



Photonic Crystal Fiber Biosensors for Non-Invasive Disease Detection via Breath Analysis

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ABSTRACT

Non-invasive diagnostic methods are pivotal in modern healthcare, enabling timely and accurate disease detection while minimizing patient risk and enhancing compliance. Photonic crystal fibers (PCFs) microstructured optical fibers with periodic air holes offer unparalleled light-matter interaction capabilities, positioning them as a transformative platform for developing highly sensitive and specific biosensors. This review article extensively overviews PCFs in non-invasive disease diagnosis. It highlights their fundamental principles, various sensing mechanisms, and essential applications in detecting illnesses such as cancer, diabetes, and respiratory conditions through breath analysis. Remarkably, PCF based platforms have shown outstanding performance, achieving sensitivity levels as low as sub-nanogram-per-millilitre in biomarker detection.

This article compares PCF sensors with conventional diagnostic approaches, highlighting their superior precision and versatility. Recent advancements, including innovations in sensor design, material functionalization, and integration with microfluidic and computational systems, are critically evaluated. Furthermore, the review addresses key challenges, such as fabrication complexity, cost-effectiveness, biological interfacing, and clinical translation, offering insights into overcoming these barriers. By synthesizing cutting-edge research, this article is an invaluable resource for researchers, clinicians, and engineers advancing next-generation non-invasive diagnostic tools.

Keywords: Photonic crystal fiber, non-invasive diagnosis, optical sensing, biosensors, biomarker detection

1. INTRODUCTION

The paradigm of modern healthcare is increasingly defined by the pursuit of early, accurate, and patient-centric disease diagnosis, a cornerstone for improving clinical outcomes and enhancing quality of life. Non-invasive diagnostic techniques, which leverage biological samples such as breath, saliva, urine, or interstitial fluid, have emerged as transformative tools, eliminating the pain, infection risks, and logistical burdens associated with invasive procedures like blood draws or biopsies [1]. These methods are particularly critical for early disease detection, where timely intervention can significantly improve survival rates, as evidenced in cancer diagnostics, and facilitate continuous monitoring of chronic conditions such as diabetes [2]. However, traditional diagnostic modalities, including magnetic resonance imaging (MRI), computed tomography (CT), and laboratory-based assays, often entail high costs, bulky equipment, or invasive sampling, limiting their accessibility and suitability for point-of-care (POC) applications [3].

In this context, optical biosensing technologies have garnered significant attention for their potential to deliver rapid, sensitive, and compact diagnostic solutions. Among these, photonic crystal fibers (PCFs), introduced in 1996, represent a groundbreaking advancement in fiber optics, distinguished by their



microstructured cladding of periodic air holes that enable unprecedented control over light propagation [4]. Unlike conventional step-index optical fibers, PCFs offer tailored optical properties, including endlessly single-mode operation, customizable dispersion, and enhanced light-matter interactions, achieved through designs such as solid-core, hollow-core, or complex variants like D-shaped or plasmonic-coated fibers [5,6]. These attributes make PCFs exceptionally suited for biosensing, where tight light confinement and strong analyte interactions enable the detection of minute biomarker concentrations, such as proteins, glucose, or volatile organic compounds (VOCs) in breath [7].

The rapid development of biosensing technologies has significantly enhanced the prospects of non-invasive disease diagnostics. Among these, breath analysis has emerged as a highly promising technique, primarily due to its non-invasiveness, rapid response, and potential for real-time monitoring of various physiological and pathological conditions [8]. The human breath contains a complex mixture of volatile organic compounds (VOCs), gases, and biomolecular markers that are reflective of the body's metabolic and disease states [9]. Breath biomarkers such as ammonia, acetone, hydrogen peroxide, and carbon monoxide are correlated with diseases including renal failure, diabetes, bronchiectasis, and hyperbilirubinemia [10-12].

To accurately detect these breath biomarkers, biosensors must be highly sensitive, selective, stable, and capable of real-time operation. Photonic crystal fiber (PCF)-based biosensors are rapidly gaining attention for these purposes due to their superior optical properties and capacity for functional integration with plasmonic materials and biochemical receptors [13]. Photonic crystal fibers are a subclass of optical fibers that use periodic microstructures to confine and guide light, offering exceptional flexibility in tailoring their modal and dispersion characteristics [14].

By leveraging PCF designs with surface plasmon resonance (SPR), sensitivity to analyte refractive index changes can be significantly enhanced. When noble metals like gold or silver are incorporated into the PCF structure, localized plasmonic fields are generated that enhance the interaction between light and target molecules [15,16]. These hybrid configurations are particularly well-suited for detecting gaseous biomarkers in breath due to their high signal-to-noise ratios, low detection limits, and rapid response times [17].

Ammonia, a common biomarker in exhaled breath associated with renal disorders, has been effectively detected using PCFs featuring elliptical core holes and tunable confinement properties [12]. Similar structures have demonstrated sensitivity upwards of 81%, highlighting their potential for clinical application. Further, CO detection—indicative of hyperbilirubinemia—has been achieved through a hollow-core hexagonal PCF sensor with a reported sensitivity of 64.28% and low confinement loss [11]. This approach shows promise for diseases like jaundice where CO levels in breath correlate with bilirubin concentration.

One of the principal strengths of PCF biosensors is their structural adaptability, which enables multiplexed detection of multiple biomarkers. For instance, dual- or multi-core PCFs can support simultaneous detection of distinct analytes by leveraging spatially separated sensing regions within a single fiber [18]. Such designs facilitate monitoring of diseases like malaria across various parasitic stages through refractive index variation of red blood cells [19].

Innovations such as D-type fibers, slotted geometries, and nanocoating layers further refine the sensitivity and selectivity of these biosensors [14,17]. Incorporation of two-dimensional materials such as phosphorene and graphene into the sensing layers enhances SPR stability and reduces oxidation effects, crucial for repeatable and durable measurements [20].

In addition to physical architecture, the integration of signal processing techniques such as artificial neural networks (ANN) with PCF biosensors can facilitate rapid and intelligent breath biomarker interpretation. A recent example includes a smartphone-based ANN system capable of detecting hydrogen peroxide in breath—a marker for bronchiectasis—with a correlation coefficient of 0.941 [9].

Photonic crystal fiber biosensors are also highly adaptable to fabrication innovations. Technologies such as chemical vapor deposition, selective etching, and femtosecond laser inscription allow precise tuning of fiber geometries and material coatings, which is vital for tailoring the sensors to specific breath analytes [21].

Finally, the miniaturization and cost-effectiveness of PCF biosensors render them especially promising for point-of-care diagnostics. Portable configurations such as liquid-crystal-based PCF lasers and dual-core SPR fibers offer fast, low-power solutions for clinical and remote health monitoring settings [22].

This review article aims to synthesize the transformative potential of PCF-based biosensors in non-invasive disease diagnosis, with a particular focus on breath analysis. By exploring their theoretical foundations, diverse sensing mechanisms, and applications in detecting critical diseases like cancer, diabetes, and respiratory conditions, we highlight the superior sensitivity, compact integration, and adaptability of PCFs compared to traditional optical fibers and free-space optics. The article critically evaluates recent



advancements in sensor design, material integration, and computational enhancements, while addressing challenges such as fabrication complexity, cost, and clinical translation. Structured to provide both foundational insights and cutting-edge perspectives, this review serves as a comprehensive resource for researchers, clinicians, and engineers driving the development of next-generation diagnostic technologies.

2. Theoretical Background and PCF Technology

Photonic Crystal Fibers (PCFs) guide light based on principles distinct from conventional optical fibers, which rely on total internal reflection (TIR) at the interface of a high-index core and a lower-index cladding. PCFs achieve light confinement through two primary mechanisms: the photonic bandgap (PBG) effect or modified total internal reflection (m-TIR), also known as index-guiding [4,6]. Their unique structure, typically a periodic array of microscopic air holes running along the fiber's length within a bulk material (commonly silica), gives rise to their exceptional properties.

2.1. Structure and Optical Properties of PCFs

The cross-sectional structure of a PCF is defined by parameters such as the pitch (distance between the centers of adjacent air holes, Λ), hole diameter (d) and the ratio d/Λ . These parameters, along with the arrangement of the holes (e.g., triangular, square, or honeycomb lattice), determine the fiber's optical characteristics.

Index-Guiding PCFs (Solid-Core PCFs): These PCFs typically have a solid core formed by a missing air hole or a region of higher refractive index material at the center of the periodic cladding structure. Light is confined to this core because the microstructured cladding has an effectively lower average refractive index than the core. The air holes act to lower the effective refractive index of the cladding region. These fibers operate on a principle analogous to TIR in conventional fibers but offer greater flexibility. They can be designed to be "endlessly single-mode," meaning they support only the fundamental mode over an extremely broad range of wavelengths [23]. The evanescent field, which extends into the cladding holes, can interact with any material present within them, forming the basis for sensing.

Photonic Bandgap PCFs (Hollow-Core PCFs): In these fibers, light is confined to a low-index core (often an air-filled hollow core) by the photonic bandgap effect of the surrounding microstructured cladding. The periodic cladding acts as a two-dimensional photonic crystal, exhibiting photonic bandgaps—frequency ranges where light cannot propagate through the cladding. If the operating wavelength falls within such a bandgap, light is trapped and guided within the hollow core. Hollow-core PCFs (HC-PCFs) are particularly advantageous for sensing applications where a large portion of the guided light needs to interact directly with gaseous or liquid analytes filling the core, leading to stronger light-matter interaction compared to evanescent field sensors [24].

Key optical properties of PCFs relevant to sensing include:

High Design Flexibility: The ability to tailor the d/Λ ratio and lattice structure allows for precise control over mode effective index, nonlinearity, dispersion, and birefringence.

Enhanced Light-Matter Interaction: In solid-core PCFs, the evanescent field can be engineered to have significant overlap with analytes in the air holes. In HC-PCFs, the overlap can approach 100% within the core.

Tunable Birefringence: By introducing asymmetry into the cladding structure (e.g., elliptical holes or different hole sizes along orthogonal axes), high birefringence can be achieved, which is useful for polarization-sensitive measurements.

Broad Wavelength Guidance: PCFs can be designed to guide light from the ultraviolet (UV) to the mid-infrared (MIR) regions, opening up possibilities for various spectroscopic techniques [25].

2.2. Mechanisms of PCF Use in Biosensing

PCF-based biosensors predominantly rely on detecting changes in optical properties (refractive index, absorption, fluorescence, Raman scattering) induced by the interaction of light with target biological analytes.

Refractive Index (RI) Sensing: This is one of the most common sensing modalities. The presence of target biomolecules or changes in their concentration alters the effective refractive index of the medium within the PCF's air holes or core. This RI change, Δn , causes a shift in the guided mode's properties, which can be detected through various interrogation techniques:

Resonance-Based Sensing: Incorporating resonant structures like long-period gratings (LPGs), Fabry-Pérot interferometers, or Mach-Zehnder interferometers within the PCF allows for sharp spectral features that shift significantly with small RI changes. Surface Plasmon Resonance (SPR) can also be excited on metallic layers deposited within PCF holes, providing extremely high RI sensitivity [26].

Interferometric Sensing: Changes in the optical path length due to RI variations can be detected using interferometric setups, often Sagnac or Mach-Zehnder interferometers incorporating a PCF sensing arm [27].

Spectral Shift Detection: Simple transmission or reflection spectra can show shifts in interference fringes or cut-off wavelengths due to RI changes in the analyte.

Absorption Spectroscopy: If the analyte has specific absorption bands at certain wavelengths (e.g., in the near-infrared or mid-infrared for molecules like glucose or methane), Beer-Lambert's law can be applied. HC-PCFs are ideal for this, as the analyte can be filled into the core, allowing for long interaction lengths and thus high sensitivity.

Fluorescence Spectroscopy: PCFs can be used to efficiently excite and collect fluorescence from labeled biomolecules or intrinsic fluorophores. The tight light confinement can enhance excitation efficiency, and the fiber structure can optimize collection of the emitted fluorescence signal. This is valuable for detecting specific DNA sequences or proteins.

Surface Enhanced Raman Scattering (SERS): By coating the internal surfaces of PCF holes with plasmonically active nanoparticles (e.g., gold or silver), the Raman signal from adsorbed analytes can be enormously amplified. This allows for highly specific molecular fingerprinting and detection of trace analytes [28].

2.3. PCF Structure and Interaction with Biological Samples

For biosensing, the PCF must be interfaced with the biological sample. This often involves infiltrating the liquid or gaseous sample into the air holes or the hollow core. Microfluidic systems are commonly integrated with PCFs to precisely deliver small sample volumes and control the interaction environment. The internal surfaces of the PCF may also be functionalized with specific capture molecules (e.g., antibodies, aptamers, enzymes) to ensure selective binding of the target analyte, thereby enhancing specificity and sensitivity. Recent advances have shown that dual-functionalization of PCFs with nanocavities and aptamers can significantly improve capture efficiency and detection limits for biomarkers, achieving femtomolar-level sensitivity in clinical samples [29].

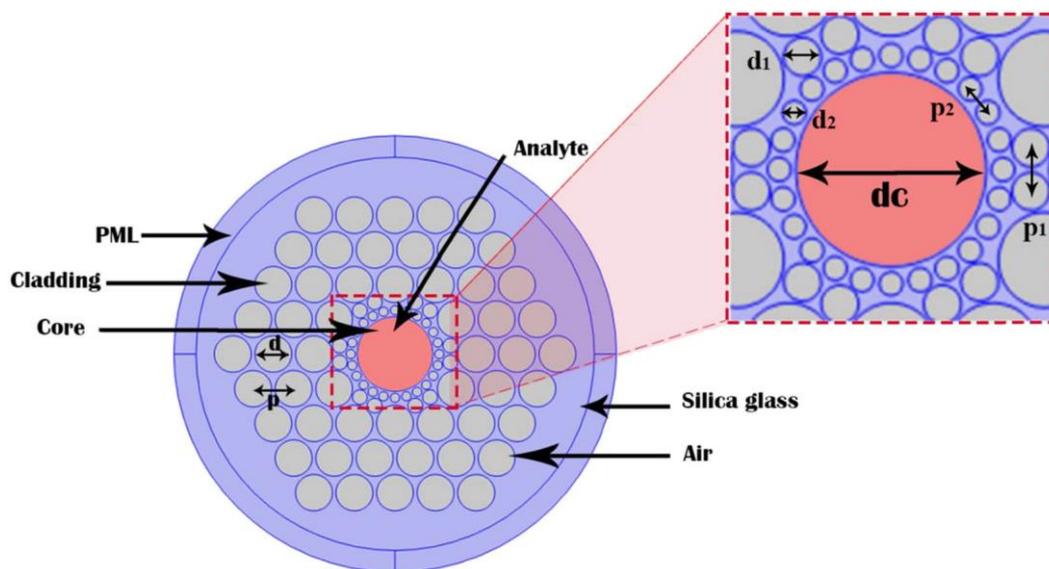


Fig. 1. Schematic diagram of a hollow-core photonic crystal fiber for biosensing applications [30].

3. Applications in Non-Invasive Disease Diagnosis

The utilization of photonic crystal fiber (PCF) biosensors in disease diagnostics represents a transformative shift from traditional invasive and imaging-based modalities toward rapid, non-invasive, and cost-effective solutions. These biosensors exploit the unique optical properties of PCFs such as high sensitivity, tunable modal confinement, and surface plasmon resonance (SPR) to detect specific biomarkers present in exhaled breath, offering real-time and early-stage disease diagnosis without physical discomfort or clinical complexity.

Exhaled breath contains a spectrum of volatile organic compounds (VOCs), gases, and metabolites that are associated with metabolic and systemic diseases. Ammonia is a recognized marker of renal dysfunction and hepatic encephalopathy [12], while carbon monoxide levels in breath can be correlated with hyperbilirubinemia [11]. Similarly, acetone is linked to diabetes, and hydrogen peroxide (H_2O_2) has been identified as a key marker in bronchiectasis and respiratory inflammation [9,10].

PCF biosensors are capable of selectively detecting these biomarkers at parts-per-billion (ppb) or even parts-per-trillion (ppt) levels. This is enabled by tailored photonic structures that amplify light-matter interactions and signal transduction with extremely low detection limits [20]. As a result, diseases such as diabetes, kidney failure, respiratory infections, malaria, and various cancers can be diagnosed and monitored continuously using breath-based PCF biosensors.

Traditional diagnostic methods such as magnetic resonance imaging (MRI), computed tomography (CT), blood tests, and biopsies, while effective, are often invasive, expensive, require specialized equipment, and involve discomfort for the patient. In contrast, PCF biosensors offer non-invasive, portable, real-time detection that can be administered at the point of care or even in home settings [13].

Table 1. Comparison of PCF Biosensors vs Traditional Diagnostic Modalities

Feature	PCF Biosensors	MRI/CT Imaging	Blood Tests / Biopsy
Invasiveness	Non-invasive	Non-invasive / Minimally invasive	Invasive (blood draw, tissue removal)

Detection Speed	Seconds to minutes	Minutes to hours	Hours to days
Sample Required	Exhaled breath	Entire body scan	Blood/tissue
Cost per Test	Low	High	Medium
Equipment Required	Portable, fiber-optic	Large, expensive imaging systems	Lab analyzers
Usability in Remote Areas	Excellent	Poor	Moderate
Real-time Monitoring	Yes	No	No
Operator Skill Needed	Minimal	High	Moderate
Risk to Patient	None	Radiation (CT), Contrast agents (MRI)	Infection, pain, complications
Suitability for Screening	Excellent (fast, scalable)	Poor (costly, slow)	Moderate

Table 2. Diseases Detectable via Photonic Crystal Fiber (PCF) Sensors Using Breath Analysis

Disease	Breath Biomarker	PCF Type / Structure	Sensitivity	Reference
Renal Failure	Ammonia (NH ₃)	Elliptical-hole PCF with silver coating	~81.05% relative sensitivity	[12]
Hyperbilirubinemia	Carbon Monoxide (CO)	Hollow-core hexagonal PCF	64.28% sensitivity, 3.81 × 10 ⁻³ dB/m loss	[11]
Diabetes	Acetone	Liquid crystal-based fiber laser sensor	LOD ≈ 65 ppm, R ² = 0.99 correlation	[10]
Bronchiectasis	Hydrogen Peroxide (H ₂ O ₂)	Colorimetric sensor + neural network processing	LOD ≈ 0.011 ppm	[9]
Malaria	Refractive index of RBCs	Multi-layer elliptical-lattice PCF with SPR	Up to 14,285.71 nm/RIU (wavelength sensitivity)	[19]
Cancers (Breast, Skin, etc.)	RI of malignant cells	Gold/TiO ₂ -coated PCF with dual microchannels	Up to 24,285.71 nm/RIU (for breast cancer)	[15]

4. Conclusion

In conclusion, the convergence of photonic crystal fiber (PCF) technology and breath-based biomarker analysis represents a paradigm shift in biomedical diagnostics. As global healthcare systems accelerate the transition from reactive treatment to proactive and preventive care, the urgent need for diagnostic tools that are rapid, non-invasive, cost-effective, and highly sensitive becomes paramount. PCF biosensors are uniquely positioned to meet this demand by leveraging their microstructured design, tunable optical properties, and surface plasmon resonance (SPR) enhancements to enable the real-time, trace-level detection of volatile organic compounds and disease-specific gases in exhaled breath. This review has highlighted the vast potential of PCF-based platforms across a spectrum of diseases including renal failure, diabetes, respiratory infections, hyperbilirubinemia, malaria, and various cancers demonstrating their capability for non-invasive diagnosis via exhaled biomarkers. Beyond offering superior analytical performance compared to conventional methods such as CT, MRI, and blood-based assays, these devices provide unparalleled portability, ease of integration with IoT and AI systems, and suitability for deployment at the point-of-care and in low-resource settings. Significant technological advancements, encompassing a range of PCF geometries from hollow-core and slotted to advanced dual-core and D-type structures, indicate that PCF biosensors are rapidly evolving beyond theoretical constructs into clinically relevant instruments with tangible real-world applicability. The integration of novel functional materials like graphene, phosphorene, and TiO_2 , alongside sophisticated adaptive signal processing techniques such as neural networks, further enhances their diagnostic precision and operational stability. Despite their immense promise, the successful widespread deployment of these technologies necessitates addressing crucial challenges. Rigorous clinical validation, the establishment of robust calibration protocols, and the definition of universal biomarker baselines across diverse populations and conditions are essential prerequisites. Furthermore, seamless integration with advanced AI platforms, secure cloud-based data infrastructure, and wearable systems will be critical for fully realizing their utility within clinical and personalized healthcare ecosystems. Ultimately, photonic crystal fiber biosensors signify more than just an incremental technological improvement; they herald a genuine diagnostic renaissance. By transforming breath into a readily readable, reliable biomarker stream, they open new frontiers for truly non-invasive, intelligent, and patient-centric medicine. With continued innovation, dedicated interdisciplinary collaboration, and a strong translational focus, these intricate fibers of light hold the potential to become vital new lifelines in the future of preventive and personalized healthcare.

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