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Advances in intelligent fiber-optic microfluidic-embedded technologies for empowered sensing performance: a review

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Abstract: The convergence of Lab-on-Fiber (LoF) technology, microfluidics, and artificial intelligence (AI) is emerging as a new and powerful paradigm for next-generation intelligent sensing systems. Combining AI with LoF-microfluidic devices can cover the residual gap by enhancing precise microfluidic control, data analysis, adaptive calibration, and predictive sensing, thereby opening new pathways for intelligent, miniaturized, reliable, and multifunctional devices for biomedical sensing and environmental monitoring. Microfluidic technologies leverage high-precision and flow rate-controlled sample delivery, reagent optimization, and simple prototyping, which make them excellent for real-time sensing. LoF devices showcase unique light control at the nanoscale level and their integration onto microfluidic chips empowers signal-to-noise ratio and, ultimately, limit of detection in a controlled environment. Advances in materials science and engineering have allowed the realization of different types of nanostructures which are integrated onto fiber sensors whose performance can be optimally tuned to detect a variety of markers and molecules. However, open challenges still exist, such as scalability, reproducibility of results, detection of multiple targets, effective compensation of interfering parameters and fast data processing. Innovative AI-driven solutions and novel functional bio-/materials are being developed to overcome these barriers and possibly meet the future demands. A roadmap toward intelligent LoF-microfluidic platforms is finally envisioned.

Keywords: optical fiber sensors; biophotonics; microfluidics; artificial intelligence

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1 Introduction

The development of advanced, portable, reliable and high-performance sensing platforms for the detection of molecules surely represents a cutting-edge scientific field, with involvement in a very broad range of applications like biomedical diagnosis, environmental monitoring and pharmaceutics above all[1–5].

The convergence of microfluidic systems and photonic biosensors has facilitated the realization of multiple laboratory functions within a single chip, thereby fostering the advancement of photonic lab-on-a-chip technology. While significant strides have been made to incorporate such sensors into compact and user-friendly platforms, several critical applications—such as effective and reliable point-of-care (PoC) diagnostics and in vivo biosensing—continue to necessitate sensor probes capable of conducting measurements in specific, often challenging-to-access locations. Optical fibers, owing to their unique light control at nanoscale and capability to transmit light to remote sites, represent an optimal solution to address these conditions. This has spurred the integration of the superior performance characteristics of photonic biosensors deployed on chips with the distinct advantages offered by optical fibers,

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culminating in the development of Lab-on-Fiber (LoF) technology[6–8]. The synergy of hardware integration with artificial intelligence (AI)-driven data analysis can dramatically advance microfluidic-embedded LoF technologies with empowered sensing performance toward becoming intelligent sensing systems capable of adaptive, autonomous, and predictive operation, thus bringing them to the same level of lab-on-a-chip technology.

The concept of LoF lies in the integration of functionalized materials on micro- and nanoscale dimensions referred to as "labs" with optical fibers, enabling the creation of miniaturized, sophisticated, and fully fiber-based platforms. Such innovations hold significant promise for applications in label-free chemical and biological sensing, among others. LoF technology is categorized into three primary paradigms based on the specific location where functional materials are integrated with optical fibers. These include "lab-on-tip" where functional materials are applied to the tip of the optical fiber; "lab-around-fiber", where functional materials are embedded on the external surface of optical fibers; and "lab-in-fiber", where functional materials are incorporated within the internal holey structure of specialty optical fibers like microstructure optical fibers (MOFs) and photonic crystal fibers (PCFs).

LoF technology integrated with microfluidics has undergone huge advances in recent years for ample sensing applications. The combination of microfluidics into fiber optic platforms dramatically empowers the sensitivity while making them ideal for real-time measurements in both harsh environments and biomedical settings. Moreover, this combination leverages portability along with miniaturization that in turn enhances their practical use in different applications. The detection capability of biochemical signals using optical fiber sensors has already been proved to reach remarkable performance[9–11], enabling biomarker tracking in clinically-mimicking scenarios toward the development of advanced non-invasive PoC devices[12–14].

LoF technology has seen the crucial step forward when nanomaterials have started to be integrated with optical fibers[15], which created sensitive platforms and also improved manufacturing methods like 3D printing and then made quick prototyping and customization of these devices easy[16]. This capability is vital for producing devices that are both effective for real-world deployment and adaptable for various sensing scenarios[17–19]. The design of microfluidic-embedded optical fiber systems showcased the adaptability of LoF in biochemical sensing by means of the integration of functional coatings and nanostructured surfaces, significantly improving surface sensitivity and then detection capability[20–22]. These advances have provided an innovative method to realize portable, sensitive diagnostic equipment with real-time analytical capacity, hence paving new paths in patient monitoring and clinical diagnostics[23]. A significant development in LoF technology has been the use of cavity-enhanced structures, which enabled stronger light confinement and interaction length, hence promoting improved limit of detection (LoD) and faster detection time[20,24]. Plasmonic nanoparticles on fiber tips have shown extraordinary biosensing properties by increasing light scattering and greater interaction efficiency[25,26]. The polymer-assisted transfer techniques further augmented these capabilities, allowing for the precise deposition of plasmonic elements onto the optical fibers which can be customized depending on the sensing requirements[24,27]. Such methodological innovations are pivotal for creating flexible, multifunctional platforms capable of operating effectively in diverse real-world applications[8,28].Techniques such as femtosecond laser-induced polymerization have enabled intricate micro- and nanoscale structures to be formed on the optical fibers, paving the way for multifunctional diagnostic capabilities[29,30].

Another important application of LoF technology lies in wearable devices thanks to continuously monitor response behavior. Microfluidic-embedded wearable devices enable capture and real-time analysis to provide instant physiological condition feedbacks. Nyein et al. proposed a microfluidic sensor patch to collect sweat effectively to dynamically analyze the level of glucose and electrolytes, which plays a critical role in managing diabetes[31,32]. Different studies have also noted the significance of creating environmentally responsive materials for LoF systems. By adjusting the sensing structure and/or sensing principle of fiber sensor or the design of microfluidic channels such degrees of freedom allow the assessment of changes in chemical composition or physical states and open a wide application range from environmental sensing to medical diagnostics[33,34].

Overall, the synergistic combination of microfluidics with LoF systems has opened up new visions for sensing technologies[29,35]. To fully realize this potential and make sure that these integrated systems successfully satisfy the requirements of modern applications, ongoing research and development initiatives are still necessary. Therefore, this review aims at providing a thorough understanding of the fundamental concepts and developments of LoF systems that use microfluidic technologies to dramatically improve sensing capabilities, together with a specific focus on cutting-edge application areas as environmental monitoring, and healthcare diagnostics. Each application presents different challenges that LoF technology aims to address, ranging from specificity and multiplexing capabilities to real-time data acquisition and processing. Furthermore, this review not only analyzes the LoF systems in terms of performance metrics, such as sensitivity, specificity, robustness, reliability, and LoD, but also underlines the advantages and constraints faced during sensor fabrication. To envisage a wider deployment of LoF technology, manufacturing scalability, cost-effectiveness, and integration with current diagnostic systems should be considered.

Understanding these challenges is essential for progressing research and promoting future developments that improve the functionality and capabilities of optical fiber-based sensors. An additional focus of this review is the emerging role of AI and opto-electronic integration in LoF systems, where AI-driven approaches can remarkably enhance data analysis, adaptive calibration, and predictive sensing, while hybrid opto-electronic platforms improve sensitivity and reliability for intelligent biomedical diagnostics and environmental monitoring. The insights gained from this analysis will enhance comprehension of the foundational technologies and motivate future research efforts to address current issues and unveil new possibilities in this emerging sector[27,36]. At the end, a strategic roadmap toward the development of intelligent LoF-microfluidic platforms is envisioned.

2 Fundamentals of Lab-on-Fiber technology

LoF technology underscores a notable progression in the integration of optics with micro-nanostructures, facilitating multifunctional applications in diverse domains such as bio/chemical sensing, diagnostics, and environmental monitoring. This novel technology adeptly integrates the distinct characteristics of optical fibers with the functionalities of nanophotonic structures, remarkably boosting the detection performance and downsizing[35,37]. LoF technology fundamentally relies on the deposition of metallic and dielectric nanostructures of different shapes manufactured on the fiber tip (Fig 1(a)), inside the inherent fiber structure (Fig 1(b)) or around the sensitive region of the optical fiber (Fig 1(c))[37,38]. These nanostructures enhance the light-matter interactions and hence empower the device-target binding signals[39] and the system versatility by employing different types of optical fibers tailored for specific applications, from particle counting to biochemical detection[40,41]. Advancements in manufacturing methods, such as two-photon polymerization, have enabled researchers to construct intricate micro- and nanoscale structures directly on optical fiber substrates. This adaptability in manufacturing methods not only improves the incorporation of functional materials but also facilitates scaling for industrial applications[42,43]. Recently, the integration of AI in LoF-based systems is opening up a new avenue by creating novel options for real-time data processing and cluster analysis, with the chance of improving sensitivity and specificity across many sensing domains[36,44].

Each of the three LoF sensing configurations has advantages and disadvantages, and different domains of application. "Lab-on-Tip" (Fig. 1(a)), despite the lower sensitivity with respect to "lab-around-fiber" that might prevent its use in applications where it is required to reach a very low LoD, possesses the inherent condition to be used for *in vivo* sensing[45,46]. In this case, any microfluidics is necessary since the fiber probe is directly in contact with the sample (e.g., liquid solution, culture medium, cell tissue or cell) to be analyzed. This application domain is undoubtedly one of the most promising and innovative approach, with outstanding outcomes in the recent years, especially when applied to local treatments of cancers[47].

"Lab-in-Fiber" (Fig. 1(b)), despite its remarkable potential to exploit in-fiber microchannels as both the sensing region and embedded microfluidic channels, is still at an early stage of technological maturity. Key challenges remain related to the reliable and repeatable functionalization of the inner microchannels, long-term surface stability, and selective biorecognition in confined geometries. In addition, the micrometer-scale dimensions of the channels impose constraints on mass transport and surface accessibility, which can affect detection specificity and response time. Moreover, when

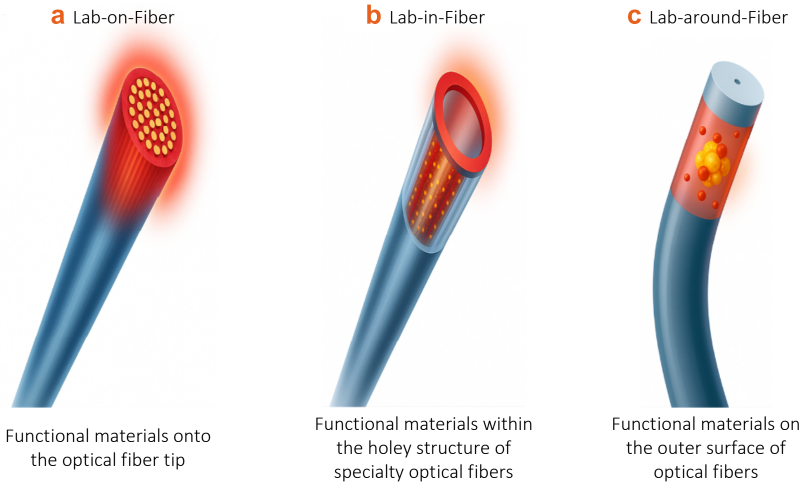


Fig. 1 | Lab-on-Fiber technology is classified into three main paradigms. (a) "Lab-on-Tip", where functional materials are integrated onto the optical fiber tip. (b) "Lab-in-Fiber", where functional materials are integrated within the holey structure of specialty optical fibers and (c) "Lab-around-Fiber", where functional materials are integrated on the outer surface of optical fibers.

dealing with biosensing in complex matrices, clogging can be a further concern. However, these limitations are mainly technological rather than conceptual, and ongoing advances in micro/nano-fabrication, surface chemistry, and nanomaterials science are steadily addressing these issues, making "Lab-in-Fiber" a highly promising platform for future fully-integrated optofluidic devices.

Finally, "Lab-around-Fiber" (Fig. 1(c)) has residual potential to be used for *in vivo*/ex vivo sensing, but combined with nanomaterials to further enhance the light-matter interaction, and with microfluidics to get rid of sensor cross-sensitivities and to reliably control over the sample handling, has gained a huge interest in biochemical sensing in the last decade[48–56]. In addition to the extraordinary sensitivity that it is possible to attain of about 10^3–10^4 nm·RIU^{-1}, this configuration enables to envisage high-performance PoC devices to be used in very diverse applications, also supported by a high versatility and a large degree of customization.

3 The role of nanomaterials in LoF technology

Many materials can be incorporated with optical fibers thanks to the huge step forward in micro/nano-fabrication and technology over the years. This crucial step enables to dramatically improve the interaction strength of the electromagnetic field of the fiber mode with the surrounding environment, thus empowering their sensing capabilities. Graphene and related materials, 2D materials, metal-organic framework or metal-oxides are significant for their excellent morphological, chemical, and electro-optical characteristics, which may match and open up different detection methods. Among all, plasmonic materials, including thin metallic films and metallic nanoparticles (NPs), are often used in hybrid plasmonic fiber sensors to achieve augmented performance[57,58]. Surface plasmon resonance (SPR) and localized surface plasmon resonance (LSPR), two of the most well-known phenomena in sensing, can be generated by incorporating metallic coatings or NPs with optical fibers. Figure 2(a) showcases the possible applications of LoF technology, while Fig. 2(b) details the types of nanomaterials that can be used to empower optical fiber sensors depending on the different application. Finally, Fig. 2(c) provides a sketch of a LoF-based sensing system and underscores the advantages and open challenges of this technology.

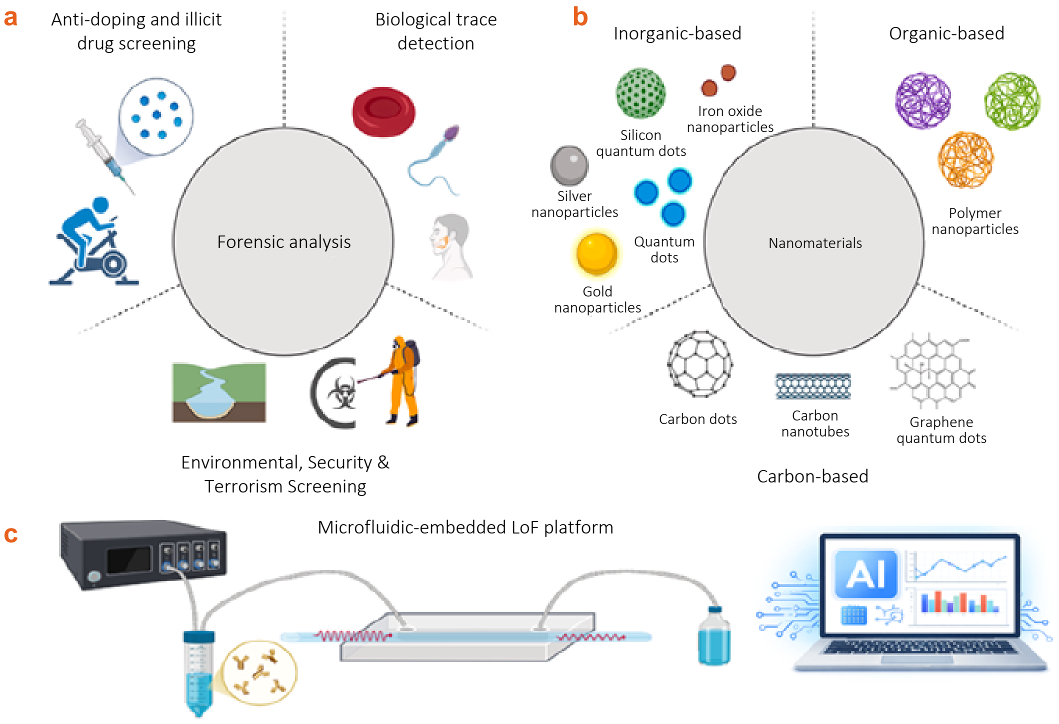
In microfluidic-embedded LoF platforms, the role of nanomaterials extends beyond simple sensitivity enhancement and directly impacts mass transport, selectivity/specificity, and response dynamics. For example, 2D materials, such as carbon-based materials, graphene and transition-metal dichalcogenides, can provide ultra-high surface-to-volume ratios and abundant functional groups, thus enabling efficient biomolecule grafting with fast binding kinetics under laminar flow conditions[59–61]. Similarly, metal-organic frameworks can provide the previous advantages owing to their tunable pore size, high porosity, and chemical selectivity. Therefore, when such materials are integrated onto LoF-microfluidic devices, they can tailor analyte–surface interactions, reduce diffusion times, and improve signal stability, so making them particularly advantageous for real-time and multiplexed biosensing[62].

4 Microfluidics designed for LoF technology

Microfluidic technology has become one of the leading technologies to develop sensing platforms designed for biomedical diagnostics and environmental monitoring[63]. This technology has particular advantages due to its capacity to precisely handle small fluid amounts and its incorporation with detecting methods and devices. Microfluidics, especially when combined with LoF systems, is leading the integration of diagnostic functions with medicine delivery, leveraging it as a revolutionary technology in contemporary medicine. Its capacity to provide quick, precise, and possibly economical solutions for illness identification, treatment and management continues to stimulate advancements in both laboratory research and clinical practice. The continuous improvement in design, materials, and the integration of various technologies will likely provide greater functions and wider applications for microfluidic systems in the future[61,64]. However, challenges about optical and fluidic interface optimization and integration are still open[65].

Microfabrication methods like photolithography and soft lithography are already used in lab-on-a-chip systems. Photolithography has shown superior spatial resolution; however, it is usually expensive and time consuming for complex designs. Conversely, soft lithography, using polydimethylsiloxane (PDMS) pieces, is cost-effective, user-friendly, and efficient, allowing rapid redesigns without the need of a cleanroom environment[66,67]. 3D printing, a recent and promising technique capable of producing microscale pieces, is garnering attention in microdevice manufacturing for its capacity to realize items quite easily. It has shown the capability to fabricate pieces with elevated aspect ratios; however, this technique cannot still guarantee a spatial resolution of a few or tens nanometer. The technique is surely cost-effective and intuitive, streamlining prototype and production procedures[68,69].

A recent study by Zheng et al. highlights the potential of LoF platforms to address difficulties associated with detection efficiency, but also underlines the elevated costs associated to SERS-based LoF systems[70]. Caputo et al. showcase a minimally-invasive platform based on LoF technology integrated in a microfluidic device for light-triggered delivery of drug-loaded particles, precise dosing and targeted transport in order to leverage loco-regional therapy[71]. Bazaz et al.



Advantages

- Unique light control
- Fast response time
- High miniaturization
- Low sample volume
- Remote sensing and multiplexing

Open challenges

- Reproducibility
- Cross-sensitivity
- Variable cost
- Multi-target detection
- Fast data processing

Fig. 2 | Overview of LoF-based sensing technology in terms of (a) applications, (b) nanomaterials that can be used in different applications and are classified into inorganic, organic, and carbon-based types (reproduced with permission under the Creative Commons CC-BY license from ref.[59], Elsevier B.V.) and (c) inherent advantages and open challenges of a microfluidic-embedded LoF sensing platform empowered by AI (created in https://bioart.niaid.nih.gov/).

suggest that 3D printing technology enables researchers to fabricate advanced microfluidic devices without requiring significant microfabrication skills, thereby making access to advanced diagnostic tools[72]. Sanka et al. observed that the creation of libraries for standardized microfluidic equipment might speed up the prototype of devices used in laboratory automation, which is crucial for optimizing processes in research and clinical environments[73].

Figure 3(a) shows a fascinating design using a spiral microchannel to optimize interaction between the sample and the sensing area[74]. The sensor employs a long period grating (LPG) structure integrated into the optical fiber (Fig. 3(b)). The inset illustrates the sensing process in which glucose oxidase (GOx) catalyzes the conversion of glucose into gluconic acid, resulting in a decrease in pH and subsequent hydrogel swelling (Fig. 3(c)). This swelling modifies the local RI next to the LPG sensor, enabling optical signal detection associated with analyte concentration. Figure 3(d) illustrates another example of LoF prototype employing a LSPR-based sensor integrated inside a PDMS microfluidic channel[75]. The tip sensor that is connected to the light source and the detector via an optical fiber coupler (Fig. 3(e)), allows real-time monitoring of biological processes inside the reaction chamber. SEM pictures (Fig. 3(f)) the nanostructure deposited over the LSPR sensor surface, essential for generating the LSPR phenomenon.

Table 1 points out the recent advancements in the integration of optical fibers with microfluidic devices to enhance sensing capabilities and detection performance. These devices implement different sensing schemes, such as LPG, D-shaped fibers, fiber tip, and micro-optics for diverse applications, highlighting the adaptability and increasing capability and functionality of these platforms in biological and analytical fields. In order to thoroughly benchmark against different microfluidic-embedded LoF platforms, Table 1 encompasses quantitative metrics, such as volume sensitivity (S_{vol}), LoD, dynamic range (DR), response time (τ), type of matrix, temperature compensation (T-comp.), and validation in real samples.

It can be observed that the combination of microfluidic systems with LoF technology is an effective and reliable approach for synergistic fluid manipulation and enhanced

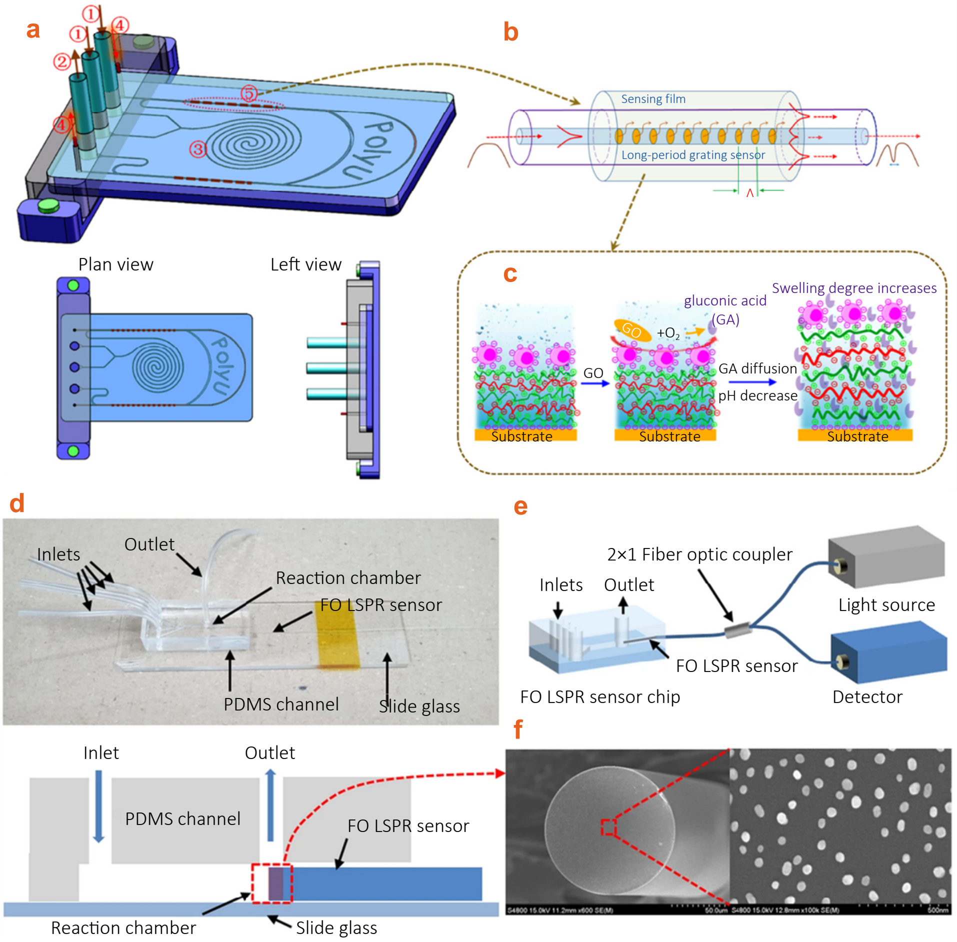


Fig. 3 | (a) Schematic and layout of a microfluidic chip with a spiral microchannel for analyte transport, including plan and left views, together with the optical fiber sensors; (b) Schematic of the used optical fiber LPG sensor coated with an hydrogel film for real-time monitoring of GO processes; (c) Working mechanism of the pH-responsive hydrogel film (previous subfigures reproduced with permission under the Creative Commons CC-BY license from ref.[74], 2016 Optical Society of America). (d) Photograph and schematic of a PDMS-based microfluidic chip integrated with an optical fiber LSPR sensor placed on a glass slide; (e) Optical setup for detection including a light source, an optical detector and a fiber coupler; (f) SEM images of the sensor tip with zoomed-in nanoparticle distribution confirming uniform nanoparticle decoration essential for LSPR generation (previous subfigures reproduced with permission under Creative Commons Attribution 4.0 International License from ref.[75], Springer Nature).

sensing across many applications, especially in biomedicine. Material fragility, precise sizing of pieces, alignment of fiber-based components, and accurate control over the flow rates are critical elements that might hinder an easy integration and use of optical fiber-based sensors in demanding environments.

5 Applications of LoF-microfluidics for sensing

5.1 Biomedical-related sensing

The pairing of LoF technology with microfluidics yields substantial progress in chemical and biological sensing applications given the very accurate and precise control of liquid flow in microfluidic environments[81] and benefitting from the distinctive characteristics of optical fibers. The integration of microfluidics with fiber optic sensors usually provides enhanced sensitivity and stability of the optical signal and hence facilitates continuous monitoring of various properties including temperature, concentration, and refractive index[82,83]. LoF technology integrated with microfluidics may use several optical detection methods, including spectroscopic approaches (like Raman or UV-visible spectroscopy), labelled methods (like fluorescence or chemi/luminescence), and label-free methods based on the excitation of surface/evanescent waves (like SPR, LSPR, gratings, interferometry, Bloch surface wave, lossy mode resonance (LMR)), which enable *in situ* detection for biological analysis, and environmental monitoring[84]. The size, portability and elevated throughput of these integrated systems make them ideal for clinical diagnosis through PoC devices, where conventional hospital apparatus is impractical. These systems usually need a minimal volume of samples

Table 1 | Microfluidic-integrated LoF platforms for advanced sensing applications: benchmark against different sensing configurations using quantitative metrics.

Sensing scheme	Sensing configuration	Target	S_{vol}	LoD	DR	τ	Matrix	T-comp.	Real-sample validation	Ref
LPG	Small-diameter LPG coated with glucose oxidase layer integrated in PDMS spiral chip	Glucose	205 nm·RIU^{-1}	1 nM	2–10 µM	70 s	Water	—	No	ref.[74]
TFBG	Au-coated TFBGs integrated into a multi-channel microfluidics	Amyloid Beta 42 (Aβ_{42})	3500 dB·RIU^{-1}	30–170 pg·mL^{-1}	0.1–1000 ng·mL^{-1}	3–7 min	CSF	Yes (inherently via Bragg wavelength)	Yes	ref.[13]
LMR	LMR D-shaped fiber coated with SnO_{2-x} embedded into a custom microfluidics	IgG	14.5 *x* 10^{3} nm·RIU^{-1}	1 fM	1 pg mL^{-1}–10 µg·mL^{-1}	~20 min	Serum	Yes (microfluidic system)	No	ref.[48]
BSW	BSW-based stack-layered D-shaped fiber embedded into a custom microfluidics	IgG	~1500 nm·RIU^{-1}	70 aM	10^{-4}–10^{4} ng mL^{-1}	~20 min	Serum	Yes (microfluidic system)	No	ref.[10]
Reflectivity	Spherical-tip fiber sensor inserted into a plastic tubing	CD44	120 dB·RIU^{-1}	4.68 aM	0.2 aM–100 nM	10 min	Serum	Yes (embedded FBG sensor)	No	ref.[53]
Reflectivity + TFBG	TFBG-based ball-resonator fiber sensor inserted into a plastic tubing	HER2	4034 dB·RIU^{-1}	151.5 ag·mL^{-1} (PBS) and 3.7 pg·mL^{-1} (Serum)	10^{-7}–10^{2} ng·mL^{-1}	—	PBS / Serum	Yes (inherently via Bragg wavelength)	No	ref.[76]
Michelson interferometry	Vernier effect-assisted Michelson interferometric microstructured fiber sensor embedded into microfluidics	cDNA	8791 nm·RIU^{-1}	19.25 nM	1 µM	—	PBS	—	No	ref.[77]
Fabry-Pérot interferometry	3D-printed fiber-tip dual-mode (Fabry-Perot interferometry + SPR) sensor inserted into a PDMS microfluidics	cDNA	~1500 nm·RIU^{-1}	1.2 nM	5–100 nM	15–20 min	PBS / FBS	Yes (dual-mode sensing)	No	ref.[78]
LSPR	Fiber-tip decorated with gold NPs and integrated into PDMS microfluidics	Thyroglobulin	—	93.11 fg·mL^{-1} (PBS) 21.18 pg·mL^{-1} (Serum)	0.001–100000 pg·mL^{-1}	5 min	PBS / Serum	—	Yes	ref.[75]
SERS	D-shaped fiber coated with gold NPs and embedded into multi-channel PDMS microfluidics	R6G / MB	—	10 pM	10^{-11}–10^{-6} M	~2 min	Water	—	No	ref.[79]
SPR	D-shaped fiber SPR sensor coated with MOF-74 and integrated into 3D micro-nano printed microfluidics	Berberine	2640 nm·RIU^{-1}	0.38 µg·mL^{-1}	1–100 µg·mL^{-1}	~20 min	PBS	Yes (matrix-based using temperature demodulation)	No	ref.[80]

* CSF: cerebrospinal fluid; LMR: lossy mode resonance; IgG: immunoglobulin G; BSW: Block surface wave; CD44: transmembrane glycoprotein; HER2: human epidermal growth factor-2; cDNA: complementary DNA; FBS: fetal bovine serum; MOF: metal organic framework.

and provide excellent reliability, making them appropriate for real-time applications in bioanalytic, organ-on-a-chip technologies, and high-resolution chemical analysis[85,86].

A representative example of the capabilities of LoF–microfluidic systems in biomedical diagnostics is illustrated in Fig. 4, which showcases a multi-channel plasmonic fiber optic biosensing platform developed for the ultrasensitive detection of Alzheimer's disease (AD) biomarkers[13]. The system integrates a custom-designed microfluidic module (Fig. 4(a)) with a gold-coated highly-tilted fiber Bragg grating (TFBG; Fig. 4(b, c)), enabling simultaneous analysis of multiple Aβ_{42} species using sub-microliter sample volumes. As shown in Fig. 4, the TFBG excites a dense comb of narrowband cladding-mode resonances that overlap with the broadband plasmonic absorption of the gold film, providing exceptionally high surface sensitivity to binding interactions. This hybrid TFBG–SPR configuration, operating in the near-infrared, offers long penetration depth and

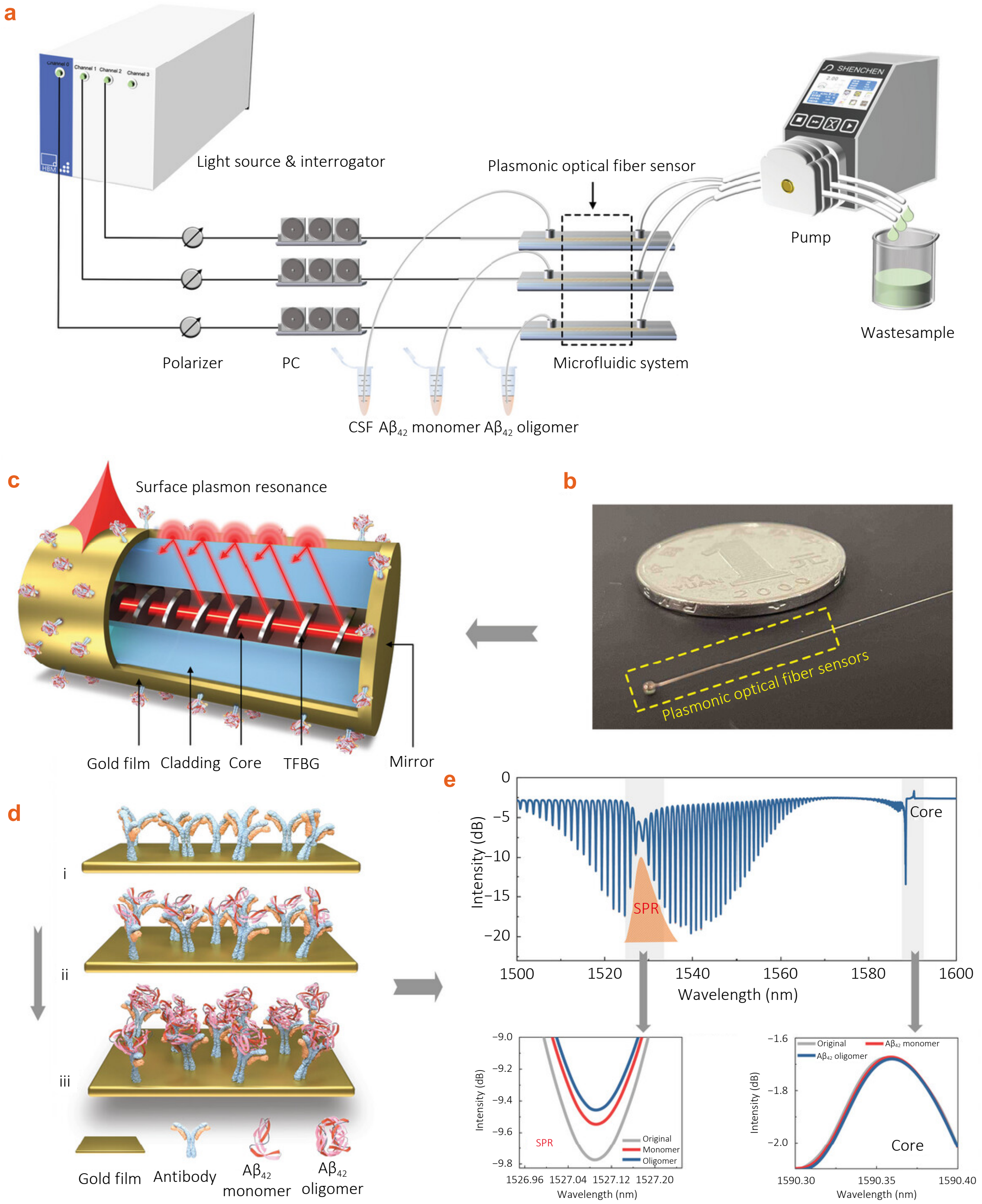


Fig. 4 | (a) Multi-channel microfluidic system integrated with a gold-coated tilted fiber Bragg grating (TFBG) for simultaneous detection of Aβ_{42} monomers and oligomers for early diagnosis of Alzheimer's disease. (b) Photograph of the compact plasmonic fiber probe. (c) Schematic of the TFBG-assisted SPR mechanism enabling high-sensitivity surface monitoring of binding interactions. (d) Stepwise binding protocol of antibodies, Aβ_{42} monomers, and Aβ_{42} oligomers on the gold film. (e) Corresponding spectral responses showing SPR modulation and sensing mechanisms for differentiation between Aβ_{42} species (previous subfigures reproduced with permission under Creative Commons Attribution 4.0 International License from ref.[13], 2024 Wiley-VCH GmbH).

strong surface confinement, allowing precise discrimination between Aβ_{42} monomers and oligomers based on binding kinetics (Fig. 4(d, e)). With LoD in the range of ≈30–170 pg·mL^{-1} well below the clinical cut-off for the early AD diagnosis, this LoF–microfluidic platform demonstrates how fiber optic sensors can deliver highly sensitive, multi-parameter, and real-time biomarker detection essential for early-stage disease diagnosis.

Still on AD, another example of LoF system based on LMR sensing phenomenon[87] is used to detect another hallmark in AD (i.e., tau protein), with high sensitivity and specificity, enabling rapid and low-volume analysis of cerebrospinal fluid (CSF) samples[88]. Regarding the detection of prostate specific antigen (PSA), microfluidic electrochemical optical fiber sensors using graphene films demonstrate potential applications in clinical diagnosis and personalized medicine[89]. Therefore, it is clear that the fusion of microfluidic systems with LoF technology presents a transformative path in biomarker and pathogen detection.

Figure 5(a) showcases another illustrative examples of the integration of microfluidic systems with LoF platforms for advanced biomarker and pathogen detection. In particular, it is worth underlining that LoF technology remarkably enables the integration of three components into a single device: laser-based fluorescence detection, photomultiplier tube readout, and vacuum-assisted cell capture[90]. Figure 5(b)

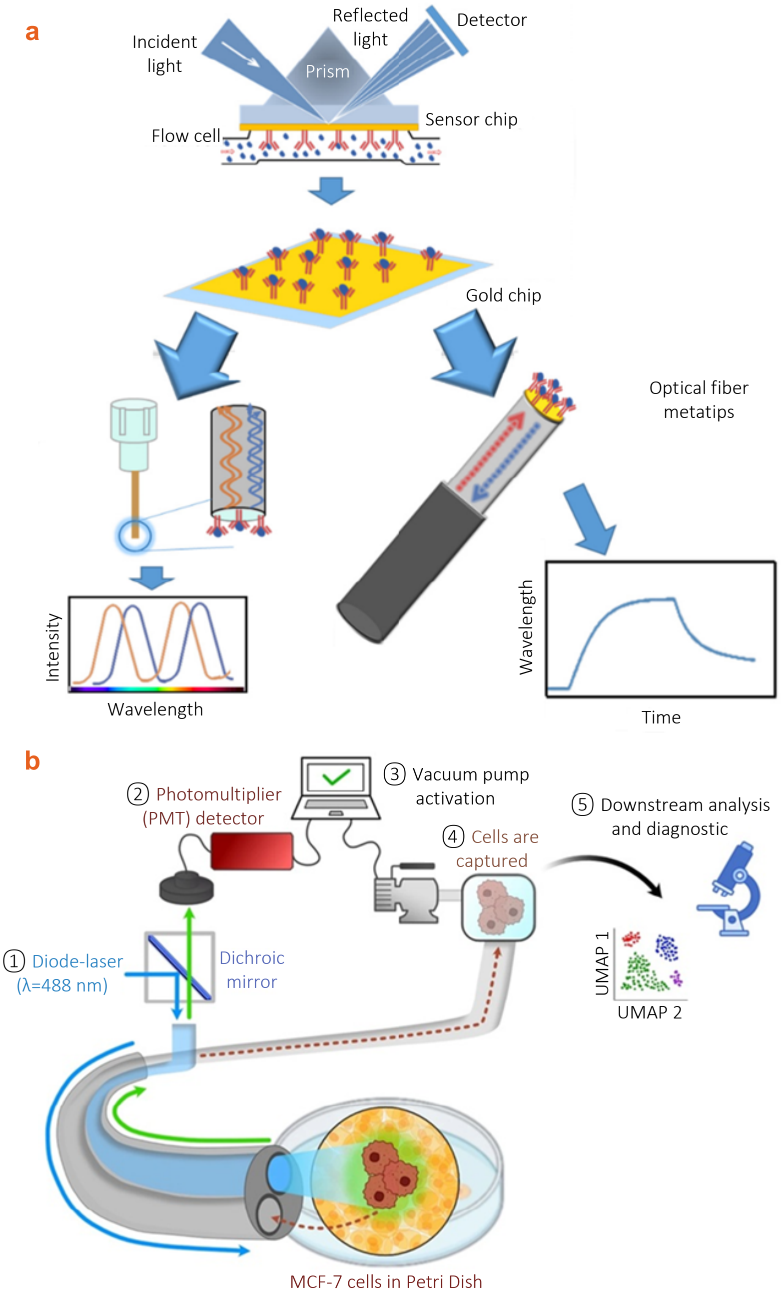


Fig. 5 | (a) A hybrid platform combining microfluidics and SPR for optimized functionalization of fiber surface and detection of target analytes via antibody immobilization (reproduced with permission under Creative Commons Attribution 4.0 International License from ref.[90], 2022 Licensee MDPI, Basel, Switzerland). (b) LoF platform for live cell capture and diagnostics using a compact laser-based fluorescence tool (reproduced with permission under Creative Commons Attribution 4.0 International License from ref.[91], Springer Nature).

illustrates a fiber-based system that selectively isolates labeled cells (e.g., MCF-7 breast cancer cells) from a culture dish, enabling downstream diagnostic and single-cell analysis while minimizing photobleaching[91].

5.2 Environmental sensing

The integration of microfluidic technology with LoF technology has provided novel opportunities for environmental monitoring and pharmaceutical analysis given the reduced reagent consumption, and hence decreased costs together with high portability[92].

Recent advancements in microfluidics have facilitated the on-site detection of heavy metals and contaminants, which is essential due to the detrimental impacts of trace heavy metal exposure on human health and ecosystems[93–95]. Microfluidic devices can be constructed on various substrates, including paper and polymers, have shown adequate sensitivity and selectivity for the detection of metal ions such as lead, cadmium, mercury, and arsenic[93,96]. These systems provide ongoing real-time monitoring with LoD that may reach sub-nanomolar levels, beyond the limitations of traditional laboratory-based equipment[94,96].

However, the design of LoF systems combined with the downsizing of microfluidic channels has dramatically improved the detection capabilities. Through the integration of materials innovation, microfabrication processes, and advanced optical detection technologies, these systems provide a highly integrated, scalable, and reliable solution for the fast and sensitive detection of heavy metal ions, including lead, mercury, and chromium[97], and other pollutants across diverse environments. These systems use diverse optical detection techniques, such as surface-enhanced Raman scattering (SERS) and SPR for instance[98,99].

Mishra et al. develop a cost-effective micro absorbance-based microfluidic system with nanoparticle immobilization for detecting chemical contaminants in drinking water, achieving 0.5 ppb as LoD and higher sensitivity compared to conventional absorbance methods[100]. Si et al. propose an electrochemical plasmonic fiber optic sensor that allows ultra-sensitive, real-time heavy metal detection with an LoD as low as 10^{-10} M and a dynamic range spanning five orders of magnitude, ideal for remote environmental monitoring[97]. Dhara et al. present an LSPR fiber optic sensor for detecting lead ions in aqueous solutions, with a sensitivity of 0.28 nm/mM[101]. Menon et al. report on a metal-organic framework-based fiber optic sensor that detects chromium(VI) ions with an LoD of 1 ppb[102]. Hengoju et al. underscore the benefits of using optical fibers in droplet microfluidics, emphasizing their flexibility, low cost, and sensitivity in detecting chemical and biological parameters[103].

On the other hand, the integration of microfluidic systems and LoF devices presents significant advantages in the detection of pharmacological substances. The ability to analyze small volumes is especially very important in the issues of global challenge of pharmacological contamination. Vikas and Saccomandi explore the design, development and testing of an indium tin oxide (ITO)-coated fiber optic LMR device specifically for ciprofloxacin detection, demonstrating both effectiveness and practicality in real-world deployment[104]. On the same topic, Huang et al. introduce a novel fluorescent optical fiber sensor with very high selectivity[105]. Wang et al. spotlight that the microfluidics integration with fiber-optic sensors makes easier the detection of biological and chemical contaminants, as well as pharmaceutical waste[106]. These developments aim at reducing the effects of pharmaceutical contamination and facilitate future research in biosensing applications related to environmental safety and public health.

Examples of optofluidic platforms integrating optical fibers with microfluidic channels for environmental sensing are presented in different research. A Fabry–Pérot microcavity formed by two gold-coated optical fiber facets is embedded within a microreactor where chromogenic reagents and phosphate-containing samples are rapidly mixed[107]. This configuration enables fast colorimetric reactions and optical readout, dramatically reducing the detection time from minutes to seconds. Another research shows a polymer-based microfluidic platform fabricated using a cyclic olefin copolymer support and PDMS microchannels. Optical fibers are aligned with the measurement chamber to provide continuous monitoring of Hg(II) ions architecture[108]. Figure 6 showcases how the combined microfluidics-optical fiber technologies together with engineered bioreceptors can effectively been used for the detection of small molecular weight targets[109]. In fact, the accurate detection of per- and polyfluoroalkyl substances (PFAS) in environmental matrices, including drinking water, necessitates the development of highly sensitive and specific sensing methodologies. The proposed label-free biosensing platform enables to address this analytical challenge by incorporating a side-polished optical fiber coated with a nanometer-scale layer of SnO_2 (Fig. 6(a)), which jointly excite the LMR sensing phenomenon, and appropriately engineered bioreceptor, such as delipidated human serum albumin (hSA; Fig. 6(b)). This system that is embedded into a custom-designed thermo-stabilized microfluidic chip (Fig. 6(c)) is employed for the detection of perfluorooctanoic acid (PFOA), a very harmful pollutant. The optical signals corresponding to the conformational changes induced by the binding interaction between hSA and PFOA are monitored through LMR spectral shifts and an LoD around 100 pg mL^{-1} is attained, so at the same concentrations required in drinking water and groundwater stated by environmental agencies, such as EPA (environmental protection agency, USA) and EEA (european environmental agency, EU).

5.3 AI-Driven sensing

AI has emerged as a transformative force in biochemical

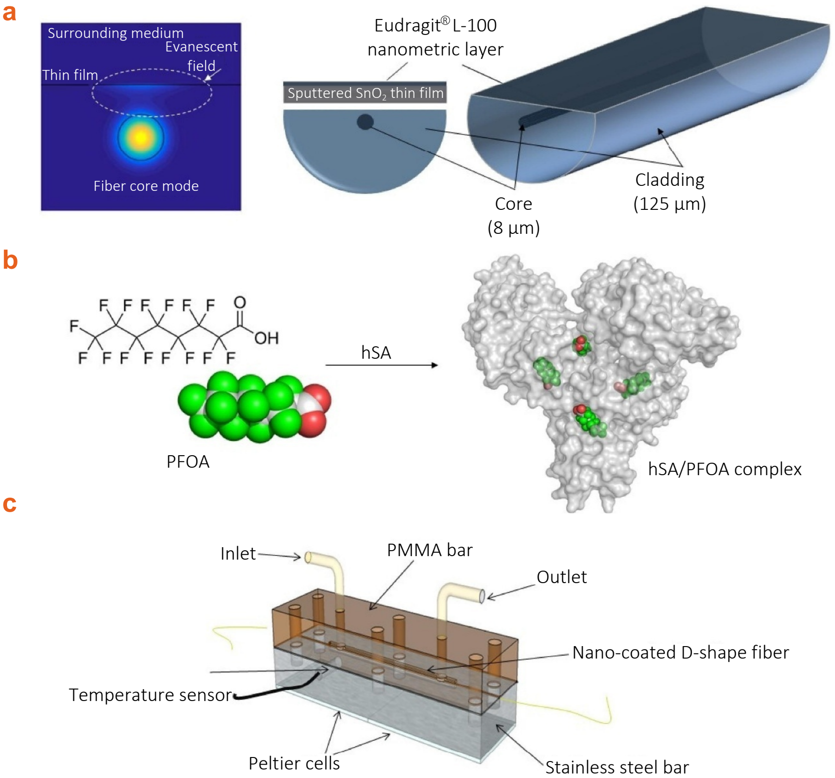


Fig. 6 | (a) Schematic of the side-polished optical fiber sensing region coated with a sputtered SnO_2 thin film and functionalized with an Eudragit® L-100 nanolayer; (b) chemical structure of the perfluorooctanoic acid (PFOA) that has the ability to form a 1:4 complex with delipidated human serum albumin, resulting in the hSA/PFOA complex; (c) advanced microfluidic system consisting of a flow channel for hosting the optical fiber sensor and equipped with a temperature stabilization mechanism based on Peltier cells (previous subfigures reproduced with permission under the Creative Commons CC-BY-NC-ND license from ref.[109], Elsevier B.V.).

sensing, particularly in enhancing real-time signal processing, pattern recognition, and predictive analytics. Concerning microfluidic-based LoF platforms, AI can drive dramatic innovation by leveraging the analysis of complex optical spectral signatures (for instance, resonance wavelength shifts, intensity variations, phase/polarization changes), their de-noising, de-trending for baseline correction, debugging and even the demodulation from multiple overlapped signatures or fingerprints. Machine learning (ML) algorithms, including regression models, neural networks, and convolutional neural networks, can extract subtle patterns from LoF outputs, remarkably improving the LoD, selectivity, reliability and reproducibility even under noisy or variable microfluidic conditions[110−113]. In addition, AI-driven approaches can envisage to facilitate multiplexed sensing and then quantify multiple targets simultaneously thanks to unmixing and pattern recognition, where multiple nanomaterial-functionalized regions or multi-points sensing along a single optical fiber produce overlapping and intricate spectral signals. This would particularly benefitting from PoC diagnostic devices, systems for biomarker quantification in complex biofluids (i.e., sweat, tears, saliva, or plasma), and overall sensing systems devoted to biochemical analysis and environmental monitoring[110,111,113]. Despite these advantages, AI integration in LoF systems faces specific challenges. The first lies in limited raw data acquisition for each sensor, necessitating strategies such as transfer learning, physics-informed machine learning, and synthetic data generation to train robust models[114]. Real-time processing on portable, low-power hardware is also critical for wearable or implantable applications, motivating edge-AI solutions optimized for optical and microfluidic signals. Furthermore, LoF platforms often combine optical, biochemical, and environmental inputs, requiring robust multimodal data-fusion frameworks to maintain accurate predictions and signal interpretability[115].

To illustrate practical implementation of AI in LoF-microfluidic platforms, representative example of workflows for both biomedical and environmental applications can be envisaged. In multiplexed biomarker detection systems as a current need in most of diseases, a great amount of spectra is collected from multiple nanomaterial-functionalized regions or from multiple measurands to be recorded along a single optical fiber sensing system, often combined with auxiliary measurements, such as temperature, strain, flow rate, etc., that sometimes are required to get rid of the cross-sensitivity issues[116]. Afterwards, AI algorithms can perform spectral de-noising, baseline drift correction (or de-trending), and multi-target signal deconvolution to extract meaningful biomarker concentrations, while detecting unplanned anomalies, such as flow issues or formation of bubbles. Under standardized metrics like LoD, sensitivity among all, models can be validated through cross-batch evaluation using datasets from different sensor fabrication runs, and specific adaptive techniques are applied to account for variations of sample matrices in terms of viscosity and complexity. Lightweight edge-AI models embedded in portable readout units can enable real-time and most-reliable biomarker quantification, while more computationally intensive training occurs on workstation servers[114].

For environmental monitoring, LoF-microfluidic platforms generate time-series of optical signals (intensity change and wavelength shift mostly) in terms of the investigated parameter (i.e., ions, heavy metals, chemical compounds, redox signal, concentration of specific element) under continuous flow conditions, with auxiliary inputs, such as pH, temperature, and humidity. AI-related tasks can therefore include noise reduction, drift correction, weak-signal extraction from low-concentration contaminants, and multi-class classification of targets or small molecules[117,118]. Validation of AI model can involve cross-site data to ensure generalization to different environmental conditions, with metrics including accuracy, selectivity, LoD, and false-positive rates. Practical deployment can rely on edge-computing-driven internet of things (IoT) implementation for continuous monitoring, with periodic uploads to cloud or workstation platforms for retraining of AI model and long-term trend analysis.

A schematic example of the overall workflow is provided in Fig. 7 and consists of data acquisition, preprocessing of data, definition of AI model and its implementation, and deployment of AI model with final assessment with standardized metrics. The workflow highlights some critical steps, such as drift correction, anomaly detection, and multi-target quantification, providing a practical framework for AI-driven LoF-microfluidic sensing systems.

Although fully operational AI-enhanced microfluidic LoF devices are just at the dawn, ongoing research suggests promising pathways for their development[119]. These include standardized spectral datasets for different LoF architectures, embedding AI models into portable readout units, and adaptive control loops that dynamically adjust microfluidic flow and sensing conditions in real time. Emerging AI paradigms such as transformer-based time-series analysis and hybrid physics-AI models are expected to further enhance predictive capabilities, reproducibility, multi-functionality and scalability by bringing the knowledge from more mature technologies[120]. Overall, by combining LoF technology, microfluidics, and AI, next-generation sensing platforms can achieve adaptive, autonomous, and predictive operation, providing real-time feedback for healthcare diagnostics, environmental monitoring, and personalized wearable devices. These intelligent platforms can represent a key step toward the integration of AI with smart photonic and microfluidic systems, advancing both analytical performance and operational reliability for an easier translation from laboratories to the market.

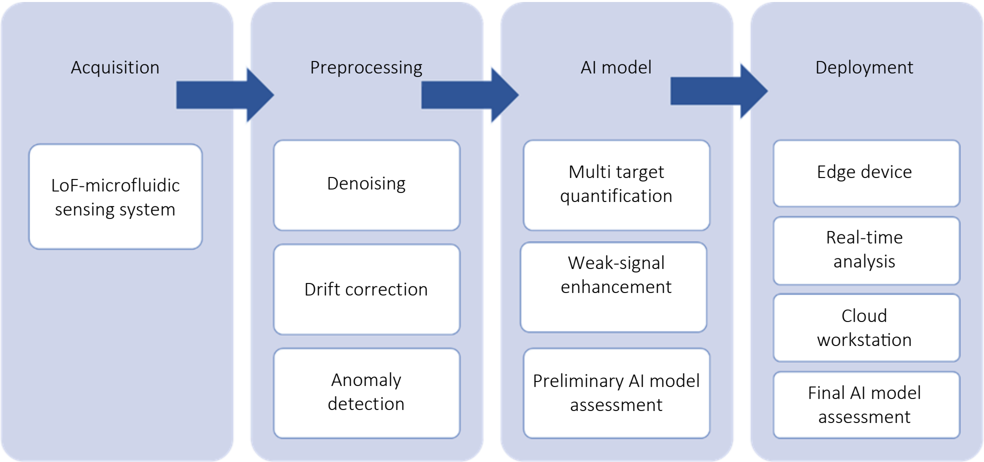


Fig. 7 | A schematic workflow for AI-driven LoF-microfluidic sensing systems consisting of data acquisition (full spectrum, intensity changes and wavelength shifts, multimodal signals such as temperature, flow, or pH), preprocessing of data (spectral denoising, baseline drift correction, anomaly detection, and signal normalization), AI model (multi-target quantification, weak-signal enhancement using neural networks, regression models, or transformer-based algorithms, and preliminary AI model assessment), and deployment by the use of evaluation metrics (accuracy, sensitivity, selectivity, LoD, cross-batch validation, domain adaptation) that can ensure model robustness and generalization. Finally, deployment highlights real-time implementation on edge-computing-driven IoT implementation for portable, wearable, environmental or biochemical monitoring applications, with optional cloud or workstation-based retraining for long-term performance optimization.

5.4 Challenges and future perspectives

Despite the remarkable advances in LoF systems integrated with microfluidics, several engineering challenges remain to bridge the gap toward their reliable, scalable, and real-world deployment. First, fabrication and bonding of microfluidic devices remain critical hurdles. Innovations like the “Click-and-Bond” method provide solvent-free, room-temperature bonding, optimizing polymer-based microfluidic production on a possible large scale[121]. Something similar can be envisaged for LoF systems too. Second, when working with real samples, microfluidic systems can be very much susceptible to clogging, channel fouling, and environmental interference, especially at very low flow rates[122]. The use of advanced antifouling coatings can get rid of such issues, also in the case of LoF devices[123]. Third, the choice of the materials among new polymers and advanced functional nanomaterials can play a crucial role in the device stability, biocompatibility, and then turn into the detection performance[124,125]. Advances in surface functionalization, hybrid nanostructures, and robust micro/nano-fabrication techniques are therefore essential for reproducible and scalable LoF-microfluidic systems, opening up the possibility for multiplexed sensing capabilities[11,15]. Fourth, despite the countless and distinct advantages of AI, its integration can introduce additional constraints, such as computational load, data infrastructure, and real-time processing requirements, and related risks as well[126]. Mitigation strategies include embedding edge-compute AI units, implementing adaptive calibration loops, and combining optical, electromechanical, and AI-driven controls to maintain stable and reliable operation. Overall, developing standardized fabrication methods, reporting detailed protocols and well-defined calibration methods, and using uniform definitions for performance metrics would definitely facilitate the comparison across different works and then improve reproducibility of the results dramatically[122,127].

Therefore, transforming laboratory LoF prototypes into industrially scalable systems continues to face limitations in terms of sensor packaging, result reproducibility and batch-to-batch variation, particularly arising from nanostructure deposition, surface chemistry, microchannel geometry, and fiber-to-fluidic coupling alignment[124,125,127]. Looking forward, since operational challenges can be mostly unveiled by means of engineering solutions, an engineering-oriented roadmap for effective and advanced LoF-microfluidic platforms is envisioned:

1) Uniform definition and application of performance metrics: Use the standardized definition of crucial sensing/biosensing metrics (volume and surface sensitivity, LoD, accuracy, stability, etc.) toward a uniform assessment of the device performance[119].

2) Standardized fabrication and detailed protocols: Develop guidelines for microchannel geometry, surface roughness, nanostructure deposition, fiber coupling alignment, and material selection[121,124,125].

3) Robust and reproducible testing: Use testing procedures that enable to assess the performance metrics taking into account the possible reusability, and reproducibility across batches[122,128].

4) Integration of AI and real-time control: thanks to IoT, employ edge computing for adaptive calibration, anomaly detection (clogging, flow interruptions), and multi-parameter data fusion[114].

5) Packaging and scalability: Optimize bonding techniques, modular design approaches, and low-cost materials (e.g., polyethylene) to enable industrial-scale deployment[129,130].

6) Application-specific optimization: Tailor nanomaterial functionalization, flow rates, and sensor configuration for biomedical, environmental, or wearable sensing contexts.

By following this roadmap, LoF-microfluidic platforms might effectively move from the laboratory stage to reliable, reproducible, and commercially viable devices. Multidisciplinary collaboration across experts on optics, photonics, microfluidics, materials science, and AI will be essential to realize the full potential of these compact, versatile, and intelligent sensing systems. With continued innovation and standardized engineering practices, LoF-based optofluidic sensing technologies are poised to become integral tools for next-generation biomedical and environmental monitoring applications.

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Author contributions

Shadab Dabagh and Francesco Chiavaioli conceived of the idea and designed the review. Rukmani Singh, Claudia Borri, Hamed Ghorbanpoor, Golara Ghorban Dordinejad, and Mahdi Bahadoran created and edited the figures. Shadab Dabagh led the manuscript writing – original draft. Shadab Dabagh, Ambra Giannetti, Francesco Baldini, Huseyin Avci, and Francesco Chiavaioli led the manuscript writing – review & editing. All authors participated in the review and discussion of the manuscript.

Competing interests

The authors declare no competing financial interests.

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