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Review

Emerging Trends in Optical Fiber Biosensing for Non-Invasive Biomedical Analysis

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Abstract

Optical fiber biosensors have evolved into powerful tools for non-invasive biomedical analysis. While foundational principles are well-established, recent years have marked a paradigm shift, driven by advancements in nanomaterials, fabrication techniques, and data processing. This review provides a focused overview of these emerging trends, critically analyzing the innovations that distinguish the current generation of optical fiber biosensors from their predecessors. We begin with a concise summary of fundamental sensing principles, including Surface Plasmon Resonance (SPR) and Fiber Bragg Gratings (FBGs), before delving into the latest breakthroughs. Key areas of focus include integrating novel 2D materials and nanostructures to dramatically enhance sensitivity and advancing synergy with Lab-on-a-Chip (LOC) platforms. A significant portion of this review is dedicated to the rapid expansion of clinical applications, particularly in early cancer detection, infectious disease diagnostics, and continuous glucose monitoring. We highlight the pivotal trend towards wearable and in vivo sensors and explore the transformative role of artificial intelligence (AI) and machine learning (ML) in processing complex sensor data to improve diagnostic accuracy. Finally, we address the persistent challenges—biocompatibility, long-term stability, and scalable manufacturing—that must be overcome for widespread clinical adoption and commercialization, offering a forward-looking perspective on the future of this dynamic field.

Keywords: optical fiber biosensor; non-invasive analysis; surface plasmon resonance (SPR); nanomaterials; biomarker

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1. Introduction

The advancement of non-invasive diagnostic technologies is a cornerstone of modern biomedical engineering, promising to revolutionize healthcare through early disease detection, continuous patient monitoring, and personalized medicine. At the heart of this revolution are biosensors, and among them, optical fiber biosensors (OFBs) have garnered immense attention due to their intrinsic advantages: miniaturization, remote sensing capabilities, and immunity to electromagnetic interference (EMI) [1–3].

This paper examines the latest uses and accomplishments of optical fiber sensors (OFSs) and technology in the realm of biosensing. Optical fiber sensing has emerged as a cost-effective and adaptable technology suitable for a wide range of applications. Although research on OFSs started in the 1960s, it was not until the 1980s that the technology was fully harnessed, thanks to advancements in low-loss fiber optics that transitioned it from

experimental to practical use [4]. Initial studies on low-loss optical fiber sensing were carried out in the early 1970s [5]. The advantages of OFS, such as compact size, lightweight nature, resistance to electromagnetic interference, long-distance transmission, and real-time monitoring, have generated significant interest in tracking parameter changes. Consequently, OFSs are extensively employed across various fields to measure parameters such as strain, temperature, vibration, and displacement [6]. Furthermore, the evolution of specialty optical fibers has significantly expanded the horizons of sensing applications beyond standard telecommunication fibers. These advanced fibers enable the development of sophisticated biomedical instrumentation, such as optical scanning endoscopes utilizing single multimode fibers. Such devices leverage wavefront shaping techniques to achieve high-resolution, minimally invasive imaging of deep tissues, demonstrating the transformative potential of specialty fibers in clinical diagnostics [7,8]. Although the optical fiber is primarily recognized for its role in communications, it also plays an important part in the field of sensing technology. While the influence of optical fiber sensors (OFSs) on the global market is not as widespread as that of telecommunications, their impact remains noteworthy [9].

The recent rise and recurrence of pandemics and epidemics worldwide have underscored the critical need for more sophisticated diagnostic technologies [10]. Advanced biosensors play an essential role in the rapid identification and management of infectious diseases, which can spread quickly and have a significant negative impact on economies and public health [11]. These tools facilitate the detection of pathogens at very low concentrations, often before the onset of symptoms, thereby shortening response times and enabling more effective containment strategies. Furthermore, improvements in biosensor technology can assist in monitoring the transmission and mutation of diseases, providing crucial data that inform public health policies and vaccine development efforts. Consequently, the creation of highly sensitive biosensors is not simply a technical achievement; it is a fundamental pillar for strengthening global security against both current and future biological threats [12,13]. Biosensors function as analytical instruments that integrate a biological recognition element with a physicochemical transducer to detect and measure chemical substances, often at exceptionally low levels. These devices are vital across numerous sectors such as medical diagnostics, environmental surveillance, food safety assurance, and biotechnology. Biological components such as enzymes, antibodies, and nucleic acids are chosen for their specific interactions with the target analyte. This interaction generates a signal that the sensor system detects and processes, and is correlated with the concentration of the substance. By merging biological sensing with electronic systems, researchers have developed highly selective and sensitive biosensors that are capable of providing fast, real-time, and often portable results. This field is continuously expanding and fueled by progress in biotechnology, nanotechnology, and materials science, which in turn enables novel applications to solve complex analytical problems in various industries [14,15]. The growing demand within modern medicine for diagnostic tools that are fast, precise, and noninvasive has spurred considerable innovation in biosensor technology [16]. Among the many available platforms, optical fiber biosensors have attracted significant interest. This is because of their distinct benefits, which include high sensitivity, resistance to electromagnetic interference, potential for miniaturization, and suitability for remote and in vivo monitoring. These sensors work by modulating the properties of light in response to biological events on the fiber surface, making them a powerful tool for analyzing biological samples in real time [17]. The core operational principle is frequently based on the interaction between the target analytes and the evanescent wave, which is the portion of guided light that extends into the surrounding medium, allowing for label-free detection methods [18].

Extraordinary detection limits can be achieved by integrating technologies such as Surface Plasmon Resonance (SPR), Localized Surface Plasmon Resonance (LSPR), and interferometry with optical fiber platforms. These systems can often detect concentrations in the picomolar or femtomolar range [19]. This level of sensitivity is crucial for early disease diagnosis, where biomarkers may be present in exceedingly low quantities within complex biological fluids like blood, saliva, or urine. The ability to perform analysis without extensive sample preparation or the use of chemical labels simplifies diagnostic workflows. It reduces costs, making these sensors highly suitable for point-of-care (POC) applications [20]. While optical fiber biosensors exhibit significant potential, their progression from laboratory research to routine clinical application is impeded by several persistent challenges. A primary concern is non-specific binding, or biofouling, wherein extraneous molecules from the sample matrix adhere to the sensor's surface, resulting in false signals and diminished measurement precision. Furthermore, the stability and orientation of immobilized bioreceptors—the biological entities responsible for capturing the target analyte—are critical for ensuring the sensor's reproducibility and overall efficacy [21]. The random orientation of these bioreceptors can substantially decrease their binding efficiency, thereby affecting the sensitivity of the sensor. Consequently, it is imperative to optimize sensor assay design and develop robust surface functionalization methods to address these challenges and enhance signal-to-noise ratios, particularly when working with small sample volumes [22].

For many years, the potential of OFBs has been recognized, but the main obstacle has been achieving the required sensitivity and specificity for non-invasive biomarker detection, as these biomarkers are often found in very low concentrations in easily accessible biofluids, such as saliva, sweat, or interstitial fluid. However, the last five years have witnessed a remarkable surge in innovation, reshaping the performance capabilities of this technology. This rapid progress is fueled by combined advancements in specialized fiber design, such as microstructured and hollow-core fibers; the incorporation of advanced nanomaterials, including plasmonic nanoparticles and two-dimensional materials such as graphene, for signal enhancement; and advanced surface functionalization chemistries that allow for highly specific molecular recognition. This swift development has opened up new opportunities for real-time, label-free detection, making a thorough review of these recent advancements both timely and essential [23].

In response to recent advancements, the field of optical fiber biosensing is rapidly evolving from a specialized academic interest to a fundamental component of next-generation diagnostic systems. This review systematically examines the landscape of optical fiber biosensors, with a particular focus on noninvasive biomedical analysis. This paper is structured first to categorize various types of optical fiber biosensors and elucidate their operational principles. This is followed by a comprehensive overview of recent progress in fabrication techniques, functional materials, and biorecognition strategies that have significantly enhanced sensor performance. Subsequently, we explored specific applications in healthcare, demonstrating their potential in disease detection, therapeutic monitoring, and personalized medicine. This review also underscores emerging trends, such as integration with a lab-on-a-chip platform and the development of flexible sensors. Finally, we address the key challenges that must be overcome to transition from laboratory innovation to clinical adoption and provide insights into the future trajectory of this promising research field.

2. Classification of Optical Fiber Biosensors

Optical fiber biosensors can be categorized based on optical parameters that change owing to biological interactions. These changes can influence the intensity, wavelength,

phase, and polarization of light. Each method has its own set of benefits and drawbacks, making it appropriate for different applications. Based on the notes provided, we propose an outline for this paper on the latest trends in optical fiber biosensing for noninvasive biomedical analysis [24,25]. Intensity-based sensors detect variations in light intensity due to absorption or scattering by the analyte. These sensors are relatively easy to build and understand, but can be influenced by external factors, such as fluctuations in the light source. Wavelength-based sensors, such as those using surface plasmon resonance (SPR), identify shifts in the resonant wavelength of light due to biomolecular interactions. These techniques provide high sensitivity but may require sophisticated equipment [26,27]. Phase-based sensors use interferometric techniques to measure changes in the phase of light traveling through a fiber. They can achieve very high sensitivity, but may be more vulnerable to environmental changes. Polarization-based sensors identify changes in the polarization state of light due to interactions with biomolecules, offering another highly sensitive detection method [28]. Recent progress in optical fiber biosensing has concentrated on enhancing the sensitivity, selectivity, and multiplexing capabilities. This includes the creation of innovative fiber designs, such as microstructured or photonic crystal fibers, which improve light–matter interactions. Furthermore, the incorporation of nanomaterials and plasmonic structures has created new opportunities for ultrasensitive biomolecule detection [29]. The main sensor types are classified and illustrated in Figure 1 and discussed in the following sections.

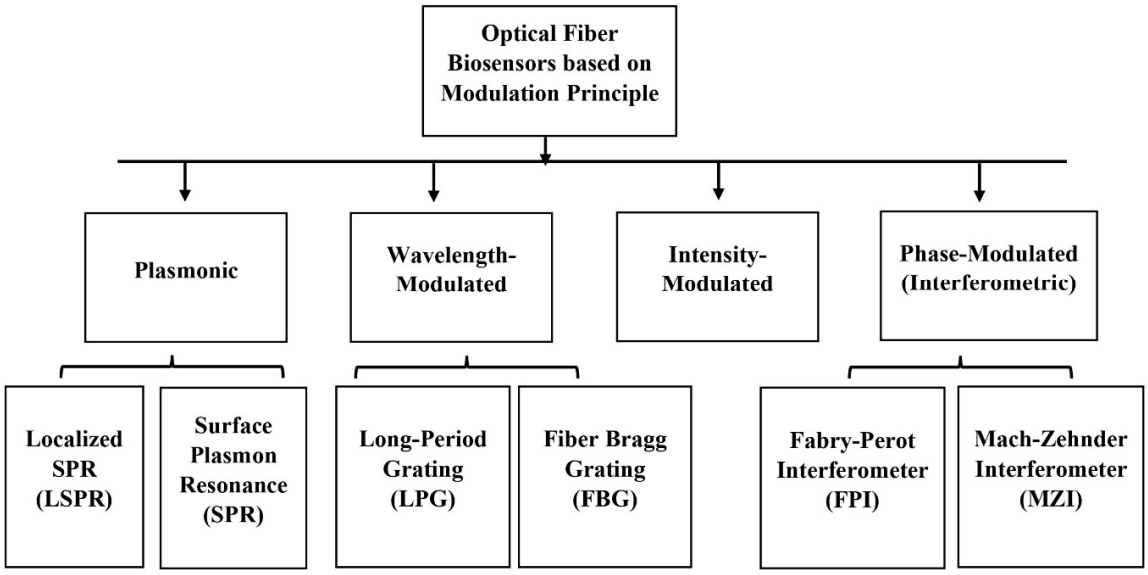

Figure 1. Classification of major optical fiber biosensor types based on the modulated optical parameter.

2.1. Intensity-Modulated Sensors

Intensity-modulated setups refer to a type of fiber optic sensor in which the light intensity is altered by the measurand. This group includes the most basic form of optical fiber biosensors, in which the presence or amount of the target analyte leads to a variation in the intensity of light that is either transmitted or reflected. Such variations can arise from processes such as absorption, fluorescence, scattering, or losses owing to changes in the refractive index of the medium around the fiber. For instance, in a fluorescence-based sensor, the target analyte interacts with a molecule labeled with a fluorescent marker, and the excitation light passing through the fiber induces a fluorescence emission. The light intensity gathered by the fiber correlates with analyte concentration [30,31]. Structurally, intensity-modulated sensors are often implemented using straightforward designs such

as straight, open-ended fibers, U-shaped probes, or tapered fibers. U-shaped probes extend the interaction length between the evanescent wave and the sample, thus boosting sensitivity, while tapered fibers focus the light field in the waist area, making them highly responsive to surface-binding events. The production of these sensors is generally simple and often involves simple techniques such as cleaving, bending, or chemical etching. For fluorescence-based sensors, the fiber tip is typically functionalized with a bioreceptor-fluorophore conjugate, which can be achieved through various surface chemistry methods, such as silanization followed by covalent bonding [32,33]. Recent progress has aimed to address the inherent drawbacks of intensity-modulated sensors, especially their vulnerability to signal drift. Traditionally, organic fluorophores such as fluorescein isothiocyanate (FITC) and rhodamine B have been widely employed as signal transducers in fiber-optic fluorescence assays due to their high quantum yield and ease of bioconjugation [32]. However, the practical utility of these organic dyes is often compromised by rapid photobleaching, pH sensitivity, and narrow Stokes shifts, which can lead to significant background autofluorescence and signal degradation over time. To address these inherent drawbacks, a notable trend is the adoption of innovative nanomaterials as robust signal enhancers. Quantum dots (QDs) and upconversion nanoparticles (UCNPs) are increasingly replacing traditional organic fluorophores. For instance, core–shell QDs (e.g., CdSe/ZnS) offer superior photostability and broad absorption spectra coupled with narrow, size-tunable emission peaks. Similarly, UCNPs (typically lanthanide-doped nanocrystals like NaYF4:Yb,Er) utilize anti-Stokes emission, converting near-infrared excitation into visible light, which effectively eliminates background noise from biological samples [34,35]. A practical application of these advantages is demonstrated by Cui et al. [34], who developed a stable fiber-optic biosensor for Staphylococcus aureus detection using QDs. As illustrated in Figure 2, their system employs a precise optical setup (Figure 2a) and a double-antibody sandwich structure (Figure 2b) to utilize the high photostability of QDs for creating a functional benchtop prototype (Figure 2c).

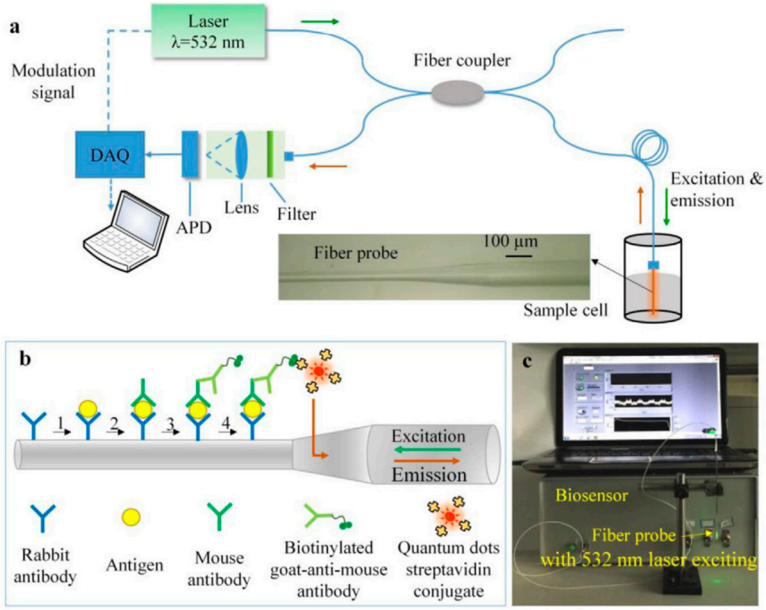

Figure 2. Implementation of a Quantum Dot-based optical fiber biosensor. (**a**) Schematic diagram of the optical setup, utilizing a 532 nm laser for excitation and an avalanche photodiode (APD) for signal detection. (**b**) The sensing mechanism on the fiber probe surface: A double-antibody sandwich structure is formed where QDs are conjugated to the detection antibody via streptavidin-biotin interaction. (**c**) Photograph of the actual experimental prototype and the data acquisition interface [36].

The structural design of intensity-modulated biosensors generally includes a light source (such as a laser diode), an optical fiber, a sensing region functionalized with biorecognition elements, and a photodetector. Light travels through the fiber and interacts with the analyte in the sensing region, causing variations in the transmitted or reflected light intensity. These variations are then detected and correlated to analyte concentration [37]. Recent innovations in sensor design include the use of long-period fiber gratings (LPFG), specifically turnaround-point LPFGs, which allow for intensity-based signal interrogation instead of complex spectrum analysis. This approach significantly reduces cost and complexity while maintaining high sensitivity, making it suitable for applications such as DNA analysis [38]. To enhance measurement sensitivity, resonator structures like Fabry–Perot cavities have been implemented. These resonators allow multiple reflections of excitation light within the fiber, amplifying the intensity that reaches the sensing region. Experimental results have demonstrated up to an eight-fold increase in signal strength using high-reflectivity coatings [39].

Measurement of light intensity is typically carried out using photodiodes, photomultiplier tubes, or spectrometers. The output is analyzed based on models such as the Stern-Volmer equation (for fluorescence quenching) or linear absorption trends. For instance, a recent study used carbon quantum dots (CQDs) embedded in a cellulose acetate matrix on the fiber tip to detect glucose levels. The sensor exhibited excellent linearity and sensitivity in both micromolar and nanomolar ranges, with fluorescence intensity changes tightly correlated to analyte concentration [40,41]. Spectral shift measurements can also complement intensity data. For example, a fiber optic fluorescence sensor used to differentiate between normal and cancerous breast tissues observed a redshift in emission peak wavelength (from 511 nm in normal to 518 nm in tumor core tissue), along with a decrease in fluorescence peak intensity ratio, highlighting its utility in diagnostic applications [42].

Recent advances in material science have enabled the use of novel biocompatible and eco-friendly materials in the fabrication of intensity-modulated fiber optic biosensors. For example, chitinase enzymes have been successfully immobilized onto a chitosan film derived from tofu waste to create a biosensor capable of detecting heavy metal ions like Cd (II). The biosensor demonstrated excellent sensitivity, selectivity, and environmental sustainability, with reproducible results and a low detection limit of 0.00076 ppm [43]. Innovative fiber geometries and fabrication approaches have also improved the optical and sensing performance of these devices. A new design utilizing U-shaped liquid-core optical fibers filled with silica particles and coated with a molecularly imprinted polymer membrane has shown high selectivity and sensitivity for detecting 4-chlorophenol. This configuration enhances the light–analyte interaction by increasing surface luminous intensity and optimizing refractive index modulation in the fiber core [44]. Moreover, distributed biosensing strategies have been implemented using fiber tip-based Fabry–Perot etalons, which are functionalized with specific capture layers and fabricated in varying lengths to enable coherence multiplexing. This allows for simultaneous, label-free detection of multiple biomolecular interactions on a single fiber through intensity interrogation methods. These biosensors demonstrate promising applications in real-time protein interaction studies and high-throughput diagnostics [45].

- Advantages: Simple structure, low cost, and ease of signal processing are the main benefits of this type of sensor.
- Disadvantages: These sensors are highly sensitive to fluctuations in the light source, fiber bending losses, and changes in light coupling, which can lead to unreliable results. These limitations have reduced their use in applications requiring high precision [46].
- A schematic representation of an intensity-modulated microbend fiber optic sensor is shown in Figure 3.

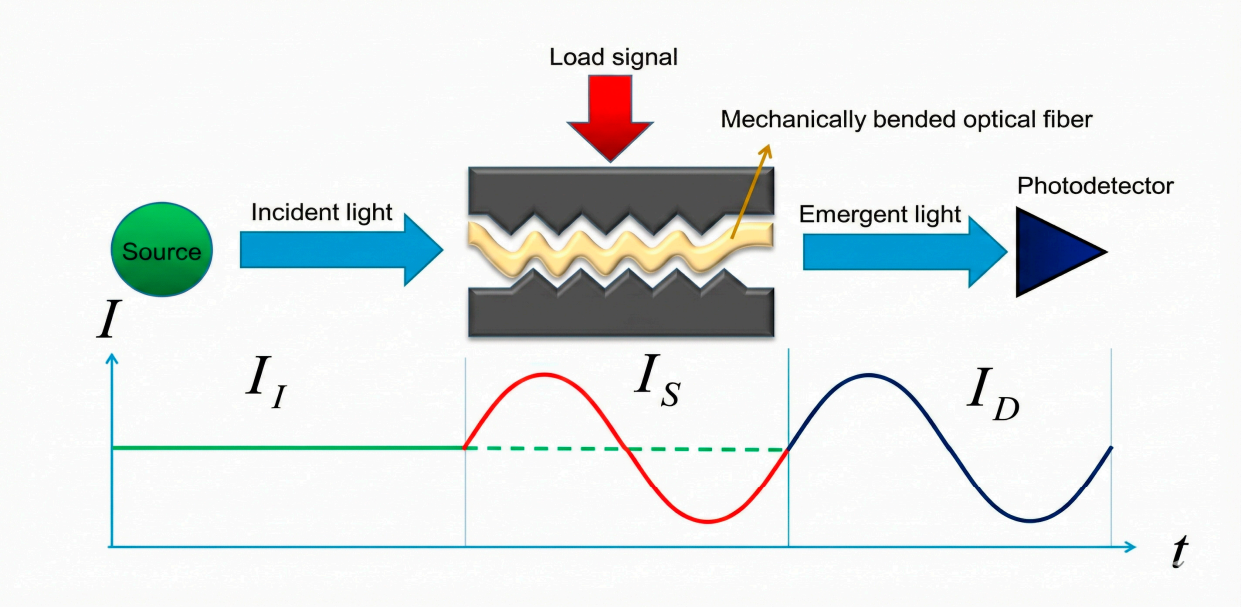

Figure 3. Schematic representation of an intensity-modulated microbend fiber optic sensor. The setup illustrates how a mechanical load induces micro-curvatures in the optical fiber, causing radiation losses. The incident light (I_I) is modulated by the mechanical disturbance, resulting in a variation in the emergent light intensity (I_D) detected by the photodetector [47].

2.2. Wavelength-Modulated Sensors

In these sensors, the measurement parameter is the change or shift in specific wavelengths. This approach is more robust against light-intensity fluctuations because the information is encoded in the wavelength domain. The general operating principle involves illuminating the sensing element using a broadband light source. The sensor structure, such as a grating, is designed to interact with light only within a narrow spectral band, creating a distinct peak or dip in the spectrum. When a biorecognition event occurs on the functionalized fiber surface, for instance, an antigen binding to an immobilized antibody, the accumulation of mass alters the local refractive index (RI) in the immediate vicinity of the fiber's evanescent field [48].

This change in the local RI modifies the resonance condition of the sensing structure, resulting in a measurable shift in the resonant wavelength. This spectral shift is the primary output signal and is directly proportional to the concentration of the analyte. The shift is monitored in real-time using an optical spectrum analyzer (OSA) or a dedicated, often more compact, and cost-effective interrogator device [49]. Because the sensing information is encoded in the spectral position of a feature rather than its absolute power, the measurement is inherently self-referential. This makes the sensor highly immune to power drifts from the light source, variable connector losses, or fiber bending, which is a significant advantage over intensity-based schemes [50]. The two main structures in this category are Fiber Bragg Gratings (FBGs) and Long-Period Gratings (LPGs).

2.2.1. Fiber Bragg Grating (FBG)

A Fiber Bragg Grating (FBG) is an optical structure created by inducing a periodic modulation of the refractive index within the core of an optical fiber. This periodic structure causes the device to function as a highly selective spectral filter, reflecting a narrow band of light at a specific wavelength, which is termed the Bragg wavelength. The value of this wavelength is determined by two parameters: the effective refractive index of the fiber core and the period of the grating modulation. For biosensing applications, the fiber surface is functionalized with bioreceptors. The subsequent binding of target analytes to these

receptors alters the refractive index of the external medium within the evanescent wave field. This change is detected as a measurable shift in the Bragg wavelength (Figure 4). To augment the device's performance, methods such as chemical etching are often utilized to reduce the fiber's diameter in the grating region, thereby enhancing the interaction between the evanescent wave and the surrounding sample [51].

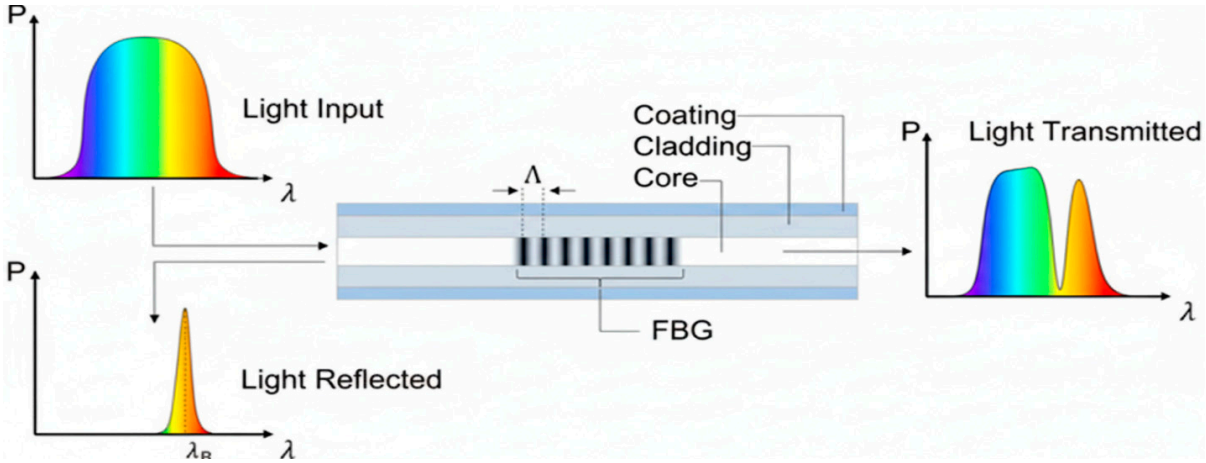

Figure 4. Working principle of a Fiber Bragg Grating (FBG) sensor. The grating reflects a specific wavelength (λ_B) from a broadband source, while the rest of the light is transmitted. Changes in the FBG (e.g., from strain or temperature) shift this reflected wavelength, enabling sensing. The rainbow spectrum illustrates the broadband light source input, while the single reflected peak corresponds to the specific Bragg wavelength reflected by the grating [51].

2.2.2. Long-Period Grating (LPG)

A Long-Period Grating (LPG) operates by coupling light from the guided core mode to co-propagating cladding modes. This energy transfer occurs at discrete wavelengths known as resonant wavelengths, which appear as attenuation bands in the transmission spectrum [52]. A key characteristic of these resonant wavelengths is their pronounced sensitivity to the refractive index of the medium surrounding the fiber cladding. Consequently, any change in this external refractive index, such as that caused by the immobilization of biological molecules on the fiber surface, induces a significant shift in the spectral position of these attenuation bands. Generally, LPGs demonstrate a substantially higher sensitivity to external refractive index changes compared to standard FBGs, making them highly effective for chemical and biological sensing [53]. The schematic diagram of the LPG structure and its operating principle are illustrated in Figure 5.

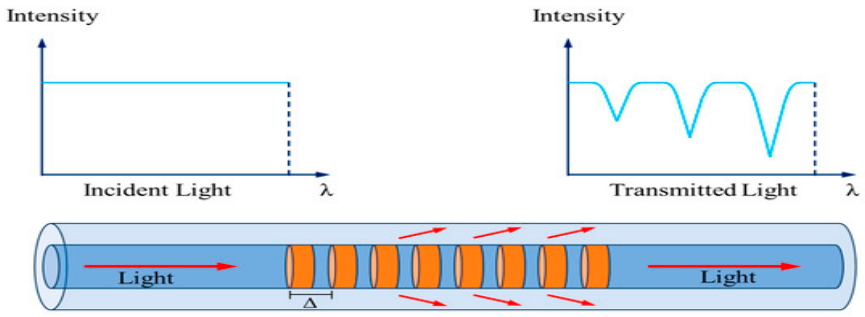

Figure 5. Schematic of Long-Period Grating (LPG) operation. The periodic grating (period Δ) facilitates the transfer of optical energy from the core mode to the cladding modes. This manifests as characteristic attenuation bands in the transmission spectrum (top-right graph). The sensitivity of these resonant wavelengths to the external refractive index enables the LPG's function as a sensor [53].

2.2.3. Whispering Gallery Mode (WGM) Resonators

Beyond fiber gratings, optical micro-resonators operating on the Whispering Gallery Mode (WGM) principle represent a powerful class of wavelength-modulated sensors. Unlike gratings that rely on periodic refractive index modulations, WGM sensors confine light within a circular microstructure—such as microspheres, microrings, or microtoroids—through continuous total internal reflection (TIR) along the curved interface [54]. Originating from the acoustic phenomenon observed by Lord Rayleigh in St. Paul's Cathedral, this optical confinement allows light to circulate multiple times within the cavity, creating constructive interference at specific resonant wavelengths. This unique geometry enables the confinement of light in extremely small volumes while maintaining interaction with the surrounding medium via the evanescent field. A defining characteristic of WGM resonators is their exceptionally high Quality factor (Q-factor), which quantifies the photon lifetime within the cavity. Depending on the geometry and fabrication quality, Q-factors can range from 10^4 in typical microring resonators to exceeding 10^8 or even 10^9 in crystalline microspheres and microtoroids [55]. This high Q-factor translates to a significantly extended effective interaction length between the light and the analyte, far surpassing the physical dimensions of the sensor itself. Consequently, WGM resonators exhibit superior sensitivity to environmental perturbations compared to traditional single-pass waveguides, making them highly effective for detecting low-concentration biomarkers. The sensing mechanism in WGM devices relies on the interaction between the evanescent wave tail and the biological layer on the resonator surface. When target biomolecules (e.g., proteins or DNA) bind to the functionalized surface, they displace the surrounding medium (buffer) and alter the effective refractive index in the evanescent field region. According to the first-order perturbation theory, this refractive index change induces a quantifiable shift in the resonant wavelength (δλ), which is directly proportional to the surface density of the bound molecules. Due to their ultra-high sensitivity, WGM sensors can achieve detection limits (LOD) as low as 10^{-8} to 10^{-9} RIU, enabling label-free, single-molecule detection and early-stage diagnosis of diseases such as cancer [56,57]. Figure 6 shows the schematic configuration of a Whispering Gallery Mode (WGM) microsphere resonator sensor, where light is coupled via a tapered fiber.

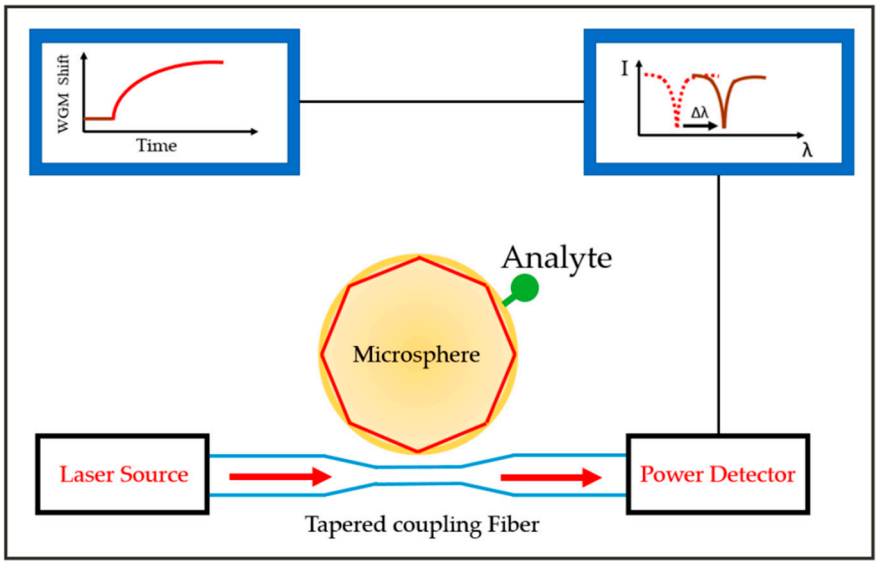

Figure 6. Schematic configuration of a Whispering Gallery Mode (WGM) microsphere resonator sensor. Light is coupled into the microsphere via a tapered optical fiber. The binding of analytes on the sphere's surface alters the refractive index, causing a measurable shift in the resonant wavelength (as shown in the inset graphs), enabling high-sensitivity label-free detection [57].

A compelling demonstration of the biosensing capabilities of WGM resonators is the multiplexed detection of cancer biomarkers. For instance, functionalized dielectric microspheres have been successfully employed to detect Cancer Antigen 125 (CA-125), a primary biomarker for ovarian cancer, alongside Tumor Necrosis Factor-alpha (TNF-α) 1. In this setup, microspheres of different diameters were coated with specific antibodies to target distinct analytes simultaneously. As shown in the experimental results in Figure 7, the sensor exhibits a distinct linear response where the resonant wavelength shifts proportionally with increasing concentrations of CA-125 and TNF-α 2. This linear correlation (R^2 linearity) not only validates the high sensitivity of the WGM platform but also demonstrates its potential for quantitative, real-time clinical diagnostics without the need for complex labeling processes [57].

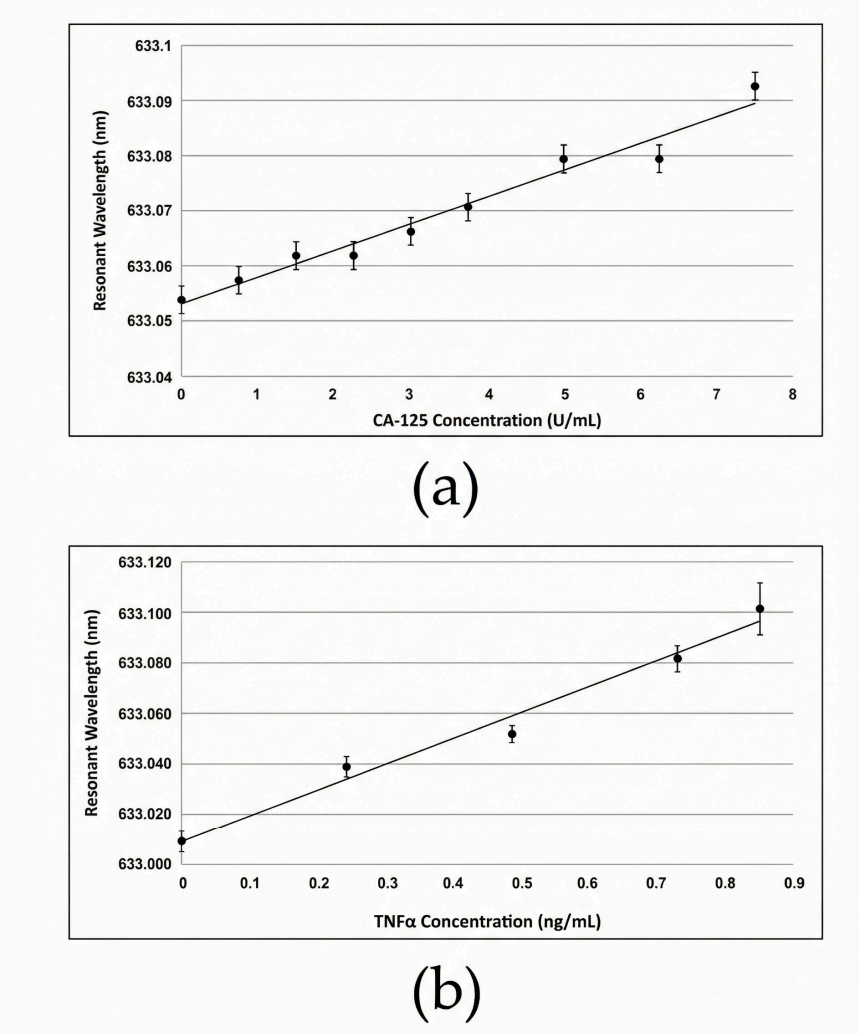

Figure 7. Experimental calibration curves demonstrating the biosensing performance of WGM microsphere resonators. The graphs show the linear shift in resonant wavelength as a function of analyte concentration for (**a**) CA-125 (an ovarian cancer biomarker) and (**b**) TNF-α. The distinct linear response confirms the sensor's capability for quantitative detection in clinical ranges [57].

Recent advances in wavelength-modulated optical fiber biosensors have focused on simplifying fabrication methods while maintaining high sensitivity. For instance, a miniaturized Fabry–Perot fiber sensor was recently developed for rapid DNA detection using a straightforward and reusable structure. This sensor achieved a 1.1 nm wavelength shift within just 6 min for 1 μM DNA solutions, all at room temperature. Its compact design and low-cost manufacturing make it highly suitable for point-of-care diagnostics

and real-time biosensing [58]. Another innovation includes shallow-tapered optical fibers functionalized via salinization to detect cancer biomarkers like CD44. These sensors, fabricated in under 20 s using a CO_2 laser splicer, eliminate the need for traditional reflectors such as gratings. Despite this simplification, they maintained high sensitivity—up to 1.33 nm/RIU—thanks to the use of MgO nanoparticle-doped fibers. Their robustness and reproducibility make them an excellent candidate for in situ and clinical diagnostic tools [59]. The integration of plasmonic materials and dual-core fiber designs has also enhanced wavelength selectivity and detection resolution. A newly proposed plasmonic biosensor using slanted metal gratings on the end facet of dual-core single-mode optical fibers enables high-sensitivity operation without the need for traditional interrogation components like circulators. With predicted surface sensitivities of 1 nm/nm and bulk sensitivities of 880 nm/RIU, this platform simplifies the design and opens possibilities for remote and in vivo sensing applications [60]. In terms of material innovation, D-shaped polymer optical fibers coated with gold have been developed for early breast cancer detection. By immobilizing HER2-specific aptamers on a gold-coated fiber surface, the sensor achieves a wavelength shift of ~1.37 nm for just 1 μg/mL of HER2 protein. This low-cost and fast-response biosensor (with detection in as little as 5 s) offers promise for portable clinical screening tools [61].

2.3. Phase-Modulated Sensors

These sensors, also known as interferometric sensors, offer very high sensitivity. Their working principle is based on measuring changes in the phase of light resulting from a change in the optical path length. These changes are caused by the binding of analytes to the fiber surface and the subsequent change in the effective refractive index. The core principle of interferometric sensing lies in splitting light into at least two paths, where one—the sensing arm—is exposed to the target environment, and the other—the reference arm—is isolated or acts as a benchmark. The optical path length (OPL) of the sensing arm is altered when biorecognition events change the effective refractive index (neff). When the light from both paths is recombined, they interfere, creating a spectral pattern of constructive and destructive fringes. The phase difference ($\Delta\phi$) between the arms dictates this pattern and is highly sensitive to minute changes in the OPL, as described by the relation $\Delta\phi = (2\pi/\lambda)\,\Delta\text{neff}\cdot L$, where L is the interaction length [62]. This direct relationship means that even a very small number of bound molecules can induce a detectable phase shift, leading to the technique's hallmark ultra-high sensitivity.

The practical realization of these interferometers in an optical fiber format involves sophisticated microfabrication techniques. Creating distinct sensing and reference arms can be achieved by splicing together different types of fibers (e.g., single-mode, multi-mode, or hollow-core fibers) or by using fiber couplers. More advanced methods involve using a femtosecond laser to inscribe waveguides or create micro-cavities directly within the fiber structure [63]. For Fabry-Pérot interferometers, for instance, a common approach is to create two parallel reflective surfaces within a single fiber. This can be done by splicing a short segment of a different fiber, creating an air gap, or using laser-machined mirrors. The region between these reflectors forms the sensing cavity, which can be open to the external environment for biosensing applications. Signal interrogation involves tracking the spectral shifts of the interference fringes. As analytes bind to the functionalized surface of the sensing arm, the entire interference spectrum shifts towards longer or shorter wavelengths. By precisely monitoring the displacement of a specific fringe minimum or maximum, a quantitative, real-time measurement of the binding kinetics can be obtained [64]. While interferometric methods offer exceptional sensitivity, they are inherently susceptible to external perturbations, particularly temperature fluctuations and mechanical vibrations,

which can induce refractive index changes indistinguishable from the biological signal. To address this vulnerability, recent advancements have focused on engineered configurations with enhanced anti-interference performance. For instance, suspended-core fiber Sagnac interferometers utilize a common-path geometry that inherently cancels out thermal noise, offering superior stability compared to traditional path-imbalanced MZIs [64]. In contrast, microcantilever-based FPIs, while providing rapid response times for applications like antibiotic susceptibility testing, require rigorous stabilization to isolate biological signals from mechanical noise [65]. Significant progress has also been made in active compensation strategies; Kammer et al. (2018) demonstrated a temperature-compensated MZI sensor that effectively decoupled thermal drift from binding events, achieving a signal drift of <2% over prolonged monitoring periods [66]. Such quantitative improvements are critical for transitioning interferometric biosensors from controlled laboratory environments to robust point-of-care applications.

2.3.1. Mach-Zehnder Interferometer (MZI)

A Mach-Zehnder Interferometer (MZI) implemented with optical fiber operates by dividing an input light signal into two distinct pathways: a sensing arm, which is designed for interaction with the sample medium, and a reference arm. Following propagation through their respective channels, the two light beams are recombined, or superimposed, to generate an interference pattern. The detection principle is based on the phase relationship between the two arms; any alteration in the refractive index of the environment surrounding the sensing arm induces a phase difference. This difference manifests as a measurable displacement in the interference pattern, which can be monitored with high sensitivity. The operational principle of an MZI relies on the division of a single light source into two separate optical paths, followed by their subsequent recombination. The interaction between the recombined beams generates an interference pattern, the nature of which (i.e., constructive or destructive) is dependent on the phase shift induced by the physical parameter being measured. This interferometric method is exceptionally sensitive, enabling the conversion of subtle environmental changes into quantifiable shifts in the output interference pattern [64,67]. As illustrated in Figure 8, the experimental apparatus in this study employs a fiber-optic MZI configured for the detection of magnetic fields and alternating currents.

2.3.2. Fabry–Perot Interferometer (FPI)

A Fabry–Perot Interferometer (FPI) is designed with an optical cavity formed between two parallel reflective surfaces. This setup can be easily constructed at the tip of an optical fiber. The sensor operates by identifying variations in the optical path length within this cavity, which can result from changes in the refractive index or the cavity's physical length. These variations lead to a noticeable shift in the spectrum of the reflected interference signal. Due to their small size and high sensitivity, FPI sensors are particularly suitable for point sensing applications [68]. Using Frequency Division Multiplexing (FDM) with unbalanced Fabry–Perot Interferometers (FPIs) involves modulating the light source's frequency to drive each interferometer over a distinct and integral number of fringes. This process, however, generates a pseudo-heterodyne carrier for each sensing element that is susceptible to crosstalk. This issue is not unique to FDM; similar crosstalk problems can arise in FPI systems. Specifically, coherent signals originating from highly scattering objects, which may be located at a sample depth similar to the sensor's coherence length, can interfere and generate spurious signals. This phenomenon is a critical limitation as it restricts the total number of sensors that can be effectively multiplexed on a single system. To address this drawback, a fiber-optic sensor system based on coherence multiplexing

has been constructed [69]. In this configuration, a super-luminescent diode (SLD) source injects light into two FPI sensors. These sensors are fabricated by cleaving a single-mode optical fiber and housing them within a compact capillary tube (as shown in the inset of Figure 9). A crucial design principle is that the individual path length of each FPI, as well as the difference between their path lengths, is engineered to be greater than the coherence length of the SLD source. Detection of the interferometric signals is then accomplished using a bulk-optic Michelson interferometer. This processing interferometer sequentially matches the path length differences of each FPI sensor to retrieve their individual signals. As depicted in the setup in Figure 6, the coherence length of the light source itself can be estimated by analyzing the visibilities of the interference fringes as a translation stage moves at a constant velocity through the zero path-length mismatch point [69].

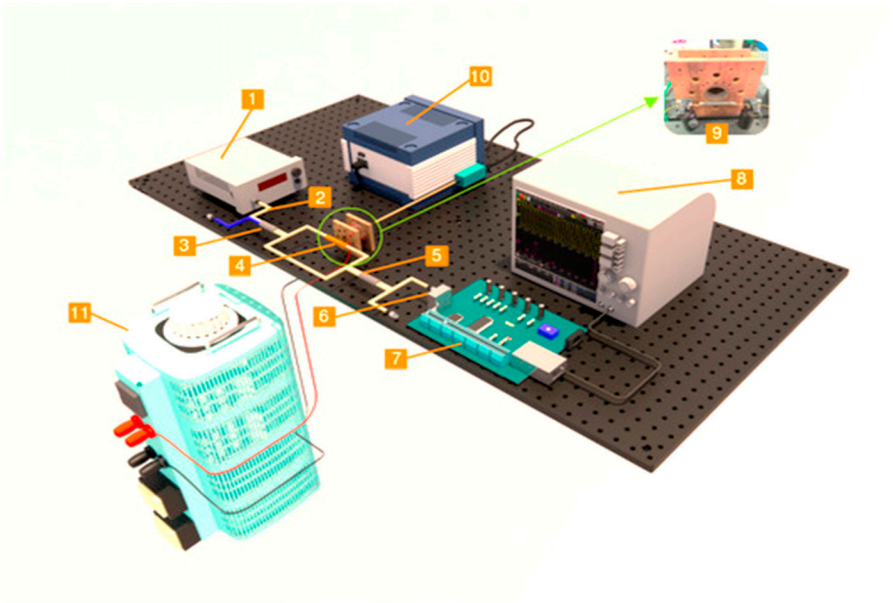

Figure 8. Schematic of the experimental setup used for monitoring alternating current and magnetic fields. The system is based on a fiber-optic Mach-Zehnder interferometer (MZI), with the output signal processed and displayed on an oscilloscope. The components are: (1) [Light Source/Power Supply], (2) [MZI Sensor Head/Sensing Element], (3) [Optical Fiber Path 1], (4) [Optical Fiber Path 2], (5) [Photodetector], (6) [Data Acquisition Module/Signal Processing Unit], (7) [Computer/Control Unit], (8) Oscilloscope, (9) [Close-up of Sensor Head], (10) [Interrogator/Optical Spectrum Analyzer], and (11) [AC/Magnetic Field Source/Helmholtz Coils] [67].

Recent innovations in Fabry–Perot interferometric biosensors have enabled simpler and more compact fabrication without sacrificing sensitivity. A 2024 study introduced a miniature fiber-optic Fabry–Perot biosensor designed for rapid DNA detection. The sensor employed a straightforward splicing and cavity design while maintaining the ability to detect 1 μM DNA in under 6 min with a 1.1 nm wavelength shift. Its reusability and fast fabrication process support scalable production and point-of-care integration [58]. Tapered fiber sensors, often used in Mach-Zehnder interferometers (MZIs), have also seen advancements. A portable biosensing system was recently developed using tapered fibers functionalized with selective biomolecular layers. The phase sensitivity of this structure is enhanced by the tapered geometry, which increases the interaction of the evanescent field with the surrounding analyte. Real-time, stable phase measurements were achieved, and the system showed excellent potential for compact and field-deployable diagnostics [70]. In another approach, a microcantilever-based Fabry–Perot fiber interferometer was fabricated for antibiotic susceptibility testing. By integrating a single-mode fiber with

a flexible cantilever, the biosensor could detect bacterial motion through interference shifts, providing quantitative results within 30 min. The microcantilever served both as a mechanical sensor and an optical cavity, allowing rapid fabrication and effective pathogen detection—highlighting new design directions in phase-modulated sensing systems [71].

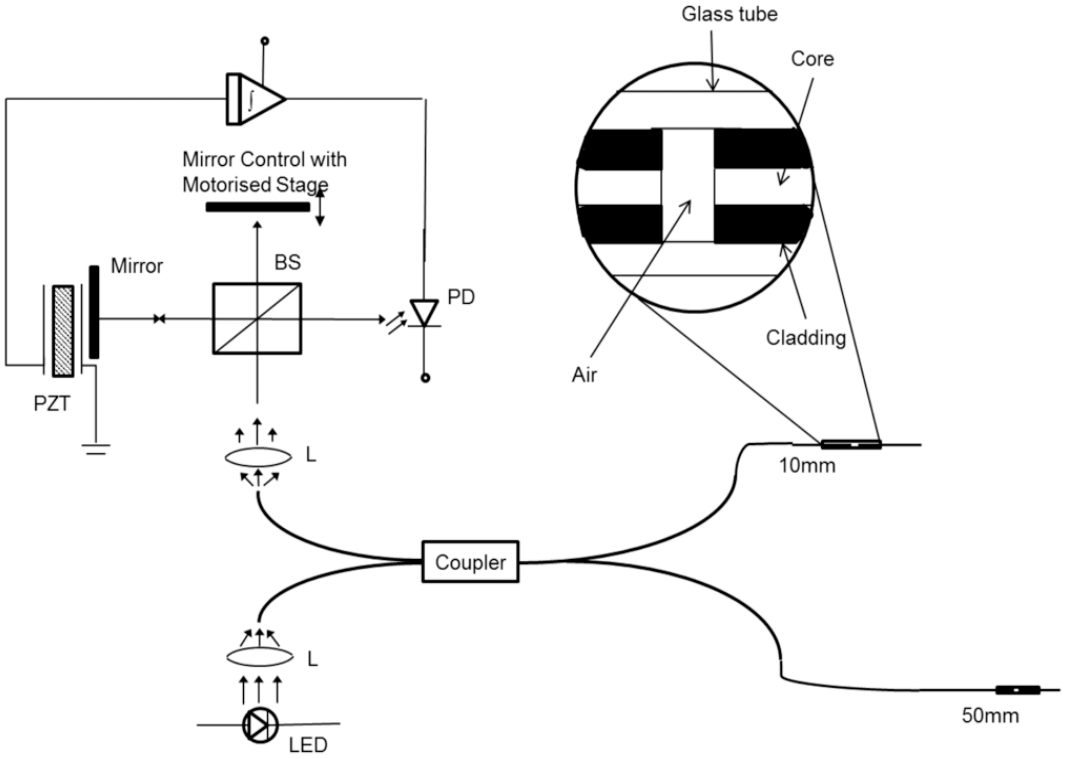

Figure 9. Schematic of the experimental setup for coherence multiplexing of Fabry–Perot sensors. Light from an LED is collimated (L) and divided by a fiber coupler. The sensing arm terminates in two FPI sensors (detailed in the circular inset). The signal processing is performed by a Michelson interferometer composed of a PZT-mounted mirror, a mirror on a motorized stage, a beam splitter (BS), and a photodiode (PD) for detection [60].

2.4. Plasmonic Optical Fiber Biosensors

Plasmonic sensors are a class of devices that operate based on the excitation of surface plasmons and are distinguished by their exceptional sensitivity to fluctuations in the refractive index at a metal-dielectric interface. The fundamental principle behind this technology is the generation of surface plasmon waves, which are collective, coherent oscillations of free electrons that travel along the boundary between a noble metal (such as gold or silver) and an adjacent dielectric material. In the context of an optical fiber-based system, the evanescent field of the light propagating within the fiber extends slightly into the surrounding medium. When this field interacts with a deposited plasmonic metal film, it can couple its energy to the electrons. This coupling excites a surface plasmon wave, but only if a precise phase-matching condition between the incident photons and the surface plasmons is satisfied [72,73]. At a specific resonance wavelength where this condition is met, the energy transfer is maximized, which is observed as a sharp attenuation dip in the output light spectrum. The performance of the sensor is critically dependent on its physical structure. For sensors based on Surface Plasmon Resonance (SPR), a typical design involves stripping a segment of the fiber's cladding and then depositing a thin, uniform film of a plasmonic metal. Gold is often chosen for this purpose due to its excellent chemical stability and superior plasmonic characteristics. The thickness of this metallic layer, typically between 40 and 50 nm, is a crucial parameter that requires precise control to

ensure optimal resonance conditions [74]. In contrast, sensors based on Localized Surface Plasmon Resonance (LSPR) utilize a different architecture. In this case, the structure involves immobilizing metallic nanoparticles onto the fiber's surface. The resonance is created by the collective, localized oscillation of electrons within these nanoparticles. Key parameters such as the geometry, size, and spacing of these nanoparticles heavily influence the resonance wavelength and overall sensitivity, providing a high degree of tunability for sensor design [75].

The detection mechanism itself is extremely sensitive to molecular binding events on the sensor surface. The process begins with the functionalization of the fiber by attaching specific bioreceptors (e.g., antibodies, aptamers) that are designed to selectively capture a target analyte. When a sample containing the analyte is introduced, these target molecules bind to the receptors, leading to an accumulation of biological mass. This accumulation alters the local refractive index at the metal-dielectric interface, thereby disrupting the precise phase-matching condition necessary for plasmon excitation. The disruption results in a measurable shift in the resonance wavelength. This spectral shift can be monitored in real-time, serving as a direct, label-free indicator of the analyte's concentration in the sample [76].

Recent advancements in plasmonic fiber sensors focus on enhancing sensitivity and specificity even further. One promising avenue is the use of novel materials beyond gold and silver. Two-dimensional materials like graphene and MXenes have been integrated with plasmonic layers. Graphene, for instance, can protect the metal layer from oxidation and provide a large surface area for enhanced biomolecule immobilization, thereby amplifying the sensor's response. Another significant trend is the development of hybrid sensor platforms, such as combining plasmonic coatings with fiber gratings (FBG or LPG). These hybrid structures can produce sharper resonance peaks and offer intrinsic temperature compensation capabilities, addressing one of the key challenges in plasmonic sensing and paving the way for more robust and reliable diagnostic tools [77].

2.4.1. Surface Plasmon Resonance (SPR)

The fabrication of a fiber-optic sensor for Surface Plasmon Resonance (SPR) involves removing a section of the fiber's cladding and depositing a thin metallic film, typically made of gold, onto the exposed core. When light propagates within the fiber, its evanescent wave penetrates the metal layer. Under specific conditions of wavelength and angle, this wave can resonantly excite the free electrons at the metal's surface, generating a surface plasmon wave. This resonance results in a sharp attenuation of light at a specific wavelength, which is observable as a distinct dip in the output spectrum. The precise position of this resonant wavelength is highly sensitive to the refractive index of the medium adjacent to the metal. Therefore, the binding of biological molecules to the sensor surface alters this refractive index, causing a measurable spectral shift [78,79].

2.4.2. Localized Surface Plasmon Resonance (LSPR)

In contrast to the continuous metal film used in SPR, sensors based on Localized Surface Plasmon Resonance (LSPR) utilize discrete metallic nanoparticles (e.g., gold or silver) immobilized on the optical fiber's surface. In this approach, the interaction of light with these nanoparticles induces a collective oscillation of their electrons, which leads to a strong absorption peak in the optical spectrum. The central wavelength of this absorption peak is directly dependent on the local dielectric environment surrounding the nanoparticles. Compared to SPR, LSPR sensors generally have a simpler architecture, and their optical characteristics can be effectively tuned by modifying the size and shape of the nanoparticles used [80].

Recent developments in plasmonic optical fiber biosensors have emphasized precise micro- and nano-fabrication techniques to enhance sensitivity and enable integration into compact platforms. For instance, Mahani et al. [60] developed a plasmonic biosensor on the end facet of a dual-core fiber by patterning slanted metal gratings using focused ion beam milling and metal evaporation. This configuration enabled efficient core-to-core plasmon coupling and remote sensing capability without the need for complex optical isolators, significantly simplifying interrogation setups [60]. Material innovation has also played a critical role. In particular, graphene, antimonene, and other 2D materials have been introduced as supplementary plasmonic layers or coatings due to their exceptional optical and chemical properties. A 2023 study by Vikas and Saccomandi demonstrated that a graphene-antimonene coating on tapered fiber SPR sensors significantly improved binding affinity and biocompatibility for cancer cell detection. The layered materials contributed to enhanced refractive index sensitivity and broader analyte detection range, demonstrating their effectiveness in biomedical diagnostics [81]. Hybrid sensor designs integrating plasmonic layers with conventional optical fiber structures have also gained momentum. Fatkhutdinova et al. [82] fabricated a gold-coated tilted fiber Bragg grating (TFBG) sensor embedded within a thermostabilized microfluidic chip, demonstrating highly stable and selective biosensing in varying environmental conditions. The gold film thickness and uniformity were tightly controlled to maximize surface plasmon resonance, and thermal perturbations were actively compensated using a PID-regulated Peltier device, thus improving measurement repeatability and stability [82]. Finally, novel fabrication strategies are enhancing LSPR-based sensor geometries. Lei et al. [83] introduced a method for constructing Au nanoparticle multimers on fiber end-faces to amplify the LSPR signal via hot-spot generation. This hierarchical nanoparticle assembly, achieved through layer-by-layer deposition using chemical spacers, increased the local electromagnetic field strength, enabling a 3.4-fold increase in peak shift and an eightfold improvement in detection limit compared to conventional nanoparticle layers. Such fabrication techniques highlight the crucial role of precise nano-structuring in pushing the boundaries of LSPR-based biosensor sensitivity [83]. The fabrication process and sensing workflow are illustrated in Figure 10.

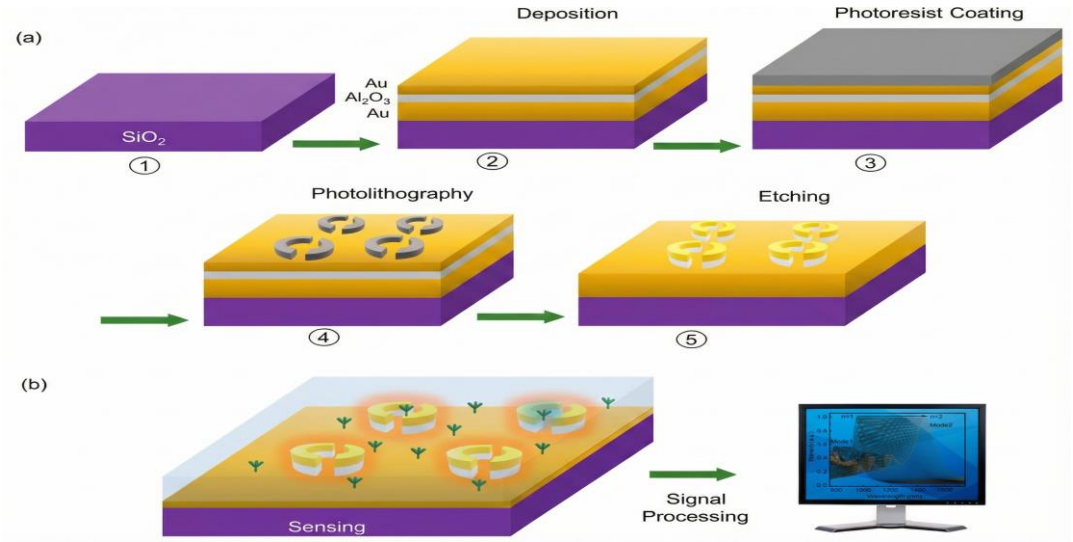

Figure 10. Schematic illustration of the fabrication and sensing workflow for plasmonic nanostructure-based biosensors. (**a**) The photolithography fabrication process for creating arrayed split-ring nanostructures, comprising substrate cleaning, metal-dielectric deposition, photoresist coating, patterning, and etching. (**b**) Conceptual representation of the biosensing chip interface, demonstrating the interaction with biological samples and subsequent signal processing for refractive index sensing [84].

2.5. Photonic Crystal Fiber (PCF) Biosensors

Photonic Crystal Fibers (PCFs) are a unique type of optical fiber distinguished by a periodic arrangement of air holes that extends along the entire length of the fiber. This microstructure serves as the cladding, and its distinctive design offers exceptional control over the light-guiding characteristics, which is not possible with traditional step-index fibers. PCFs are generally divided into two categories: index-guiding PCFs, which possess a solid core and guide light through a modified version of total internal reflection, and photonic bandgap (PBG) PCFs, which have a hollow core and trap light within this core using the photonic bandgap effect, enabling light to travel in a low-index medium such as air or a liquid [85,86]. The defining structural feature of a PCF is its cross-section, which is typically composed of a single material, such as fused silica, patterned with a lattice of microscopic air holes. The arrangement of these holes, commonly in a triangular or honeycomb lattice, and their geometric parameters—namely the hole diameter (d) and the center-to-center spacing, known as the pitch (Λ)—are the primary determinants of the fiber's optical characteristics. The ratio d/Λ, in particular, dictates the number of guided modes, the effective mode area, and the dispersion properties. By precisely engineering these parameters during the fabrication process, which often involves the "stack-and-draw" technique, it is possible to create fibers with properties like endlessly single-mode operation, large mode area, or highly tailored dispersion profiles, features that are fundamental to their application in advanced sensing platforms [87,88]. The exceptional design flexibility of PCFs makes them a powerful platform for biosensing. The air holes can be selectively filled with a liquid or gaseous analyte, enabling a remarkably strong interaction between the guided light and the sample. In solid-core PCFs, the evanescent field extends into the air holes, and infiltrating these holes with a sample containing the target analyte leads to a significant change in the effective refractive index of the guided mode. In hollow-core PCFs, the interaction is even more direct, as a substantial portion of the light propagates directly through the analyte-filled core, maximizing the light-matter interaction and leading to extremely high sensitivity [89]. This configuration is particularly advantageous as it requires minuscule sample volumes, often in the nanoliter range, making it ideal for analyzing precious biological samples. For biosensing applications, the inner surfaces of the PCF's microchannels are functionalized with specific bioreceptors. Although this process is more complex than functionalizing the exterior of a standard fiber, several methods have been devised to accomplish it. The detection mechanism is based on observing alterations in the fiber's optical characteristics, such as changes in the resonant wavelength of an inscribed grating, modifications in the output spectrum of an interferometric setup, or shifts in SPR conditions when the holes are coated with a metal layer. The distinctive capability to tailor the dispersion and modal properties of PCFs enables the enhancement of the sensor's performance for particular applications, offering the potential for significant progress in creating highly sensitive and selective lab-on-a-fiber diagnostic systems [90].

One key development is the incorporation of plasmonic materials such as silver (Ag) with protective interlayers like titanium dioxide (TiO_2). For instance, Azadi et al. [91] designed a D-shaped dual-core PCF biosensor with Ag-TiO_2 layers to stabilize silver's optical properties and adhesion. This configuration achieved a high wavelength sensitivity of 10,000 nm/RIU and excellent resolution, making it highly suitable for biochemical assays [91]. Another trend involves the use of 2D materials like phosphorene to enhance the durability and sensitivity of PCF sensors. Hajiani et al. [92] demonstrated that integrating silver with phosphorene nanoribbons improved oxidation resistance and sensing precision in near-infrared applications. Their sensor achieved wavelength sensitivity up to 1800 nm/RIU, showcasing how layered materials can fine-tune optical responses in PCFs [92]. Moreover, advanced structural geometries such as flower-core and porous-core

PCFs have emerged as powerful platforms for biosensing. Veluchamy et al. (2024) introduced a flower-core PCF design that reached a peak sensitivity of over 22,000 nm/RIU for breast cancer biomarker detection, demonstrating the potential of intricate core configurations for enhanced light–analyte interaction [93]. Finally, hybrid integration approaches continue to gain traction. Chakrabortty et al. [94] proposed a microchannel-based D-shaped PCF with gold and TiO_2 coatings. This biosensor achieved an ultra-high sensitivity of 23,500 nm/RIU, driven by precise layer engineering and channel design, ideal for small-volume biological samples [94].

As detailed in the preceding sections, each type of optical fiber biosensor possesses unique operating principles, structures, and characteristics. Selecting a suitable platform for a specific biomedical engineering application requires a thorough understanding of the strengths and weaknesses of each approach. Factors such as the required sensitivity, fabrication complexity, cost, noise immunity, and the nature of the biological sample all play a crucial role in this decision-making process. To provide a comprehensive overview and facilitate this selection, Table 1 compares these sensing platforms based on key criteria.

The versatility of PCF platforms extends beyond biochemical assays to multi-parameter physical sensing. Recent studies have demonstrated PCF-based Surface Plasmon Resonance (SPR) sensors capable of simultaneous magnetic field and temperature monitoring. By infiltrating the air holes with functional materials like magnetic fluids and utilizing selective plasmonic coatings, these sensors achieve high sensitivity and effective discrimination between physical parameters, proving their utility in complex environmental monitoring [95]. Figure 11 illustrates the cross-sectional geometry and operating principle of the proposed photonic crystal fiber structure.

Table 1. A Comparative Analysis of Different Optical Fiber Biosensor Types.

Sensor Type	Sensing Principle	Typical LOD	Response Time	Sample Matrix	Key Advantages	Key Disadvantages	Ref.
Intensity-Modulated	Measures light intensity change (absorption/scattering)	µM to mM range (e.g., ~0.76 ppm)	Seconds to Minutes	Sweat, Saliva, Water	Simple design, low cost, easy to implement	Prone to power fluctuation errors; lower accuracy	[38]
Wavelength-Modulated (FBG)	Bragg wavelength shift due to strain/RI	~1.0 µM (DNA)	Minutes (e.g., ~6 min)	Serum, Buffer	Multiplexing capability; stable in harsh conditions	Temperature cross-sensitivity; needs calibration	[96]
Wavelength-Modulated (LPG)	Resonance wavelength shift (cladding mode coupling)	~10^{-4} to 10^{-5} RIU	Minutes	Serum, Plasma	High sensitivity to external RI; tunable	Broad resonance bandwidth; temperature sensitive	[97]
Phase-Modulated (MZI)	Phase difference measurement (Interferometric)	pM to nM range	Sub-second	Tears, Serum	Ultra-high sensitivity; multiplexing potential	Complex fabrication; susceptible to mechanical noise	[98]
Phase-Modulated (FPI)	Interference from microcavity reflections	~4.1 nM (Glucose)	~0.7 s	Microfluidic samples	Compact; high measurement accuracy	Fabrication complexity; signal processing required	[99]
Plasmonic (SPR)	Surface Plasmon Resonance on metal film	fM to pM range (e.g., 10^{-7} RIU)	Real-time (<5 s)	Blood, Urine, Saliva	Extremely sensitive; label-free; real-time	Requires metal coating; sensitive to thermal drift	[100]
Plasmonic (LSPR)	Localized oscillation in nanoparticles	pM range	Real-time	Virus solution, Serum	High spatial resolution; portable integration	Limited dynamic range; reproducibility issues	[101]
Photonic Crystal Fiber (PCF)	Interaction in micro-structured holes	~10^{-6} RIU (Femtomolar)	Real-time	Gas, Liquid analytes	Tunable geometry; superior sensitivity	High fabrication cost; difficulty in filling holes	[102,103]

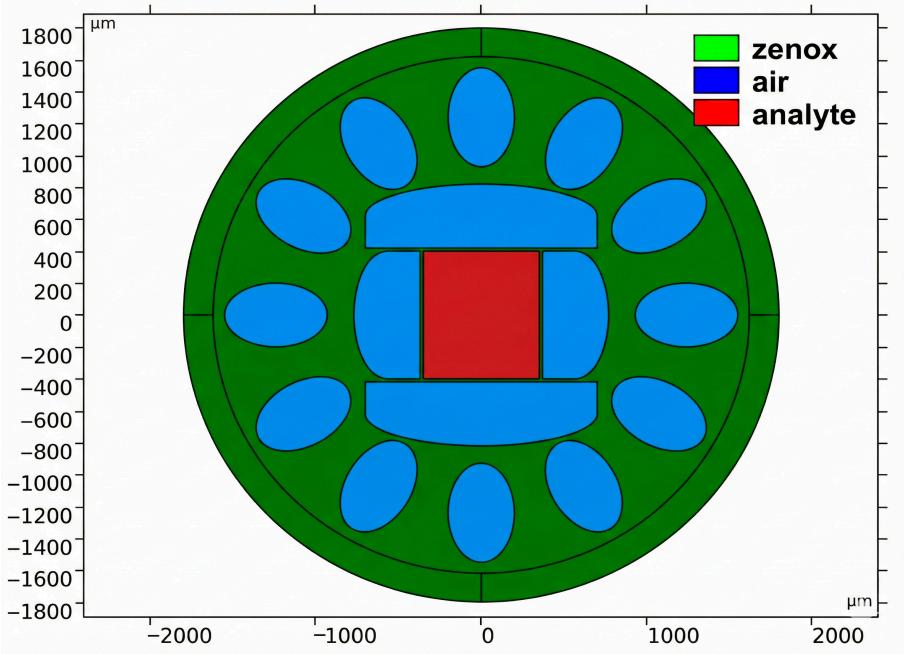

Figure 11. Operating principle of a PCF-based biosensor. Cross-sectional geometry of a Zeonex-based Photonic Crystal Fiber (PCF) sensor designed for terahertz sensing. The structure features a central rectangular core for analyte infiltration, surrounded by a hybrid cladding composed of inner rectangular air holes for mode shaping and an outer ring of elliptical air holes for enhanced confinement [104].

3. Applications in Healthcare

By virtue of their exceptional characteristics—including high sensitivity, suitability for miniaturization, capacity for remote sensing, and label-free detection capabilities—optical fiber biosensors possess a profound potential to transform the landscape of medical diagnostics and monitoring. These devices facilitate the noninvasive or minimally invasive analysis of key biomarkers in a variety of biological fluids, such as blood, urine, saliva, and interstitial fluid. This section highlights some of the most impactful applications of this technology in the healthcare field.

A central objective in contemporary medicine is the advancement of noninvasive or minimally invasive diagnostic techniques to improve patient comfort, reduce the risk of infection, and allow for more frequent health monitoring. The capacity of optical fiber biosensors to analyze a wide range of biological fluids is a significant advantage in this regard. For instance, samples like saliva and urine are completely noninvasive and easy to collect, rendering them ideal for large-scale population screening or for use in pediatric care. Conversely, fluids such as blood and interstitial fluid, which require minimally invasive collection, offer a direct view of the body's systemic condition, yielding vital information for managing chronic diseases and acute health issues. The adaptability of these sensors to function reliably within such diverse and complex biological matrices underscores their robustness and extensive applicability in clinical environments [105].

3.1. Early Cancer Detection

Detecting cancer at an early stage greatly enhances the likelihood of effective treatment. Optical fiber biosensors are highly effective in identifying cancer biomarkers even at extremely low concentrations, ranging from picomolar to femtomolar levels. These sensors are capable of detecting specific proteins such as Prostate-Specific Antigen (PSA) for prostate cancer, Cancer Antigen 125 (CA-125) for ovarian cancer, or Circulating Tumor Cells

(CTCs) that have separated from the primary tumor and entered the bloodstream [106]. Platforms utilizing SPR and LSPR are extensively used to create immunosensors for these biomarkers due to their exceptional sensitivity to refractive index changes resulting from antigen–antibody interactions. Moreover, interferometric sensors, known for their high phase sensitivity, are well-suited for identifying a minimal number of target molecules. Recent progress in fiber optic technologies has shown promising potential in early cancer detection, offering high sensitivity, real-time analysis, and minimally invasive procedures. Fiber optic biosensors, particularly those based on surface plasmon resonance (SPR), have proven to be effective in detecting various cancer cell types at an early stage by identifying minute refractive index changes caused by cancerous biomarkers. A notable design is a graphene-antimonene-coated tapered fiber optic SPR sensor, which exhibits high sensitivity for detecting skin, cervical, blood, and adrenal gland cancers. This sensor leverages antimonene for its excellent biomolecule adsorption and extensive active surface area, achieving sensitivities up to 15.24 μm/RIU and a detection limit (LOD) as low as 7.2×10^{-5} RIU [81]. Similarly, a high-performance sensor using cerium oxide and tungsten disulfide coatings has achieved a sensitivity of 29,642.9 nm/RIU for cancer cell detection, targeting cells such as HeLa and MCF7 with enhanced oxidation resistance and signal stability [107].

Further innovations include a plasmonic-photonic hybrid fiber optic sensor capable of detecting tumor markers like PD-L1 with a sensitivity of 386.3 nm/RIU. This sensor integrates Fabry–Perot interference and localized surface plasmon resonance for enhanced detection of tumor heterogeneity, offering potential for real-time and label-free clinical applications [108]. Another approach combines optical microfibers with gold nanorods and Ti_3C_2 MXene interfaces for the detection of renal cancer biomarkers. This system achieved ultralow detection limits—13.8 zM in buffer and 0.19 aM in serum—showing its power in both protein and whole-cell detection [109].

In summary, fiber optic sensors, through various material innovations and sensing configurations, are becoming powerful diagnostic tools for early cancer detection across a range of cancer types.

3.2. Infectious Disease Diagnostics

Recent advances in fiber optic biosensors have significantly improved the diagnosis of infectious diseases by enabling rapid, sensitive, and label-free detection of various pathogens. These biosensors leverage optical principles like surface plasmon resonance (SPR) and Mach–Zehnder interference, offering real-time monitoring and integration with point-of-care systems, especially valuable in healthcare settings where timely diagnosis is critical.

The outbreak of global pandemics like COVID-19 has highlighted the urgent need for rapid, accurate, and portable diagnostic tools. Optical fiber biosensors can quickly identify pathogens (viruses and bacteria) by detecting their specific genetic sequences (DNA/RNA) or surface antigens. For example, plasmonic sensors functionalized with aptamers or specific antibodies against the spike protein of the SARS-CoV-2 virus have shown the ability to detect the virus in saliva or nasal swab samples in under a few minutes [110]. Photonic Crystal Fibers (PCFs) also provide an ideal platform for developing highly sensitive sensors for detecting low viral loads, thanks to their capability for strong light-matter interaction in very small volumes [111].

One major development is the use of plasmonic fiber optic absorbance biosensors (P-FAB) for detecting viral RNA, such as SARS-CoV-2, without the need for amplification. This U-bent fiber optic sensor utilizes gold nanoparticles and complementary oligonucleotides to target viral RNA, achieving detection limits as low as 100 copies/μL in under 30 min [112]. Similarly, a fiber-based WaveFlex biosensor has been developed for detect-

ing *Staphylococcus aureus* in food and clinical samples. This system uses tapered fibers functionalized with gold nanoparticles and nanomaterials like chitosan-coated iron oxide and WS_2 quantum dots, reaching detection limits as low as 6.67 CFU/mL [113]. Further innovation is demonstrated in erbium-doped fiber laser (EDFL) biosensors that can detect single cells of *Staphylococcus aureus*. This system achieves detection down to 1 CFU/mL using interferometric filtering, offering extremely high sensitivity and specificity suitable for real-time clinical diagnostics [114]. Additionally, lossy mode resonance (LMR) fiber optic biosensors have been applied to detect inflammation-related biomarkers like C-reactive protein (CRP), which is relevant in infectious disease diagnostics. These sensors, employing tapered structures and antibody immobilization, demonstrate excellent specificity with detection limits below 0.3 μg/mL [115]. Beyond clinical settings, fiber optic biosensors are also being adapted for mobile health diagnostics. Integration with smartphones enables on-site disease detection through portable and real-time biosensing. This opens opportunities for decentralized healthcare, especially in low-resource areas [116]. Moreover, review studies emphasize the utility of fiber optic SPR biosensors for diagnosing infectious and inflammatory diseases due to their high specificity, rapid detection, and adaptability to new pathogens [117].

In addition to conventional fiber optic biosensors, photonic crystal fibers (PCFs) have emerged as a powerful platform for infectious disease diagnostics due to their highly customizable microstructured designs and superior light-matter interaction. Their internal microstructure enables precise control over optical properties, allowing for enhanced sensitivity and miniaturization—critical features for detecting low-concentration biomarkers in complex biological samples. For example, a novel PCF-based biosensor has been developed for detecting *Pseudomonas aeruginosa*, a common pathogen in hospital-acquired infections. This sensor uses surface plasmon resonance (SPR) mechanisms with a maximum wavelength sensitivity of 5000 nm/RIU, enabling detection in the refractive index range of 1.37 to 1.39 [118]. The sensor shows strong potential for microbiological diagnostics and environmental monitoring due to its high sensitivity and specificity. Another notable example is a photonic crystal fiber biosensor designed for *Chikungunya virus* detection in blood components. This biosensor employs dual-side polishing and microchannel integration with gold and TiO_2 coatings to enhance SPR effects. It demonstrated high wavelength sensitivities—up to 18,000 nm/RIU for red blood cells—making it suitable for label-free virus detection directly from complex fluids [119]. Additionally, suspended-core PCFs have been applied to surface-enhanced Raman spectroscopy (SERS)-based diagnostics, providing long interaction paths for analyte molecules and metal nanoparticles. This architecture improves Raman signal amplification and enables sensitive detection of nucleic acids like DNA and molecules such as adenine, highlighting PCFs' role in molecular-level diagnostics [120].

Together, these innovations underscore the importance of photonic crystal fiber technology in enhancing the capabilities of infectious disease diagnostics through high sensitivity, tunable optical properties, and integration into compact sensing platforms.

3.3. Glucose Monitoring for Diabetes Management

Recent research has focused on developing implantable sensors that can be placed in the subcutaneous interstitial fluid for long periods, transmitting glucose data wirelessly to an external device. Recent advances in optical fiber biosensing have opened up transformative opportunities in non-invasive glucose monitoring for diabetes management, providing alternatives to painful and inconvenient finger-prick testing. These biosensors harness light-based technologies and bio-functionalized materials to detect glucose in sweat, saliva, tears, and interstitial fluids, offering real-time, continuous monitoring suitable for wearable

healthcare solutions. Effective diabetes management requires continuous and accurate monitoring of blood glucose levels. Optical fiber biosensors have the potential to create minimally invasive or non-invasive continuous glucose monitoring (CGM) systems. A common approach involves functionalizing the fiber surface with the enzyme glucose oxidase (GOx). In the presence of glucose, this enzyme catalyzes a reaction that leads to a change in local pH or oxygen consumption. These changes can be measured by FBG, LPG, or interferometric sensors that are sensitive to refractive index variations [121].

One study highlights the growing promise of fiber optic sensors, noting their non-invasiveness, high precision, and compatibility with miniaturization—making them ideal for biomedical use, including glucose detection in diabetic patients [122]. Another work developed a highly stretchable and strain-insensitive wearable electrochemical biosensor using gold fibers to detect glucose in sweat, showing excellent sensitivity (11.7 $\mu A\ mM^{-1}\ cm^{-2}$) and performance under mechanical stress, indicating strong potential for textile integration [123].

Furthermore, novel sensor architectures using tilted fiber gratings coupled with biofunctionalized gold nanoparticles have enabled ultrasensitive detection of glucose even in artificial urine, with a detection limit as low as 2.5 nM. These sensors exploit enhanced localized surface plasmon resonance to achieve high sensitivity and specificity [124]. Additionally, a self-powered fiber-optic biosensor designed for tear-based glucose analysis achieved remarkable performance, with a detection limit of 4.1 nM and fast response time (0.7 s), demonstrating excellent selectivity and integration potential for point-of-care applications [125]. Clinical trials have also validated the reliability of optical biosensor-based wearables. A photoplethysmographic (PPG) sensor worn on the wrist showed strong correlation with traditional invasive methods in both fasting and post-meal states, with mean errors of only 7.4–7.5%, placing it within clinically acceptable accuracy ranges [126].

3.4. Real-Time Monitoring of Therapeutic Drugs

Personalized medicine requires adjusting drug dosages based on individual patient responses. Optical fiber biosensors can monitor drug concentrations in the body in real time, allowing physicians to optimize the dosage for maximum efficacy and minimal side effects. This application is particularly crucial for drugs with narrow therapeutic windows, such as chemotherapy agents and certain antibiotics. By functionalizing a fiber with specific receptors (such as aptamers) against a particular drug, its concentration in the bloodstream can be continuously measured [127]. The implications of real-time therapeutic drug monitoring (TDM) extend far beyond simple dose adjustments. The continuous data streams generated by these biosensors can fuel sophisticated pharmacokinetic and pharmacodynamic (PK/PD) models, enabling a shift from static, population-averaged dosing regimens to dynamic, personalized therapeutic strategies. This paves the way for the ultimate goal of closed-loop therapeutic systems, where the real-time feedback of the sensor is algorithmically linked to an automated drug delivery device (e.g., an infusion pump). Such a system could autonomously maintain drug concentrations within the optimal therapeutic window, maximizing efficacy while proactively preventing toxicity, representing a paradigm shift in the management of critical care and chronic conditions [128]. Building upon the foundational role of optical fiber biosensors in personalized medicine, recent advances have demonstrated their practical utility in real-time therapeutic drug monitoring (TDM). One notable development is a high-sensitivity biosensor using a tapered coreless optical fiber coated with titanium dioxide nanoparticles, which successfully measured drug concentrations by detecting refractive index changes in various drug solutions. This design achieved a sensitivity of up to 361.11 nm/RIU, offering fast, real-time readouts with high precision. Its compact and low-cost architecture supports integration into portable and wearable

healthcare systems, making it ideal for point-of-care applications in managing critical drug therapies [129]. Earlier innovations also laid important groundwork. A micromachined optical fiber biosensor based on Fabry–Perot interferometry was developed specifically for in vivo drug delivery monitoring. By embedding this sensor into a multimode fiber using MEMS fabrication techniques, researchers created a compact system capable of continuously detecting drug levels during administration. The approach allows precise real-time tracking of drug release kinetics, with potential applications in microfluidics and chronic disease management requiring tightly controlled dosing, such as oncology and immunotherapy [130].

3.5. Point-of-Care Testing (POCT)

One of the most exciting prospects for optical fiber biosensors is the development of point-of-care testing (POCT) devices. These devices are small, portable, inexpensive, and easy to use, and can provide rapid diagnostics at the patient's bedside, in clinics, or even in remote areas without the need for sophisticated laboratories. The miniaturization capability of optical fibers, their label-free operation, and the potential for integration with microfluidic platforms make them an ideal choice for this purpose. The development of smartphone-based sensors that use the phone's camera to analyze the optical signal is a significant step towards realizing fiber-optic-based POCT [131]. Recent developments in optical fiber biosensors have significantly accelerated the progress of point-of-care testing (POCT), particularly through the use of surface plasmon resonance (SPR) and localized SPR (LSPR) technology. These biosensors, often built on plastic optical fibers (POFs), are compact, low-cost, and sufficiently sensitive for rapid diagnostic use. By combining these fibers with microfluidic chips and specific bioreceptors, such as aptamers or antibodies, researchers have created portable devices capable of detecting pathogens or biomarkers in saliva, serum, or environmental samples. For example, a plasmonic POF biosensor was recently validated for detecting SARS-CoV-2 RNA and single-nucleotide mutations in sewage, highlighting its utility in public health surveillance and outbreak control [132].

Additionally, the integration of optical biosensors with enzyme-linked amplification strategies enhances the sensitivity of POCT devices. One study reported the development of a fiber-optic amplifier-based biosensor capable of detecting myoglobin and miRNA-141 with extremely low detection limits (0.5 nM and 10 pM, respectively) directly in human serum. The device, which operates in both "turn-off" and "turn-on" modes, requires no advanced laboratory equipment, making it ideal for use in remote or resource-limited settings. The entire diagnostic process is conducted in a simple centrifuge tube, underscoring its potential for global health applications [133].

To elucidate the practical utility of these diverse platforms, it is advantageous to systematically align each sensor technology with its respective healthcare application. The selection of an optimal sensor is a nuanced decision informed by the specific requirements of the diagnostic challenge, including the nature of the target biomarker, the required limit of detection, and the intended clinical environment (e.g., central laboratory versus point-of-care settings). Table 2 offers a comparative summary, highlighting the principal applications of each major optical fiber biosensor type across various medical fields, supported by recent scientific literature to illustrate the current state-of-the-art.

Table 2. Summary of Biomedical Applications for Key Optical Fiber Biosensor Platforms.

Sensor Platform	Primary Healthcare Domain	Specific Diseases/Conditions Detected	Key Biomarkers Targeted	Reference
Intensity-Modulated Sensors	Oncology	Oral and Breast Cancer	Interleukin-8 (IL-8) in saliva	[134]
	Infectious Diseases	COVID-19	Interferon-gamma (IFN-γ)	[135]
Wavelength-Modulated Sensors (FBG and LPG)	Neurology	Alzheimer's Disease	Amyloid-β42 (Aβ42)	[136]
	Oncology	Hypoxic Tumors	Carbonic Anhydrase IX (CA-IX)	[137]
Phase-Modulated (MZI and FPI)	Neurology	Alzheimer's Disease	Tau protein	[138]
	Infectious Diseases	COVID-19 RNA	cDNA of SARS-CoV-2	[139]
Plasmonic Sensors (SPR and LSPR)	Neurology	Parkinson's Disease	Dopamine	[140]
	Cardiology	Heart Failure	NT-proBNP	[141]
	Infectious Diseases	Chikungunya	CHIKV-nsP3 protein	[142]
Photonic Crystal Fiber (PCF) Sensors	Cardiology	Cardiovascular Disease	Cardiac Troponin T (cTnT)	[143]
	Neurology	Alzheimer's Disease	Amyloid-β42 (Aβ42)	[144]
	General Diagnostics	Antibody Detection (e.g., anti-IgG)	Immunoglobulins	[145]

4. Recent Advances and Emerging Trends

The field of optical fiber biosensors is a dynamic and rapidly evolving research area driven by continuous innovations in materials science, nanotechnology, photonics, and biotechnology. While the fundamental principles of many of these sensors are well established, current research is focused on overcoming existing limitations and opening new horizons for clinical applications. This section explores some of the most exciting recent advances and emerging trends that are shaping the future of noninvasive diagnostics. This evolution is largely motivated by the persistent clinical demand for diagnostic tools that are not only more sensitive and specific, but also faster, more affordable, and deployable at the point of care. Consequently, the research community is actively pursuing strategies to push the limits of detection down to the single-molecule level, enhance sensor robustness against biofouling and non-specific binding challenges inherent in complex matrices such as blood and saliva, and miniaturize and integrate optical and fluidic components into seamless, user-friendly platforms. These efforts collectively aim to bridge the gap between laboratory-based proof-of-concept demonstrations and clinically viable diagnostic devices that can have a tangible impact on patient care.

4.1. Novel Materials and Advanced Nanostructures

Beyond the gold and silver traditionally used in plasmonic sensors, recent research has explored novel materials to enhance sensor sensitivity, stability, and biocompatibility. Two-dimensional (2D) materials, such as graphene, transition metal dichalcogenides (TMDs) like MoS_2 and WS_2, and MXenes, have garnered significant attention. Graphene layers can act as a protective coating to prevent the oxidation of metal layers and, owing to their high specific surface area and ease of functionalization, can increase the adsorption capacity for biomolecules, leading to significant signal amplification [146]. Furthermore, metamaterials and metasurfaces, which are subwavelength-engineered structures, provide unprecedented control over light and can be designed to create extremely sharp resonances and enhance local electromagnetic fields, thereby increasing the sensor sensitivity severalfold [147]. Recent studies have demonstrated the power of nanodiamond-engineered plasmonic interfaces integrated onto optical fiber platforms, bringing a new dimension to sensitivity enhance-

ment. For instance, this approach provides precise morphological control over the surface structures and branching complexity, enabling tailored plasmonic resonance behavior that significantly enhances the optical sensing performance of fiber-optic biosensors. NDs drop-cast onto side-polished fiber–Au interfaces have been shown to increase the refractive index sensitivity by approximately 74%, achieving up to 3582 nm/RIU when optimized at a concentration of ~0.2 mg/mL and three casting cycles. This boost is attributed to enhanced local electromagnetic fields and stable surface functionalization, which improve signal clarity and molecular binding capacity while maintaining excellent biocompatibility and chemical robustness [148]. Embedding NDs into plasmonic fiber interfaces thus represents a promising route for noninvasive biomedical sensing with rapid response and high detection performance.

Similarly, hierarchical gold nanoisland (NI) overstructures grown directly on optical fiber end facets via a hybrid dewetting and seeded bottom-up strategy introduced a new class of fiber-integrated nanostructures. These Au NIs, decorated with branched protrusions ("multi-arm" architectures), produce sharply enhanced local fields and SERS signals, pushing detection limits down to ~10^{-7} M for standard analytes such as rhodamine 6G—approximately an order-of-magnitude improvement compared to conventional flat Au NP coatings [149].

Beyond passive signal enhancement, graphene's unique optoelectronic properties have been harnessed to create active in-fiber devices. For instance, integrating graphene coatings with Tilted Fiber Bragg Gratings (TFBG) has enabled the realization of in-fiber photoelectric devices. In this configuration, the TFBG efficiently couples core modes to the cladding-graphene interface, facilitating strong light-matter interaction and high-efficiency photoelectric conversion. This innovation opens new avenues for developing multifunctional all-fiber optoelectronics [150].

4.2. Hybrid Sensing Modalities and Multiplexing

A powerful emerging trend is the combination of multiple sensing methods into a single platform to obtain complementary information and increase the diagnostic reliability. For example, combining plasmonic sensing (SPR/LSPR) with fluorescence allows for the simultaneous detection of a molecule's binding (via the SPR signal) and confirmation of its identity or activity (via the fluorescence signal). This approach, known as dual-mode sensing, significantly improves the specificity and reduces false-positive results [151]. Significant efforts are underway to develop multiplexed sensors capable of simultaneously detecting multiple biomarkers in a single sample. This can be achieved by creating arrays of sensors on a single fiber or designing structures that respond to different biomarkers at different wavelengths. This capability is crucial for diagnosing complex diseases, such as cancer, which are often characterized by a profile of multiple biomarkers. Recent research has advanced the integration of hybrid sensing modalities within optical fiber biosensors, particularly through incorporating nanostructures and smart materials. For instance, nanophotonic catheter systems have been developed that combine multiple fiber-optic sensing techniques, such as fiber Bragg gratings, fluorescence, and Raman spectroscopy, into compact, minimally invasive devices capable of mapping tissue microstructures and monitoring biochemical parameters in real time. These multifunctional platforms utilize nanoparticle-enhanced coatings to enable plasmonic biodetection and multiplexed fluorescence sensing within the same device, thereby enhancing sensitivity and selectivity while simultaneously supporting multiple sensing functions [152]. Moreover, the application of upconversion nanoplatforms (UCNPs) has introduced a new class of hybrid biosensors that combine high-tissue-penetration near-infrared excitation with multiplexed luminescent outputs. These nanoplatforms can be engineered to detect multiple biomacromolecules,

such as nucleic acids and proteins, by finely tuning their luminescent emission and energy transfer properties. The modular nature of these probes allows for simultaneous and highly specific detection in complex biological samples, further advancing the goal of multiplexed, non-invasive diagnosis [153].

4.3. AI-Driven Data Processing and Machine Learning Integration

The raw output from optical fiber biosensors—typically high-dimensional spectral data—is frequently corrupted by environmental noise, temperature cross-sensitivity, and non-specific binding events. Traditional analysis methods, which rely on tracking simple peak wavelength shifts, often fail to capture the subtle, non-linear correlations present in complex biological matrices. To address these limitations, the integration of Artificial Intelligence (AI) and Machine Learning (ML) has emerged as a transformative approach, shifting the paradigm from univariate analysis to multivariate pattern recognition. This transition involves specific algorithmic architectures tailored to distinct sensing tasks. For spectral feature extraction and denoising, Convolutional Neural Networks (CNNs) have demonstrated superiority over traditional linear methods like Principal Component Analysis (PCA). CNNs can automatically learn hierarchical non-linear features directly from raw spectral images or 1D signal arrays, achieving high classification accuracies in differentiating between healthy and neoplastic tissues [154–157].

Following feature extraction, specific algorithms are employed based on the diagnostic objective. For qualitative classification tasks, Support Vector Machines (SVMs) are widely utilized due to their ability to map spectral data into a high-dimensional feature space and identify the optimal hyperplane that separates data classes with the maximum margin. A compelling demonstration of this capability is reported by Brusamarello et al. [158], who integrated Distributed Acoustic Sensing (DAS) with a supervised SVM classifier for structural health monitoring. By training the model with temporal and frequency domain features extracted from optical signals, they achieved a classification accuracy of 93% in distinguishing between undamaged and damaged states, validating the robustness of ML in handling complex optical data [158]. Conversely, for quantitative regression tasks—such as predicting continuous glucose concentrations—ensemble learning methods like Random Forest and XGBoost are preferred. These algorithms aggregate predictions from multiple decision trees to model complex, non-linear relationships between spectral shifts and analyte concentrations, significantly reducing prediction errors compared to simple linear regression models [155]. Finally, to address data privacy in multi-center clinical applications, Federated Learning frameworks are being adopted to train models collaboratively without sharing sensitive patient data [157]. Figure 12 illustrates the systematic workflow of such an AI-integrated sensing system, detailing the pipeline from raw data acquisition to the final algorithmic decision-making.

4.4. Towards Wearable and In Vivo Biosensors

The ultimate trajectory of optical fiber biosensing is the transition from benchtop instrumentation to fully wearable or implantable platforms capable of continuous, real-time physiological monitoring. Realizing this vision necessitates overcoming critical engineering hurdles, primarily regarding mechanical stability, autonomous power supply, and long-term biocompatibility. To address the mechanical mismatch between brittle optical fibers and soft biological tissues, recent innovations have focused on developing highly robust sensor architectures. For instance, stretchable gold fiber-based electrochemical biosensors have been engineered to withstand significant mechanical deformation, maintaining performance under strains of up to 200% [159]. This elasticity is vital for ensuring consistent data acquisition during patient movement in wearable applications. Simultaneously, the

bottleneck of power autonomy for untethered sensors is being mitigated through self-powered systems. Notable progress includes the integration of enzyme-based biofuel cells that harvest energy directly from biofluids (such as sweat or glucose), demonstrating the capability for 72 h continuous operation without external battery dependence [125].

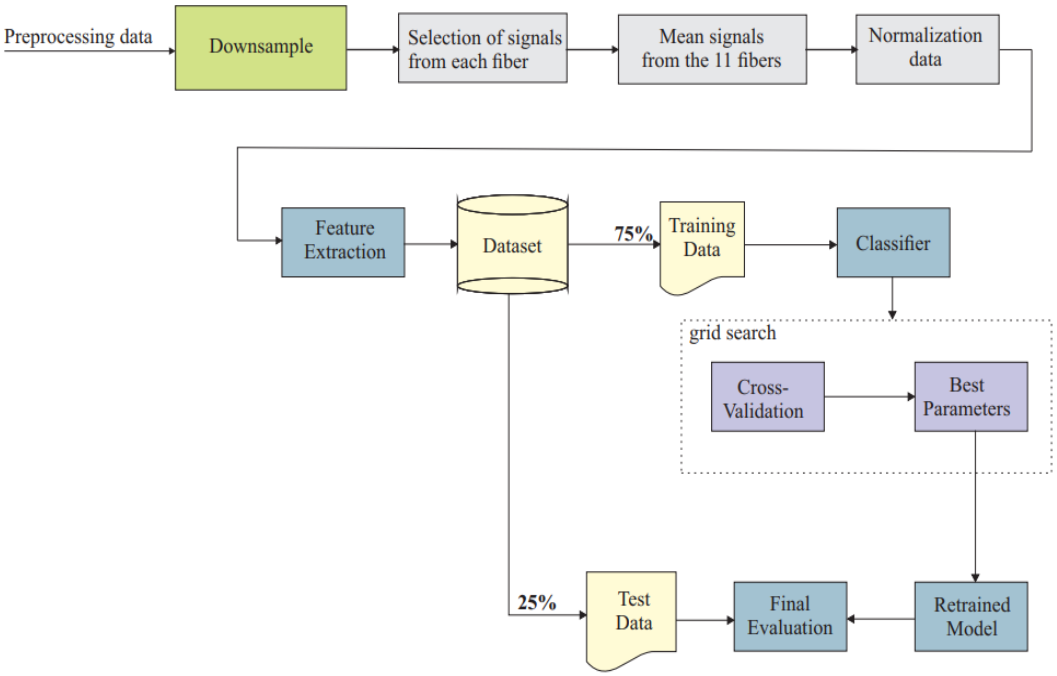

Figure 12. Systematic workflow for AI-driven data analysis in optical fiber sensing. The process illustrates the pipeline from data pre-processing and feature extraction to the training and validation of a supervised classifier (e.g., SVM), ensuring robust diagnostic performance as demonstrated in structural health monitoring applications [158].

Furthermore, ensuring seamless integration with biological systems remains a priority. Advances in materials science have introduced novel biodegradable polymer coatings and liquid metal functionalization, which not only enhance flexibility but also offer tunable degradation profiles [160]. These innovations pave the way for "transient" implantable sensors that dissolve harmlessly after their operational lifecycle, eliminating the need for surgical extraction. In parallel with these material advancements, smart textiles have accelerated the deployment of non-invasive monitoring. Biosensing fibers integrated into fabrics can now detecting pH and protease activity directly from wound exudates, enabling continuous wound healing monitoring without invasive procedures [144]. Similarly, intelligent textiles incorporating wireless data transmission and AI-assisted analysis support wearable biosensors for diverse biochemical targets in sweat and interstitial fluids [161]. In vivo applications are also advancing; for example, a Fabry–Perot interferometric sensor was recently integrated into microfluidic systems for precise, continuous drug delivery monitoring inside the body [130]. Collectively, these engineering breakthroughs suggest that wearable and implantable optical fiber biosensors are moving rapidly from experimental concepts to clinical readiness.

While the potential of these platforms is transformative, their widespread adoption faces persistent challenges. Progress necessitates concerted efforts to address fundamental interdisciplinary issues. To offer a structured perspective, Table 3 presents a forward-looking analysis of these grand challenges, moving beyond the current state-of-the-art to identify the foundational breakthroughs required for the next decade.

Table 3. A Forward-Looking Analysis of Grand Challenges and Required Breakthroughs for Next-Generation Wearable Biosensors.

Grand Challenge	Current Limitations (SOTA)	Next-Generation Solutions	Required Breakthroughs	Clinical Impact
1. Biocompatibility And Biofouling	Temporary efficacy; coating degradation; immune response.	• Living-material interfaces • Self-renewing coatings	• Synthetic bio-interfacing • Robust biointerfaces	Long-term in situ monitoring; reduced maintenance.
2. Power Management	Low energy density; instability; battery dependence.	• Enzymatic biofuel cells (sweat/glucose) • Optogenetic harvesting	• High-output enzymatic systems • Biocompatible nanogenerators	Autonomous, multi-year implant operation.
3. Data Integrity And Security	Interference; latency; vulnerability to hacking.	• Quantum encryption • Edge-AI processing	• Low-power quantum keys • Neuromorphic chips	Secure, real-time remote diagnostics.
4. Miniaturization	Size vs. sensitivity trade-off; signal crosstalk.	• Molecular photonic circuits • 3D-printed fiber systems	• Femtosecond nano-patterning • Adaptive nanophotonics	Imperceptible, multiplexed physiological monitoring.
5. Multi-Analyte Monitoring	Cross-reactivity; signal drift; matrix interference.	• AI-adaptive algorithms • Molecular logic gates	• On-fiber ML integration • Synthetic logic circuits	Accurate real-time diagnostics in complex fluids.
6. Stability And Degradability	Uncontrolled degradation; surgical retrieval required.	• Triggered dissolution (pH/ultrasound) • Bio-resorbable photonics	• Tunable degradation kinetics • Optically active biomaterials	Transient diagnostics; elimination of retrieval surgery.

5. Challenges and Future Prospects

Optical fiber biosensors are on the verge of revolutionizing medical diagnosis and healthcare. As reviewed in this article, the ability of these platforms to provide highly sensitive, real-time, label-free, and minimally invasive measurements offers immense potential for personalized medicine and early disease detection and management of chronic conditions. However, to fully realize this potential and transition this technology from laboratory prototypes to ubiquitous clinical tools, a series of significant scientific and engineering challenges must be addressed in the future.

One of the most persistent challenges is Biocompatibility and Biofouling. When a sensor is exposed to a complex biological fluid, such as blood, proteins, and cells, they rapidly adsorb onto the sensor surface, creating an undesirable layer. This phenomenon, known as biofouling, can severely impair the performance of the sensor, reduce its sensitivity, and lead to inaccurate results. Although anti-fouling coatings, such as hydrophilic polymers, have shown progress, their long-term stability, particularly for implantable sensors, remains a major obstacle. The development of "smart" materials that can actively resist fouling or self-cleaning is a critical area of research.

Another significant challenge is Multiplexing and Reliability. Many diseases cannot be diagnosed using a single biomarker and require the simultaneous measurement of a panel of molecules. The design of fiber-optic platforms that can accurately measure multiple analytes without signal cross-talk is technically complex. Furthermore, ensuring the Long-term Stability and Recalibration of sensors, particularly for wearable devices that must operate continuously for days or weeks, is a fundamental engineering challenge. Bioreceptors (such as antibodies) can degrade over time, necessitating strategies for in situ recalibration or the development of highly stable synthetic receptors, such as aptamers.

From a commercialization perspective, Scalable Manufacturing and Cost-Effectiveness are of paramount importance. Many advanced fiber-optic structures fabricated in laboratories require complex and expensive processes. For instance, the traditional "stack-and-draw" method utilized for Photonic Crystal Fibers (PCFs) relies on manual assembly of preforms, which severely restricts reproducibility and limits the potential for mass production [88]. To overcome these scalability issues, emerging technologies such as 3D-printed fiber structures are being explored to enable the automated and high-precision fabrication of complex geometries [161]. In parallel with structural fabrication, surface metallization presents a formidable challenge, particularly for plasmonic sensors requiring uniform films (e.g., 40–50 nm Au). Conventional line-of-sight deposition methods often fail to achieve conformal coatings inside high-aspect-ratio microstructures, leading to signal instability. Moreover, the weak adhesion of noble metals to silica under mechanical stress, such as bending, can result in film delamination. To mitigate these issues, advanced techniques like Atomic Layer Deposition (ALD) are increasingly adopted to ensure atomic-level uniformity and robust adhesion. The development of manufacturing methods that can produce these sophisticated sensors at low cost and high volume is essential for their entry into the market and healthcare systems. Finally, the path to Regulatory Approval for any new medical device is long and costly, requiring rigorous proof of the device's safety, reliability, and clinical efficacy.

Despite these challenges, the future outlook for optical fiber biosensors is exceptionally bright. Converging advances in materials science, artificial intelligence, and microfluidic systems have opened new frontiers. We are moving towards a new generation of "smart" and integrated devices that not only collect data but also interpret it using machine learning algorithms to provide actionable clinical insights. The ultimate vision is the realization of predictive and preventative medicine, where a discreet wearable or implantable sensor continuously monitors the body's physiology and can predict the onset of a disease before clinical symptoms appear, allowing individuals to take preventive action. These sensors will form the backbone of closed-loop therapeutic systems or "theranostics," in which real-time diagnosis automatically triggers the delivery of a precise therapeutic dose. Ultimately, this technology will not only transform how individual health is managed but will also provide powerful tools to address global health challenges, from managing pandemics to delivering advanced healthcare in remote areas.

6. Conclusions

This review charts the evolutionary trajectory of fiber-optic biosensors from seminal intensity-based concepts to contemporary, ultrasensitive, and highly engineered plasmonic and photonic crystal platforms. The field has matured to the point where the fundamental principles of photonics are well established, providing a powerful and versatile toolkit for biomedical analysis. However, the translation of these laboratory innovations into ubiquitous clinical instruments necessitates surmounting the principal obstacles within the technology's "valley of death." The key challenges—biocompatibility and biofouling, long-term stability and reliability, and scalable, cost-effective manufacturing—represent the three pillars of this field. Overcoming these challenges is the primary mission of the field in the coming decade. The future landscape is promising, as the emerging trends discussed herein are not disparate advancements but rather converging forces that directly address these challenges. The advent of synthetic bioreceptors, such as aptamers, coupled with advanced antifouling surface chemistries, is poised to resolve the critical issues of stability and biocompatibility. The integration of artificial intelligence and machine learning will substantially enhance reliability by enabling the extraction of coherent signals from noisy real-world data. In parallel, breakthroughs in nanofabrication and additive manufacturing

are paving the way for the scalable and economically viable production of these devices. The ultimate vision is the realization of predictive and preventative medicine, wherein wearable or implantable sensors continuously monitor physiological parameters and stream data to AI-driven systems to preemptively identify disease onset before clinical symptoms manifest. This will catalyze a paradigm shift from reactive treatment to a proactive, preventive, and truly personalized healthcare model. Such a transformation will unlock the full potential of closed-loop "theragnostic" (therapy + diagnostic) systems, fundamentally revolutionizing both individual patient care and global public health.

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