks 50 nm away from the WGM resonance will yield less enhancement or even a Fano dip that cancels some signal[16][19]. In research settings, one can iterate designs or select particles under a microscope, but for commercial sensors one would want robust self-alignment (perhaps designing the plasmon resonance to be slightly broadband or using multiple plasmonic elements to cover a range so that at least one overlaps the cavity mode).
* **Intrinsic Loss and Q-Factor Degradation:** Introducing metal inevitably adds loss, lowering the photonic resonance’s Q-factor. A lower Q can be beneficial up to a point (as discussed earlier, too high Q with no coupling isn’t useful), but beyond that, too much loss can degrade sensor resolution. In extreme cases, if the metal causes a lot of absorption, the resonance might broaden so much that the advantage of the cavity is lost. Achieving the right balance is tricky, especially in designs with multiple or large metallic components. There is a risk of over-coupling, where the plasmon damps the cavity critically or over-damps it[16]. In such cases, one might see only a weak blip in transmission rather than a sharp resonance. Managing loss is thus a design imperative. Using alternative plasmonic materials with lower losses (e.g., aluminum for UV, graphene plasmons in IR, or new doped semiconductor nanocrystals for mid-IR) could help in specific spectral regimes. Some groups have explored gap-plasmon configurations that confine light in a nanoscale gap with a thin dielectric spacer – these can achieve high field confinement with somewhat reduced loss by minimizing the volume of metal in the field. Nonetheless, the presence of metals sets a fundamental upper bound on the Q achievable in a hybrid; it likely won’t reach the 10^6–10^7 of a pristine microcavity, and designers must accept that trade-off.
* **Fano Interference and Signal Linearity:** Interference between plasmonic and photonic modes can produce asymmetric Fano line shapes[19][22]. While a sharp asymmetric Fano profile can be highly sensitive to perturbations (due to its steep slope), it can also complicate the sensor response. For instance, the resonance shift might not be linear with analyte concentration if one side of the Fano profile changes more than the other. In some cases, one might observe intensity changes at a fixed wavelength rather than a pure wavelength shift. This means data analysis can be less straightforward, requiring fits to Fano profiles or dual-parameter detection (monitoring both intensity and wavelength). If the goal is a simple linear sensor output proportional to analyte concentration, designs may favor an induced transparency or split-peak scenario rather than a deep Fano cancellation. Researchers like Yanik et al. used Fano resonances to achieve naked-eye detection of monolayers[19], which is impressive, but for routine biosensing one might prefer a more predictable response curve. Managing interference effects—through design or signal processing—is thus a practical consideration.
* **Surface Functionalization and Specificity:** Like any biosensor, hybrid sensors require appropriate surface functionalization (e.g., antibodies, aptamers, DNA probes) to selectively capture target analytes. The presence of both dielectric and metallic regions can complicate surface chemistry. Gold is easily functionalized with thiol chemistry, whereas silica or silicon might use silane chemistry; in a hybrid, both may be present. One must ensure a uniform coating of bioreceptors in the active sensing region without damping the resonances too much. For example, a thick polymer or biomolecular layer could fill photonic crystal holes or coat a plasmonic particle and alter the resonance. Controlling functionalization so that it is thin (~a few nm) and specific is key. Non-specific binding (fouling) is also a concern: the intense local fields of plasmonic hot spots can make hybrids more sensitive to any adventitious adsorption of biomolecules, potentially generating false signals. Thus, blocking and reference channels are critical. Some hybrid setups include a nearby reference resonator that is either not functionalized or functionalized with a nonbinding coating, to subtract out bulk changes or non-specific background signals[17]. Ensuring specificity is ultimately a biochemical challenge that hybrids share with all biosensors, but the stakes are higher when your sensor is sensitive to single molecules – a single non-specific binding event could be misinterpreted as a positive if proper controls are not in place.
* **Stability and Environmental Sensitivity:** Plasmonic structures can introduce additional temperature sensitivity (metal refractive index changes with temperature) and can even cause local heating if illuminated strongly. Photonic microcavities are already quite temperature-sensitive (slight expansion or index changes shift the resonance). A hybrid might thus require temperature stabilization or at least referencing. Additionally, metals can oxidize or corrode (though gold is stable, others like silver are not). If a hybrid uses silver for better plasmonic Q, it may degrade in aqueous environments unless protected. Mechanical stability is another aspect: many hybrid sensors (like microspheres with attached nanoparticles) are delicate. Vibrations or flow can dislodge plasmonic particles (if not chemically anchored) or disturb a microcavity’s alignment. In a fiber-coupled WGM sensor, replacing the fragile fiber taper with a prism or chip-based coupler greatly improved stability[17]. The lesson for hybrids is that robust coupling and mounting methods are needed for real-world usage. Encapsulating parts of the sensor (e.g., sealing the backside of a photonic crystal slab) can also help against bulk disturbances.
* **Scaling and Multiplexing:** Building arrays of hybrid sensors for high-throughput or multiplexed detection presents additional challenges. Each hybrid resonator in an array might need a slightly different resonance (to multiplex different targets by wavelength) or careful isolation to prevent cross-talk. Fabrication non-uniformity can lead to device-to-device variation that complicates multiplexed readouts. Some approaches use one broadband plasmonic structure coupled with multiple narrow photonic modes, or vice versa, to create distinct channels, but this adds design complexity. Nonetheless, progress is being made – e.g., multi-channel photonic crystal sensors exist, and one can imagine adding plasmonic spots to each channel.
* **Cost and Practicality:** From an application perspective, the cost and effort to produce a plasmonic–photonic hybrid sensor must be justified by its performance gains. In high-end applications (research instruments or very critical diagnostics), the superior sensitivity might justify the complexity. For point-of-care diagnostics, simplicity and low cost are paramount; hybrids will need to reach a maturity level where they can be manufactured on-chip at low cost (e.g., via wafer-scale fabrication and possibly printable plasmonic structures) to be widely adopted. Additionally, readout instrumentation must be accessible – e.g., a small spectrometer or even smartphone-based detector. Some hybrid sensors currently require laser sources and precise alignment that are not trivial outside the lab. Bridging that gap is part of the development challenge.

In summary, while plasmonic–photonic hybrid biosensors offer compelling advantages, they come with a set of challenges that are the focus of ongoing research. These include achieving reproducible nanofabrication, aligning resonances and controlling losses, dealing with complex signal shapes, maintaining stability and specificity under real-world conditions, and doing all this cost-effectively. Encouragingly, many of these issues are being actively addressed. For instance, nanoimprint lithography has been used to mass-produce photonic crystal slabs, followed by colloidal gold attachment – hinting at a path to scale-up[20]. Prism coupling has improved WGM hybrid stability[17]. New materials (like silicon nitride cavities with graphene plasmonics) are being explored to reduce loss and add tunability. As solutions to these challenges emerge, we expect hybrid sensors to transition from laboratory curiosities to practical devices.

1. Future Perspectives

The field of plasmonic–photonic hybrid biosensors is rapidly evolving, and several exciting directions are on the horizon. Future developments will likely focus on improving device performance, integrating sensors into user-friendly platforms, and expanding their capabilities beyond what is currently possible [33]. Here, we outline some perspectives on where the field is heading:

* **Advanced Materials and Designs:** Thus far, gold and silicon-based materials have been the workhorses for hybrids. In the future, we anticipate the incorporation of novel materials to further enhance performance. One example is the use of two-dimensional (2D) materials like graphene and transition metal dichalcogenides (e.g., MoS₂, WS₂) in hybrid sensors[20]. Graphene plasmons (in the mid-IR) have extremely tight field confinement and could be combined with photonic waveguides or microcavities to create tunable IR biosensors for detecting molecular vibrational signatures. Even in the visible, graphene can serve as a functionalization layer that is electrically tunable, allowing active modulation of the sensor. Another materials advance could be low-loss dielectric nanoantennas (made of high-index dielectrics like Si or TiO₂) that mimic plasmonic behavior without ohmic loss. If such dielectric antennas are coupled to photonic cavities, one might achieve “all-dielectric” hybrids that circumvent metal losses (though they may not reach the same field intensity as metals). Additionally, new plasmonic materials such as aluminum (for UV biosensing), doped oxides or nitrides (for IR sensing), or even superconducting plasmonic materials (for extremely low loss at cryogenic temperatures in quantum biosensing applications) could open fresh avenues. From a design standpoint, topologically optimized nanostructures and metamaterials might be employed to create intentional Fano resonances or mode combinations that are robust against fabrication errors. We may see hybrid metasurface sensors, where every unit cell of a metasurface is effectively a hybrid resonator engineered for a particular response. These could enable imaging-based detection of biomolecules over a broad area – essentially a camera that captures binding events through optical interference patterns.
* **Integration with Microfluidics and Lab-on-Chip Systems:** For practical applications, sensors need to be integrated into fluidic environments where samples (blood, saliva, environmental samples, etc.) can be delivered and measured. Hybrid biosensors will benefit from progress in lab-on-a-chip technologies. We envision microfluidic-integrated hybrid sensor chips where micro- or nano-fluidic channels guide samples to an array of hybrid sensors functionalized for different targets[20]. The high sensitivity of hybrids means that even a tiny sample volume (a few µL) could be sufficient for detection. The integration must address issues like flow-induced noise and maintaining alignment (for example, ensuring a flowing cell actually passes through the sensing area of a photonic crystal without disrupting the coupling). Some initial works have integrated photonic crystal slabs into microfluidic channels for cell and biomarker detection, so adding plasmonic nanostructures to those is a reasonable next step. Automated sample handling, on-chip referencing, and regeneration (flushing and reusing sensors) will also be important. In the future, one can imagine a handheld device where a disposable chip contains the hybrid sensor array and microfluidics; the device optically interrogates the chip (perhaps via an embedded laser and spectrometer) and provides a readout of multiple analytes with ultra-high sensitivity (capable of early disease detection from a finger-prick of blood, for instance).
* **Multiplexed and Multi-Modal Sensing:** The ability of hybrids to enhance signals could be combined with multi-modal sensing – detecting more than one type of signal. For example, one could design a hybrid sensor that not only measures refractive index shifts but also generates a surface-enhanced Raman scattering signal. A plasmonic–photonic structure could both trap light (to enhance Raman excitation) and guide the Raman signal into a photonic mode for efficient collection[7]. This way, the same device could provide a specific fingerprint of the analyte (via Raman spectroscopy) while also quantifying binding (via resonance shift). Another multi-modal idea is combining optical and electrical detection: graphene-based hybrids could allow simultaneous electrical readout of changes in graphene conductivity upon binding, alongside the optical resonance shift[20]. Such orthogonal signals can improve reliability (cross-verification) and add functionality (e.g., electrical gating to actively capture or release charged biomolecules). Multiplexing across different targets will be facilitated by the fact that photonic resonances can be wavelength-division multiplexed – one could fabricate many hybrid resonators each tailored to a different wavelength and functionalization. Using broadband light and a spectrometer, all resonances (hence all targets) could be read in parallel. This optical multiplexing is particularly powerful given hybrids’ sharp spectral features.
* **Towards Single-Molecule Analytics and Digital Biosensing:** The single-molecule capabilities of hybrid sensors (as discussed in Section 3.2) hint at a future where biosensing could transition from analog to digital measurement paradigms. In digital biosensing (analogous to digital PCR), one aims to count individual binding events rather than measuring an ensemble average. If hybrid sensors can be made with many tiny independent active sites (or many small resonators in an array), they could operate by producing a binary signal for each target captured. For example, an array of hybrid nanocavity sensors could be used where each sensor is so small or has such a low probability of capturing a molecule that it either shows a jump (captured) or not (empty). By counting the fraction of sensors that show binding, one could determine the concentration statistically. This could dramatically improve the precision at ultra-low concentrations and provide absolute quantification without calibration. Achieving this will require uniform micro/nano-fabrication at scale and possibly integrating thousands of sensors on a chip. Advances in CMOS-compatible photonic integration might allow electronic photonic circuits to address and read out large arrays of hybrid resonators. This leads to the vision of a “biosensor chip” that could be inserted into a reader like a microarray, but instead of fluorescence spots it has optical resonator spots that directly detect biomolecules digitally.
* **Better Theoretical Understanding and AI Optimization:** As devices become more complex, computational tools including machine learning will play a role in both designing and interpreting hybrid sensors. We might see AI-assisted design algorithms propose non-intuitive geometries for maximum field enhancement or select optimal combinations of materials. On the data analysis side, machine learning could help distinguish signal from noise in single-molecule time series or complex spectral shifts resulting from multiple interactions. A deeper theoretical understanding of the limits of hybrid sensing (for example, the Cramér–Rao bound on estimating analyte concentration from a noisy Fano resonance) will inform how much more improvement is possible. Such analyses could indicate, for instance, the ultimate limit of detection in the presence of fundamental noise sources (like thermorefractive noise in cavities or photon shot noise). This might drive innovations such as integrating low-noise lasers, using quantum light (e.g., squeezed light) to beat shot noise, or even quantum transduction schemes for biosensing – though those are more far-future ideas.
* **Commercial and Clinical Translation:** In the coming years, we expect to see the first real commercial (or at least field-deployed) instances of hybrid biosensors. Early adoption might occur in specialized settings: for example, a hybrid sensor could be used in pharmaceutical research to monitor biomolecular interactions at very low concentrations or in environmental monitoring for detecting trace contaminants. If the technology proves robust, clinical applications such as early cancer diagnostics (detecting ultra-low levels of tumor markers or rare tumor-derived vesicles) could follow[27]. The value proposition is clear – detect disease when biomarkers are vanishingly scarce, something current methods struggle with. For widespread adoption, challenges such as reducing sensor cost and coping with complex biological samples must also be overcome [33]. For clinical translation, issues of sensor regeneration (so the device can be reused for multiple tests), calibration standards, and regulatory validation will need to be addressed. It’s possible that hybrid sensors will first augment rather than replace existing methods – for instance, they might be used to validate and quantify results from a conventional assay that flags a sample as positive. Over time, as confidence builds, they could become stand-alone diagnostic tools.
* **Interdisciplinary and New Horizons:** Finally, it’s worth noting that plasmonic–photonic hybrids lie at the intersection of nanophotonics, materials science, and biology. This interdisciplinary nature will continue to spur innovation. For example, in single-cell analysis, one might integrate a hybrid sensor with an array of nanoelectrodes to stimulate a cell and optically record the release of neurotransmitters or hormones at the single-molecule level. In chemical sensing, hybrids could be used not just in aqueous solutions but also in gas sensing (combining photonic crystal fibers with plasmonic nanoparticles to detect gases at low concentrations). For instance, hybrid fiber-optic sensors have been demonstrated to extend nanoscale optical biosensing into flexible, remote formats [33]. There is also a push towards ultrafast and dynamic measurements – using pulsed lasers and hybrids to perhaps capture ultrafast binding events or conformational changes of molecules by pump–probe techniques, leveraging the enhanced signals.

In conclusion, the future of plasmonic–photonic hybrid biosensors is bright. We anticipate continued improvements in sensitivity—pushing towards the detection of ever more subtle molecular events—and increased integration that will make these sensors more practical and versatile. If the current trajectory continues, hybrid sensors could become a mainstream tool in bioscience and healthcare, enabling diagnostics and analyses that are currently beyond reach. The coming together of advanced nanofabrication, new materials, and clever engineering (often guided by machine learning and driven by urgent application needs) will determine just how far and how fast this field progresses. Given the achievements to date and the intense research interest, we may not be far from seeing ultra-sensitive hybrid biosensors breaking out of the lab and into real-world use, heralding a new generation of analytical technology for the life sciences.

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