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REVIEW

Miniaturization of fluorescence sensing in optofluidic devices

Daniel Măriuţa[1,2] · Stéphane Colin[2] · Christine Barrot-Lattes[2] · Stéphane Le Calvé[3,4] · Jan G. Korvink[1] · Lucien Baldas[2] · Jürgen J. Brandner[1]

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Abstract
Successful development of a micro-total-analysis system (μTAS, lab-on-a-chip) is strictly related to the degree of miniaturization, integration, autonomy, sensitivity, selectivity, and repeatability of its detector. Fluorescence sensing is an optical detection method used for a large variety of biological and chemical assays, and its full integration within lab-on-a-chip devices remains a challenge. Important achievements were reported during the last few years, including improvements of previously reported methodologies, as well as new integration strategies. However, a universal paradigm remains elusive. This review considers achievements in the field of fluorescence sensing miniaturization, starting from off-chip approaches, representing miniaturized versions of their lab counter-parts, continuing gradually with strategies that aim to fully integrate fluorescence detection on-chip, and reporting the results around integration strategies based on optical-fiber-based designs, optical layer integrated designs, CMOS-based fluorescence sensing, and organic electronics. Further successful development in this field would enable the implementation of sensing networks in specific environments that, when coupled to Internet-of-Things (IoT) and artificial intelligence (AI), could provide real-time data collection and, therefore, revolutionize fields like health, environmental, and industrial sensing.

Keywords Lab-on-a-chip · Off/on-chip integration strategy · Lab-on-a-CMOS · Microfluidic-PCB · In-plane optics · Organic electronics · Fluorescence detection

1 Introduction

Recent findings in the fields of microfluidics, integrated circuitry, microfabrication, and micromachining techniques have enabled considerable advancements in the miniaturized sensing technologies. Downscaling chemical and biological sensors result not only in ultra-portable devices, but in advantages such as enhanced process performance, higher analysis speed and reduced reagent consumption, significantly lowering fabrication, maintenance, and operational costs (Shakoor et al. 2018). Some fields that benefit from these achievements are healthcare monitoring (Boppart

✉ Jürgen J. Brandner
juergen.brandner@kit.edu

Daniel Măriuţa
daniel.mariuta@kit.edu

Stéphane Colin
stephane.colin@insa-toulouse.fr

Christine Barrot-Lattes
christine.lattes@insa-toulouse.fr

Stéphane Le Calvé
slecalve@unistra.fr

Jan G. Korvink
jan.korvink@kit.edu

Lucien Baldas
baldas@insa-toulouse.fr

[1] Institute of Microstructure Technology, Karlsruhe Institute of Technology, Campus Nord, Hermann-von-Helmholtz-Platz 1, Eggenstein-Leopoldshafen, Germany

[2] Institut Clément Ader (ICA), CNRS, INSA, ISAE-SUPAERO, Mines-Albi, UPS, Université de Toulouse, Toulouse, France

[3] Group of Atmospheric Physical Chemistry, Institute of Chemistry and Processes for Energy, Environment and Health (ICPEES), University of Strasbourg, Strasbourg, France

[4] In'Air Solutions, 25 rue Becquerel, Strasbourg, France

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and Richards-Kortum 2014; Wessels and Raad 2016; Zi et al. 2016; Papageorgiou et al. 2017; Sharma et al. 2018), organ-on-a-chip (Zhang et al. 2015; Si Hadj Mohand et al. 2017; Kilic et al. 2018), drug screening (Zhang et al. 2015), food monitoring (Bhattacharya et al. 2017), and environment monitoring (Ricciardi et al. 2015a; Calvé et al. 2017; Rezende et al. 2019; Măriuța et al. 2020). Potential applications are countless with a huge impact on the quality of life (Chen et al. 2012). They are also directly linked with the next generation of smart cities (Zhao et al. 2015), artificial intelligence (AI), and Internet-of-Things (IoT).

Ideally, a lab-on-a-chip device should perform all the steps of a complete analysis in an integrated and automated fashion. This may include sampling, sample pre-treatment, chemical reactions, analytical separations, analyte detection, product isolation, and data analysis (Ríos et al. 2012). Even though the achievements reported in the literature are numerous, apparently the transition of these devices from lab prototyping to market is still limited, if not negligible (Volpatti and Yetisen 2014; Mohammed et al. 2015; Ackermann et al. 2016a), and the remaining challenges are still considerable. The main challenge is to identify and optimize strategies for the integration of all analysis functions into a cost-efficient, technician-free, robust microstructure, to develop fully-autonomous micro-analysis systems.

The integration of the detection mechanisms with microfluidics may be one of the most promising directions towards the widespread application of lab-on-a-chip devices (Wu and Gu 2011; Watts et al. 2012; Llobera et al. 2015). Generally, for detection within micro-integrated systems, mechanical, optical, and electrochemical methods are primarily used (Pires et al. 2014). The optical methods are usually preferred because they are robust, very sensitive, non-destructive, broadband and can be used for in-situ or in-line monitoring (Pires et al. 2014; Rodríguez-Ruiz et al. 2016; Yang and Gijs 2018). This combination of optics and microfluidics merged towards a relatively new field named optofluidics. Optofluidic systems aim to integrate the optical functions of detection in a single chip. The roadmap (Minzioni et al. 2017), the recent achievements (Chen et al. 2019), and the new perspectives (Song and Tan 2017) in the optofluidics field for lab-on-a-chip applications have also been published in (Zhu et al. 2013; Rodríguez-Ruiz et al. 2015; Zhang et al. 2016; Song et al. 2017). Among all-optical methods, fluorescence sensing is the most common analytical and diagnostic method in biological, chemical, and medical applications (Yang et al. 2015; Hong et al. 2017a; Wei et al. 2017), and it is largely accepted due to its capability to attain ultra-low detection limits (Ryu et al. 2011; Babikian et al. 2017).

Fluorescence is the property of a molecule to absorb light at a specific wavelength and emit it at a longer wavelength, a phenomenon known as the Stoke shift (see Fig. 1). Consequently, its quantification involves a light emission source (1) and a light detector (5). The amount of fluid involved in microfluidic systems is by definition reduced; therefore, the emitted fluorescence signal is weak. The ratio between fluorescence emission intensity and excitation beam intensity is defined as the quantum yield, which is molecule specific, usually the emission being three orders of magnitude lower than the excitation. This difference between excitation intensity and emitted fluorescence intensity makes the implementation of a complex optical path necessary, involving a system of lenses to focus (4) the fluorescence onto a photon detector (5) (Wei et al. 2017). Filters are used in traditional configurations of fluorescence detectors to selectively allow light with specific wavelengths. Emission filters (2) are used to reject parasitic components of the excitation light beam (1), allowing the passage of only the specific wavelength band needed for the excitation of the analyte (3). Detection filters (4) are used to stop scattered light from reaching the detector surface (5). The background noise levels are directly linked with the filtration efficiency. Noise is an undesirable

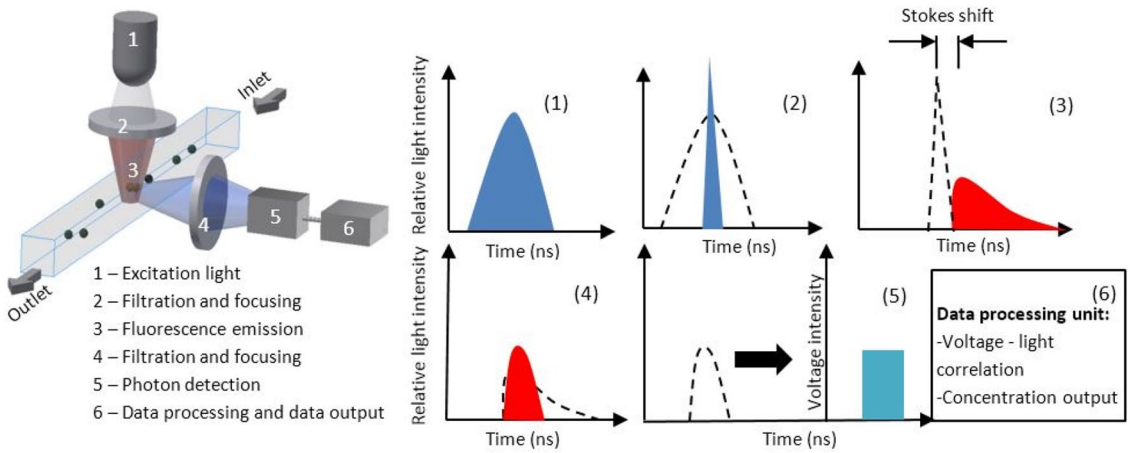

Fig. 1 General fluorescence detection scheme (orthogonal configuration)

parameter quantifying the level of parasitic light reaching the detector. The signal-to-noise ratio (SNR) is used to characterize the performance of a detector, quantifying the ratio between fluorescence and parasitic light. This multitude of optical components make a system complex, bulky, and expensive (Hong et al. 2017a).

Thus, fluorescence sensing devices are not only sophisticated products integrating multidisciplinary know-how but also key components of lab-on-a-chip systems (Dandin et al. 2007). The miniaturization of fluorescence sensing devices is challenging—often developed systems end up being chip-in-a-lab devices, instead of lab-on-a-chip platforms (Varsanik and Bernstein 2013; Shakoor et al. 2018). Different integration strategies of fluorescence optical detection have been reported during the last decade. Among them, the most promising one reviewed in this paper include optical-fiber-based designs, optical layer-integrated designs, the CMOS (complementary metal–oxide–semiconductor)-based microfluidic technologies, and organic electronics based designs. Efforts are continuously directed ahead to the identification of an integration paradigm that converges towards an ultra-miniaturized fluorescence detection scheme (Shang and Zheng 2017). This system should assure the following characteristics: full working autonomy, multiplexing, low-cost fabrication, fast response time, robustness and compactness, specificity, and ultra-sensitivity (Pfeiffer and Nagl 2015). Even if nowadays the achievements are consistent, a generic strategy fulfilling all the above-mentioned specifications is still elusive. The main aim of this review is to identify the main recent integration strategies in the miniaturization of fluorescence detection systems, emphasizing design and manufacturing procedures, limits of detection achieved, and further possible improvements.

2 Miniaturized off-chip fluorescence sensing architectures

Off-chip approaches (or free-space designs) are usually miniaturized versions of conventional fluorescence detection systems (Babikian et al. 2017; Yang and Gijs 2018) generally being linked with the use of pinholes at the focal points along the optical path, to couple macro-scale optical detection to micro-scale detection volumes. In this case, light propagates in free-space before and after interacting with the target molecule, and optical elements (filters, lenses, mirrors, light sources, detectors) are separated from the microchip. Modular configuration confers them the advantage of convenient integration within a wide variety of already existing platforms, enabling them as plug-and-play microscopes (Zhang et al. 2015). Table 1 summarizes the achievements of some identified architectures.

The fluorescence microscope developed by Ghosh et al. (2011) (see Fig. 2. a) presented a high degree of miniaturization using state-of-the-art in the field of optoelectronics. It proposed an innovative design solution, embedding all optical elements within a 2.4cm^3 polyetheretherketone (PEEK) housing. A blue LED, integrated on a 6×6mm^2 printed circuit board (PCB), was used as an excitation source. A drum lens was used to collect the emitted light, which was then passed through a 4×4mm^2 excitation filter. A dichroic mirror directed the light to the sample**,** via a focusing gradient refractive index (GRIN) objective lens. The fluorescent emission passed through the objective lens, dichroic mirror, an emission filter, and an achromatic doublet lens, which in turn focused the image onto a CMOS sensor. The 640×480 pixel CMOS sensor, mounted on a 8.4×8.4mm^2 printed circuit board had a 60% quantum efficiency at 530 nm. The LED, image sensor, micro-lenses, and filters, were made using batch fabrication, decreasing the cost per unit. The device was built in an alignment-free configuration, but not stand-alone, requiring a computer for image processing. Data acquisition between microscope and computer was intermediated using an external PCB, allowing imaging at 35 Hz or 100 Hz over 300×300 pixels subregions.

More recently, other versions of miniaturized off-chip detectors were developed with fabrication costs per unit varying from \$2000 (Fang et al. 2016) to \$10 (Zhang et al. 2015). For example, a handheld fluorescence detector with a broad range of possible applications, compact size, and capability to work independently was proposed by (Fang et al. 2016) (see Fig. 2b). This device embedded a light source (450 nm laser diode), an optical circuit module (a 450 nm band-pass filter, a dichroic mirror, a collimating lens, a 525 nm band-pass filter, a 1.0 mm aperture), an optical detector (miniaturized photomultiplier tube), and an electronic module (signal recording, processing and displaying units). The stability was tested for more than 5 h for continuous detection of 100 nM sodium fluorescein, and the relative standard deviation was below 1%. Two configurations were tested, the quasi-confocal configuration was proven to be more advantageous compared to an orthogonal configuration, mainly from the perspective of possessing more top open space to be used for installing disposable interrogation cuvettes. The configuration used for positioning the optical elements is usually a compromise between the performance and the ease-of-use of the final device. A hand-held orthogonal detector that was proposed by Pan et al. (2018), where the fluorescence collection was performed at 45°, decreased the background scattering light intensity compared with a 90° configuration. Compared to a confocal configuration, in the orthogonal configuration the excitation and collection paths were separated, leading to a reduced background signal without using complicated optical components. This

Table 1 Off-chip fluorescence detection platforms

ReferenceS	Description	Applications	Limit of detection (LOD)	Dimension	Cost
Zi et al. (2016)	Time-resolved fluorescence fluorometer made out of off-the-shelf components	Detection of immunochromatographic strip to achieve quantitative inspection and analysis of analytes in human blood or body fluid	1 μg/mL	$26\times20\times13$ cm^3	–
Zhang et al. (2015)	Cost-effective detector built from off-the-shelf components and a webcam Modular configuration with capability of being integrated with a wide variety of pre-existing platforms	Live cell imaging, long-term tracking of cellular processes, fluorescence analysis, and biosensing Monitor dynamic processes of simplified heart- and liver-on-a-chip models	–	$4.2\times5.5cm^2$ 65 g	$10
Ghosh et al. (2011)	Miniaturized microscope permitting fluorescent cell counting	Detect tuberculosis bacteria in a fluorescence assay	–	$2.4cm^3$ 1.9 g	–
Fang et al. (2016)	First report on using a 450 nm laser diode in a miniaturized LIF detector Higher miniaturization and integration level of the detector over most of the previously-reported miniaturized LIF detection systems	Capillary electrophoresis separation Online LIF detector for flow analysis systems (such as multiphase microfluidics and liquid chromatography) Could be combined with microfluidic chips, microarray chips or biosensors In-field analysis, point of care testing, environmental/industrial monitoring	0.42 nM (S/N = 3)	$9.1\times6.2\times4.1$ cm^3, 350 g	$2,000
Pan et al. (2018)	Hand-held detection device Built by integrating miniaturized modules	High speed capillary electrophoresis Colorectal cancer diagnosis for detecting KRAS mutation status	1.02 nM fluorescein	$90\times75\times77mm^3$	$500
Harmon et al. (2018)	Integrating a reflective sphere, enhancing the excitation and emission intensity	Detecting the fluorescein solution and SYBR-Green stained dsDNA	0.4 nM fluorescein	-	–

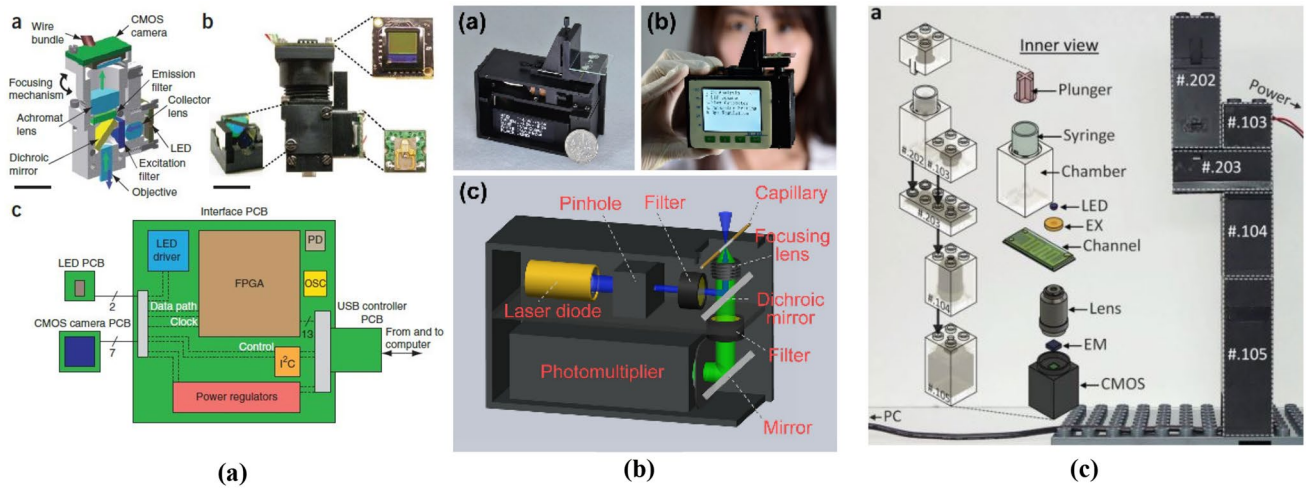

Fig. 2 **a** Integrated fluorescence microscope, 2.4cm^3 volume, 1.9 g weight. **b** Compact handheld quasi-confocal laser induced fluorescence. **c** Integration of LEGO-like blocks hosting elements of the optical, electrical, and fluidic circuits in order to modulate the optofluidic systems. (a) Reprinted from (Ghosh et al. 2011), Copyright 2011, with permission from Nature Publishing Group. (b) reprinted from (Fang et al. 2016), Copyright 2016, with permission from Elsevier. (c) Reprinted from (Lee et al. 2018), Copyright 2018, with permission from Willey

system was built for high-speed capillary electrophoresis (CE) and it integrated in a modular way a picoliter scale sample injector, short capillary-based fast CE, high-voltage power supply, orthogonal laser induced fluorescence (LIF) detection, battery, system control, on-line data acquisition, processing, storage, and a display. The proposed architecture was embedded into a monolithic black acrylonitrile butadiene styrene (ABS) block of 44 mm × 42 mm × 40 mm dimension, the overall fabrication cost reaching $150. The optical circuitry included a high intensity laser diode (18 mm length, 12 mm diameter, 80 mW) as light source, two small collimating lenses for laser beam focusing and fluorescence collection, and a photodiode (9 mm length × 6.2 mm diameter) as optical detector. The collimating lens consisted of three lenses and had a small size of 8.7 mm length × 9.6 mm diameter and 7 mm focal distance. A focusing spot of 10 µm for the laser beam could be obtained at the center of a capillary channel. The photodiodes achieved a larger degree of miniaturization compared to the photomultipliers, but the sensitivity was lower.

A design based on a reflective sphere, aiming at enhancing the excitation and collection efficiency, was proposed by Harmon et al. (2018). The interrogation volume was located in the center of a sphere, to produce effects that increased the collection efficiency. A hole was drilled in the sphere, perpendicular to the direction of a microchannel, serving as a light guide from the source located outside of the sphere. The incident light intersected the sample in the region of the interrogation volume, and the reflected light from the walls of the sphere refocused on the sample, rendering the excitation more efficient. A similar arrangement was available for the fluorescence that was collected through another drilled channel in the sphere.

A cost-efficient device built from off-the-shelf components, including a commercially-available CMOS-based universal serial bus (USB) camera was reported by Zhang et al. (2015). Four poly(methyl methacrylate) (PMMA) sheet frames with holes near the edges, for bolts/screws, were fabricated to serve as a layered modular support for the optical components. Screws were used to adjust the distance between the base and sample holders. The bottom PMMA layer contained the CMOS sensor. The lens was inverted to obtain magnification rather than the de-magnification mechanism of the camera. Resulted modularity allowed the integration with a large variety of preexisting platforms (e.g. cell culture plates, microfluidic devices, and organs-on-a-chip systems).

Time-resolved fluorescence is a methodology implemented for improving the sensitivity of the detection by sequentially powering the emitting source on and off to avoid autofluorescence or excitation light reaching the detector while fluorescence is quantified. Biotechnology, electronics and chemical technology were combined in Zi et al. (2016) to develop an integration scheme for a time-resolved fluorescence sensing system. Off-the-shelf miniaturized modules (ultraviolet light-emitting diode (UV-LED), silicon photodiode, signal processing units, displays, and optical paths) were integrated into a detection platform of 26 cm × 20 cm × 13 cm. This instrument was used for quantification of analytes in human blood and other body fluids.

Modular optofluidics is the solution proposed by Brammer and Mappes (2014) and by Lee et al. (2018), among others, aiming to make the widespread implementation of the microfluidic systems more reliable (see Fig. 2c). Lee et al. (2018) proposed a strategy based on modular blocks embedding the elements of the optical, electrical, and fluidic circuits into LEGO-like structures fabricated using rapid prototyping fabrication techniques.

3 Towards on-chip fluorescence sensing architectures

On-chip systems are defined as structures that have all the electrical, optical, chemical, and detection functions integrated within the microfluidic chip platform (Kuswandi et al. 2007). This integration strategy that combines optics and microfluidics, resulting in highly efficient liquid–solid interactions created the field of optofluidics (Yang and Gijs 2018). The development process of integrated circuits established technological methodologies that have been successfully used to solve issues in fields outside of electronics, generally known as the MicroElectroMechanical Systems or MEMS industry (Wu and Gu 2011). In this way, routes towards new technological fields appeared, such as micromechanics, microfluidics and micro-optics (integrated optics) (Hierlemann et al. 2003). Soon after this, the limitations of integrated circuits on silicon chips (material mainly used for the development of integrated circuits) became apparent. The requirements of electronics frequently collided with those of optics and mechanics, so that integration on one and the same chip (monolithic integration) proved to be hard (Gründler 2007). Thus, engineers had to consider new integration methodologies and hybrid technologies have been envisaged, i.e. the final device was composed of complex subunits, which were manufactured by different technological processes. Polymer are here considered due to their ease-of-fabrication and cost-efficiency. Within this section, a brief description of the latest achievements towards on-chip integration of fluorescence detection using hybrid technologies is provided.

3.1 Optical-fiber-based designs

Implementation of optical fibers based designs in fluorescence sensing (see Table 2) can be observed from two perspectives: (a) full-core optical fibers, and (b) microstructured hollow-core optical fibers. Integration of full-core optical fibers as waveguides intermediating the light transfer from external excitation sources towards the sample volume and/or the fluorescence transfer towards external photon detector has been one of the initial techniques used in fluorescence sensing miniaturization. Actualized theoretical aspects related to the implementation of optical fibers in fluorescence biosensing applications could be found in a comprehensive review (Benito-Peña et al. 2016).

Optical fibers were adopted as waveguides in this field due to the fact that they are characterized as high light transmission efficient, low-cost, free from electronic noise, providing protection for the electronic components when dangerous chemical environments are present (Yue et al. 2015; Yeh et al. 2017). However, their main drawback results from the fact that they are not user-friendly, requiring precise alignment, with coupling being sensitive to vibrations. Some recent works treated this topic (Matteucci et al. 2015; Rodríguez-Ruiz et al. 2015), proposing some fabrication methodologies allowing free and relatively precise alignment of the fibers. For example, (Matteucci et al. 2015) introduced a fabrication methodology that embedded standard commercially-available optical fibers with Cyclic olefin Copolymer (CoC) TOPAS 5013 hard-polymer chips, based on an injection molding technique (i.e. production-friendly). TOPAS 5013 polymer possesses characteristics that are compatible with the demands of the optofluidic chips. This polymer is highly transparent in the visible spectrum, possessing a high glass transition temperature (140 °C), very low water absorption, is resistant to acids, alkaline agents and polar solvents, and avoids biofouling (minimal surface treatments are needed). The autofluorescence of TOPAS 5013 could be decreased to values that are 20% lower than the ones resulting in silica material by the addition of a master-batch of a blank dye to the polymer granulate used for injection molding of the devices (Østergaard et al. 2015). Hatch et al. (2014) used optical fibers with ball lenses at their tip, enhancing the light optical density, enabling the implementation of cost-effective and low-power LEDs as light sources. The device was portable, but still bulky relative to the current integration trends.

Even if the current trend in the miniaturization of optical sensing is to bring the light source and the photon detector in the close vicinity of the interrogation sample, standard optical fibers are still used for those cases where robust modular systems are desired. Three-dimensional modular microfluidics has been recently introduced (Bhargava et al. 2014) as a methodology to overcome the issues appearing when monolithic design strategies fail. Modularity is one of the solutions envisaged for bringing microfluidic devices closer to its large-scale commercial implementation. Thus, standard optical fibers are still used nowadays for the development of modular and reliable miniaturized fluorescence-based optical sensors. Ackermann et al. (2016b) introduced the Chip-to-World Interface (CWI) as a plug-and-measure sensing strategy based on a CO_2-laser machining fabrication technique, to create a low-cost and robust modular interface facilitating the connection to a large variety of external photon detectors and

Table 2 Microfluidic systems using optical fiber based designs towards-on-chip integration of fluorescence detection

References	Achievements	Applications	LOD	Analyte	Further improvements [Author's suggestions]
Rodríguez-Ruiz et al. (2015)	Hassle-free optical fiber connection fabrication method within a PDMS chip Photonic and fluidic elements are fabricated in one single step, plasma activated and covalently bonded on a glass substrate	Monitoring enzymatic catalytic reactions	1.14 µM	–	–
Yang et al. (2015)	In-fiber integrated fluorescence online optofluidic sensor based on specially designed hollow optical fiber with suspended core Vertical micro holes drilled for inlet and outlet, while the molecules are excited through the evanescent field principle The optical transmission and the microfluidic detection are entirely realized in the hollow fiber	Low-cost detection of nitrides	0.1 mmol/L	Rh6G	The device architecture could be adapted for other fluids such as gas involving fluorescence quenching that can be further investigated
Shang and Zheng (2017)	Compact fluorescence sensing scheme based on hollow core Bragg fibers (HCBFs) serving as a sample cell, a collector, and a delivery channel for the desired fluorescence, as well as a filter for the residual excitation light mixed with fluorescence Photonic bandgap effect (PBG) is studied in common HCBFs, the transverse resonant behavior in the defect HCBFs. They proved that can be successfully employed as integrated filtering solutions	Multi-mode silica fibers as fully-integrated fluorescence sensing optofluidic devices	–	Rh6G	–
Matteucci et al. (2015)	Fabrication technique based on injection molding—integration of optical fibers with 2.7 ± 1.8 µm alignment accuracy Broaden the number of possible lab-on-a-chip applications: optogenetic stimulation and detection, shape recognition, and flow cytometry Implementation of TOPAS 5013 polymer optofluidic chips using injection molding fabrication technique	Self-alignement of optical fibers in optofluidic chips	–	–	The use of mechanical supports when inserting fiber to further reduce the misalignment. Integration of fiber-based Bragg gratings

Table 2 (continued)

References	Achievements	Applications	LOD	Analyte	Further improvements [Author's suggestions]
Ngernsutivorakul et al. (2017)	Free-standing probe with integrated optics that could focus and collect light from outside the probe, be easily coupled to fiber optics, and have separate input (e.g., excitation) and output (e.g., emission) paths; cost-efficient soft-lithography techniques used for fabrication	Remote detection	6 nM	Resorufin	LOD could be improved by integrating optical filters directly onto the tips of the fibers

light sources. This concept refers to the implementation of an optical fiber with coaxial radio frequency subminiature version A (SMA) connectors, allowing manipulation of the detection system without special training of a potential user. Yue et al. (2015) used also optical fibers with SMA connectors to develop a modular fluorometer for detection of fluorescein isothiocyanate. A concentration of 10 ng/mL could be measured, and the system presented a good linearity from 10 ng/mL to 10 µg/mL. The opto-electrical converter module and the signal acquisition device were modular and could be replaced for the detection of other molecules. Moreover, an optical probe is a tool used to collect light from otherwise inaccessible volumes. Ngernsutivorakul et al. (2017) proposed a 0.5 mm thick and 1 mm wide PDMS probe with two optical fibers integrated as inlet and outlet light waveguides. In addition, the probe embedded pre-aligned mirrors, lenses, allowing separate input and output optical paths. The probe was disposable, reusable from one chip to another, but not alignment-free, requiring a specific instrument to couple it to a microfluidic chip.

Next implementation level of optical fibers in the miniaturization process of fluorescence sensing is represented by the microstructured optical fiber (MOF) or photonic crystal fiber (PCF). The field of optofluidics in microstructured optical fibers was recently reviewed in Shao (2018) and Ertman et al. (2017). It gained high interest due to its capability of simplifying optical fiber sensors and improving the level of integration. Hollow-core Bragg fibers (HCBFs) working on the principle of evanescent wave are a promising solution that might converge towards a fully integrated detector (Li and Nallappan 2019). HCBFs form a particular class of photonic bandgap (PBG) fibers (Huang et al. 2004) with a guiding mechanism that is capable of confining the light in the fiber core from all incidence angles and polarizations. Due to the PBG effect, the HCBFs have features of a wideband band-pass filter. The Bragg layers can be designed in such a way that they behave as a reflective surface for specific wavelengths and absorbing surface for others. By introducing a defect layer into the common cladding band, the excitation light is rejected, while fluorescence light is transmitted towards the photon-sensing element. Also, the rejection filtering is narrowed due to the transverse resonant behavior, explained elsewhere (Chen et al. 2008). Shang and Zheng (2017) applied this principle, resulting in a very compact detection device where the detection cuvette, the collector, the delivery channel for the desired fluorescence, and the filter for residual excitation light mixed with fluorescence were all part of the fiber (see Fig. 3). In Yang et al. (2015), a hollow optical fiber with suspended core was proposed, fabricated, and characterized for detection of Rhodamine 6G. The outer diameter of the fiber was 350 µm, the inner diameter of the fiber was 210 µm and the core diameter was

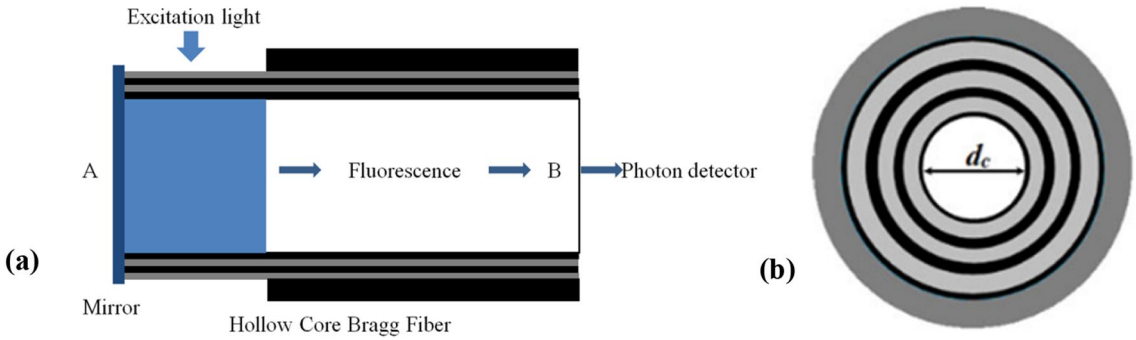

Fig. 3 **a** Compact fluorescence-sensing scheme based on hollow core Bragg fibers, serving as interrogation cuvette, collector, delivery channel for the fluorescence, and the filter for the residual noise. **b** Cross-section scheme of the device with the photonic band gaps of different refraction indexes (Shang and Zheng 2017)

40 µm. The inlets and outlets were made on the surface of the hollow fiber by CO_2 laser etching, all the others optical elements being off-chip.

3.2 Optics layer-integrated designs

The basic principle of this strategy is to integrate the active and passive optical components on a planar layer, mainly by implementing the micro- and nano-fabrication technologies (Dandin et al. 2007). Transparent materials with high refractive indexes, such as polymers, are usually used as waveguides and the light remains confined by multiple total internal reflections (Gründler 2007). Some of the main active current research directions are in-plane microfluidic lenses, printed-board microfluidics, antiresonant reflecting optical waveguides (ARROWs), and on-chip integration of solid-state light emitters (SSLE). In-plane microfluidic lenses or on-chip lens systems mainly aim to robustly integrate light beam focusing customized solutions in the same functional layer as the fluidic layer (Bates and Lu 2016). Liquid-core cladding lenses, pressure-controlled liquid–air interface and gradient refractive index lenses are some configurations recently reported in the literature tackling this subject (see Table 3).

Femtosecond lasers revolutionized the three-dimensional micro-fabrication of the materials due to their very short pulse width and high peak intensity. Known as a complicated technique, recent advancements proved the femtosecond laser micromachining as a cost-effective and reliable fabrication technique for optofluidic systems (Sugioka and Cheng 2012; He et al. 2014; Sugioka et al. 2014; Gu et al. 2015; Joseph et al. 2017; Serhatlioglu et al. 2017). An in-plane integrated microfluidic lens whose modulation could be on/off switched on demand was fabricated by Paiè et al. (2017) using femtosecond laser micromachining (FLM) fabrication technique. Modulation of the light is a common technique used to enhance the measurement sensitivity by subtracting the noise. The focused light could be modulated by dynamically changing the liquid in the lens through a droplet generation module. Femtosecond laser micromachining and radio frequency (RF) sputtering were implemented for the incorporation of a microfluidic network, excitation, filtering, and collection elements in one glass substrate, in a 90° configuration (Guduru et al. 2016). Here, the FLM was used to fabricate the microfluidic channel, the perpendicular fiber channels, perfectly aligned and embedded in the fused silica layer. A wavelength filter, behaving as a Bragg mirror, was fabricated by implementing an RF sputtering method. One-dimensional photonic crystals were used, since they are dielectric structures of different refractive indexes, permitting propagation of only specific wavelengths. They can be designed to have a photonic bandgap in the wavelength region of excitation, similar to the concept explained in the previous subchapter. On the top of the filter, a binary Fresnel lens (BFL) was fabricated, leading the collected light out of the chip. Fresnel lenses are flat, low thickness structures with concentric rings designed to focus the light (40% efficiency) in optical microfluidic devices (see Fig. 8b) Their fabrication within a microfluidic channel is based on the nanoimprint process (Siudzinska et al. 2017). Efficient beaming of the emitted radiation is very important since it can drastically affect the performance of the assay. Ricciardi et al. (2015b) proposed an optofluidic chip based on a multilayered photonic crystal structure embedded on a PDMS structure. The efficiency of fluorescence collection was experimentally demonstrated in an antibody–antigene immunoassay, resulting in a decrease of the limit-of-detection (LOD) for labelled antigenes by a factor of about 40. The measurements were demonstrated to occur in a robust and reproducible way, with reduced optical alignment issues. Here, it deserves mentioning the method proposed by Watts et al. (2012) for an efficient beaming of the excitation light. This method eliminated the need for free-space optics and high-quality light sources, through on-chip 3D hydrodynamic focusing.

Table 3 Microfluidic systems using optics layer-integrated designs towards-on-chip approaches for fluorescence detection

References	Achievements	Applications	LOD	Analyte	Further improvements [Author's suggestions]
Babikian et al. (2017)	Heterogeneous integration strategy integrating optical, electronic, electromechanical, and fluidic components on the same chip Demonstration of a digital signal processing (DSP) assisted lab-on-a-chip PCB that can extract the signal from an isotachophoresis assay PCB, ITP, microelectronics, and DSP integrated on-chip for fluorescence detection in a microfluidic-optoelectronic PCB device	Isotachophoresis assay	10 nM (SNR = 9)	Fluorescein fluorophore	More optimized designs and more sophisticated algorithms could further improve the detection sensitivity
Paiè et al. (2017)	In-plane integrated microfluidic lens, with tunable optical properties, combined with a droplet generation module The focusing of the lens could be changed by replacing the fluid streamed in the system Fabrication was done in fused silica: (1) femtosecond laser beaming; (2) ultrasonic bath etching	In-plane microfluidic lens		Rhodamine	–
Guduru et al. (2016)	The microfluidic network, the excitation, the filtering, and the collection elements were embedded in the same glass substrate Fabrication methodology: (1) microfluidic channels created by femtosecond laser irradiation followed by chemical etching technique; (2) fabrication of the Bragg mirror and the buffer layer by RF sputtering, (3) surface ablation using FLM for the Fresnel lens	Fully-integrated fluorescence sensing in glass-made devices	600 nM	Oxazine 720 perchlorate dye	Bragg mirror reflectivity could be improved by adding thermal treatment after the deposition process

Table 3 (continued)

References	Achievements	Applications	LOD	Analyte	Further improvements [Author's suggestions]
Ricciardi et al. (2015b)	Optofluidic chip based on a multilayered photonic crystal structure was employed for an efficient beaming of the emitted radiation in a fluorescent microarray assay	Efficient focusing in point-of-care devices	0.168 μg/mL	Actin-Alexa Fluor solutions	–
Novo et al. (2014)	Prism-like PDMS microfluidic device coupled with amorphous silicon photodiodes and a lateral excitation scheme at a specific angle Lateral excitation coupled to TIR to maximize the excitation light reaching the microchannel while preventing it reaching the detector	Improve the SNR using TIR principle	5.6×10^{10} antibodies/cm^2	Antibodies labeled with a organic fluorophore	By modifying the polymerization process, minimize the internal scattering of the PDMS
Berner et al. (2017)	It successfully integrated line-focused laser excitation with sensitive amorphous silicon photodiodes and novel, disposable microfluidic chips to a device that has no need for space-consuming optics or bulky sensors The innovative microfluidic chips formed by a transparent, laser-cut adhesive tape were not only essential for the presented concept, but also of general interest as an easy, versatile and scalable way to fabricate microfluidic channel chips	Point-of-care testing devices for continuous monitoring	26 nmol/L	DY636 dye	Substitution of the silicon top plate of the microfluidic chip by a plate of another material to enable low fabrication cost of the disposable microfluidic chips
Persichetti et al. (2017)	Optofluidic detection scheme based on an optofluidic jet Total internal reflection arises in a liquid jet of 150 μm diameter, leading to efficient signal excitation and collection	Pharmaceutical liquid sample analysis	0.21 ng/mL	Riboflavin	–

Table 3 (continued)

References	Achievements	Applications	LOD	Analyte	Further improvements [Author's suggestions]
Robbins et al. (2018)	Monolithical integration of a SiO_2/Ta_2O_5 multilayer interference filter and hydrogenated amorphous silicon (a-Si:H) pin photodiode Annular shape of the sensor combined with a transparent glass substrate allowed vertical illumination	Point-of-care microfluidic biochemical analysis	36 nM (SNR = 3)	Fluorescein solution	Heterogeneous integration of a GaN VCSEL on the integrated a-Si:H fluorescence sensor to fabricate a planar LIF device resulting in better light directionality
Nittala and Sen (2018)	3D heterogenous integration methodology, allowing packaging of photodetector, filters, microfluidic chip, and LED in one system Components were embedded through SU-8-based planarization and epoxy-based bonding	Point-of-care microfluidic systems	1 μM	Rhodamine B and 6G	–
Rodríguez-Ruiz et al. (2017)	Master mold based on WBR2000 dry polymer films, fabricated in standard laboratory conditions, without requiring clean room facilities Compared with SU-8 standard lithography technique, this method resulted in 10-fold reducing of the material costs	Fast, low-cost structures design and prototyping	8.5 ± 0.3 μM	Fluorescein	–

The on-chip hydrodynamic focusing is achieved through the introduction of micro-patterned optical components in an epoxy-based SU-8 photoresist layer that hosts also the fluidic components.

The printed circuit board (PCB) is a mature technology used and improved for decades in electronics, to mechanically support and electrically connect components using conductive tracks etched in layers of copper onto and/or embedded between sheets of a non-conductive substrate. The materials usually used as substrates for the fabrication of PCBs are resistant at high temperatures (> 170 °C), this characteristic making them compatible with microfabrication techniques that involves elevated temperatures. The reliability and potential of PCBs for miniaturization of fluorescence sensing systems was demonstrated recently (Novo et al. 2014; Shin et al. 2015, 2017; Babikian et al. 2017; Obahiagbon et al. 2018). A PCB offers an integration alternative to glass/polymeric microfluidic chips, which are not integration-friendly with standard, off-the-shelf optoelectronic elements (Babikian et al. 2017).

Portable systems integrating light-emitting diodes (LEDs) for multiple target analysis were proposed in Shin et al. (2015, 2017). Optical functions were modularly parallelized within three layers (see Fig. 4a, c). The first layer (filtering and detection layer) hosted a photon detector, a dichroic lens, and a color filter. The intermediate layer was represented by a PCB with three LEDs of different wavelengths mechanically mounted around a circular orifice, which illuminated the interrogation volume from the opposite direction of the photon detector. Avoiding direct illumination of the detector was relevant for increasing the signal-to-noise ratio. The circular cut assured that the emitted fluorescence was transferred from the third layer (interrogation volume) to the first layer (filtering and detection layer), while the PDMS microfluidic layer was disposable. All above-mentioned components were embedded into a portable box equipped with a display, permitting the selection of the operation. A comprehensive review about LEDs implementation with fluorescence sensors is reported in Yeh et al. (2017).

As a predictable continuation of the above-mentioned concepts, the microfluidic-PCB concept was introduced by Babikian et al. (2017). This concept involved a three-layer device, integrating with the aid of two PCB parts, all the fluidic, electrical, mechanical and optical components within a compact system (see Fig. 4b). One PCB was fixed and non-disposable, comprising all active components, and was denoted the reader chip. The second PCB, named the microfluidic chip, was disposable and encompassed the passive structures of the device such as microchannels, high voltage electrodes, and micromachined light reflector. A standard surface-mounted blue LED was used as a light source. The detection was implemented using a standard surface-mount 2-megapixel CMOS imaging array with integrated red–green–blue (RGB) filters. The CMOS sensors were inexpensive, compact, and compatible with the microfluidic-PCB approach. A surface-mounted light reflector was used to reflect the excitation light path towards the detection channel. A rectangular slit was created in the upper PCB, above and along the microfluidic channel, to avoid light scattering and autofluorescence of the PCB substrate. The background noise associated with the excitation light was further suppressed by a Söller collimator film, laminated on top of the CMOS pixel array. A Söller collimator collimates light by allowing the passage of rays that are almost parallel with its optical axis and it is used in lens-free fluorescence detection schemes since uniform spatial distribution of light was

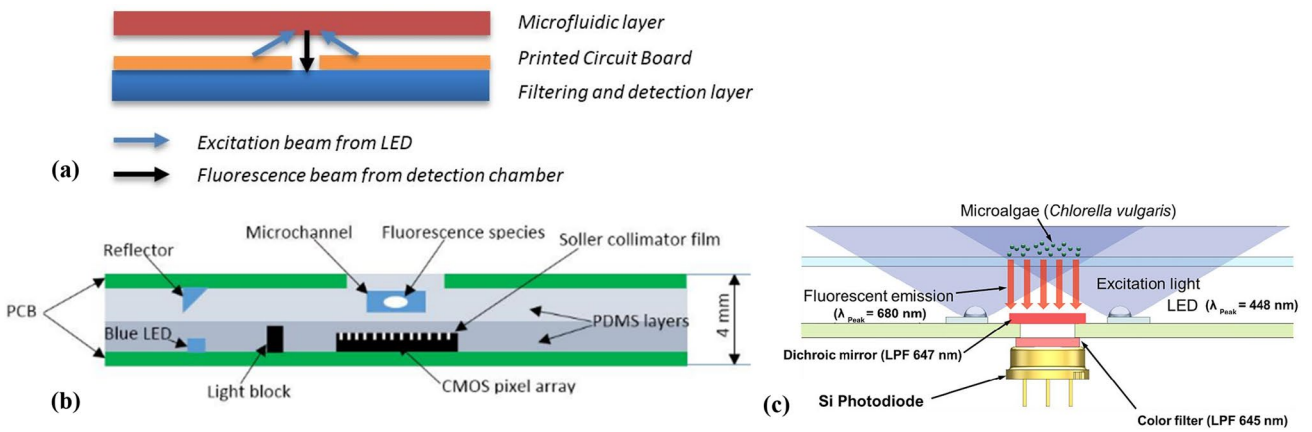

Fig. 4 **a** Parallel layering distribution of the detection functions with the PCB sandwiched in between the microfluidic layer and the detection layer (Shin et al. 2015, 2017). **b** Cross-section of the microfluidic-PCB fluorescence detector, built using two PCBs. The design strategy avoided the direct illumination of the interrogation volume, a Söller thin film collimator being coated on top of the CMOS to reduce the background noise (Babikian et al. 2017). **c** Fluorescence detection system with backside illumination scheme. Reproduced from (Shin et al. 2015, 2017), Copyright 2015, with permission from Elsevier

crucial (Balsam et al. 2012). In this work, it also avoided the cross-talking between the light source and the CMOS image sensor. This heterogeneous method embeds individually manufactured components, such as electrodes, heaters, light sources, detectors, and microfluidic components between the electrical and microfluidic layers using standard fabrication processes. All the components (light source, microchannel, optical guide, and detection sensor) were integrated within a structure having the approximate dimensions of a credit card, 7 cm × 5 cm × 4 mm.

Total internal reflection (TIR) takes place when a light beam meets a medium with a lower refraction index at an angle greater than the critical angle. This critical angle can be calculated knowing the refraction indexes of both media. The phenomenon can be used to mitigate direct illumination of the detector and, by consequence, to lower the noise level. For example, a design solution using a lateral excitation configuration, to (1) maximize the photon flux exciting the microfluidic channel while (2) preventing excitation light reaching the sensor, was proposed by Novo et al. (2014). This configuration (see Fig. 5a) involved a prism-like polydimethylsiloxane (PDMS) microchannel sealed with a glass substrate. A printed circuit board hosted a micro-fabricated a-Si–H photodiode and contained a two-level pocket, which kept a 50 µm space between the microfluidic chip and photodiode needed for the total internal reflection condition. A 405 nm laser beam was directed perpendicular to the lateral prism-like PDMS structure in which the sides made a 70° angle with the flat surface and was focused to illuminate the microchannel while experiencing total internal reflection at the glass–air interface. This configuration improved the detectability range by two orders of magnitude as compared to a normally incident excitation configuration, signal-to-noise ratio being ameliorated for detection of specific fluorophores.

Berner et al. (2017) developed a method based on sandwiching laser-cut double-sided adhesive tapes coupled with the latest generation of thin-film photodetectors, enabling miniaturization by the custom fitting of amorphous silicon-based photodiode arrays to the geometry of the flow channel.

One promising methodology using TIR phenomena was presented in Jang and Yoo (2013), where a fluorometer integrating a total internal reflector was introduced, a condensing mirror and the detection chamber (width 1.5 mm × depth 0.8 mm × length 5 mm) within a single 1.2 mm thick polycarbonate substrate. The total internal reflector enabled orthogonal detection, and the condensing mirror increased the selectivity of the fluorescence emission. The limit of detection achieved was 5 nmol/L and the linearity was 0.994 for 6-FAM fluorescence dye. The condensing mirror was coated with a 200 nm thick aluminum layer, having the role of better fluorescence collection from the sample and more

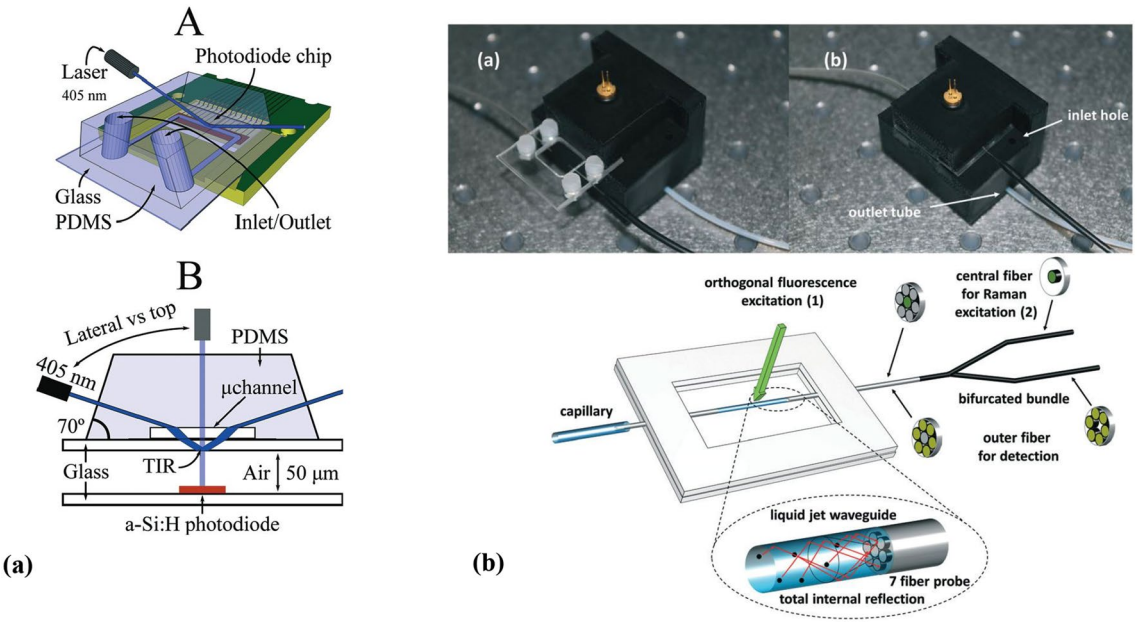

Fig. 5 **a** Lateral excitation onto a PDMS microfluidic device coupled to a photodiode PCB. The 50 µm air-gap separates the microfluidic device from the photodiode, in order to assure the TIR effect at the glass/air interface for the excitation light. **b** Multi-functional sensing device based on 150 µm optofluidic jet, equipped with a recirculation system. The detection scheme is based on the principle of the TIR in the liquid jet. Two possible ways of liquid jet excitation: (1) orthogonal fluorescence excitation, and (2) optical fiber for Raman excitation. (a) Reproduced from (Novo et al. 2014), Copyright 2014, with permission from The Royal Society of Chemistry. (b) Reproduced from (Persichetti et al. 2017), Copyright 2017, with permission from The Royal Society of Chemistry

efficient distribution to the photon detector, located on the opposite side of the fluidic chamber, while the light source (465 nm LED) and the photon detector were externally located. A system based on an optofluidic jet waveguide (see Fig. 5b)—a liquid micro-jet with 150 μm diameter—leading to highly efficient signal excitation and collection was introduced by Persichetti et al. (2017).

Alignment of the light emitter and the optical circuit is a very sensitive part of an optofluidic system. Small variations (less than 5%) may produce large performance variations that make the system unreliable (Llobera et al. 2015). Thus, monolithic integration of the solid-state light emitters (SSLEs) is a field of high importance. Llobera et al. (2015) proposed an innovative hybrid monolithic solution (see Fig. 6a) for on-chip integration of a SSLE aligned with a multiple internal reflection (MIR) system. The SSLE was made of a fluorophore-doped hybrid xerogel material. The fabrication procedure involved a low-cost photolithographic fabrication step. Air mirrors were made to assure light coupling from the light source to the MIR system. Robbins et al. (2018) introduced a compact device embedding a SiO_2/Ta_2O_5 multilayer optical interference filter, a hydrogenated amorphous silicon (a-Si:H) pin photodiode, an asymmetric microlens, and a GaN micro LED. The system was capable to collect fluorescence light in a 100 μm microfluidic channel, the device reaching a 36 nM limit of detection for fluorescein solution, but the integration of the micro LED was concluded as being difficult due to its lack of directionality. However, the fabrication procedure paved the way towards planar heterogeneous integration of GaN micro LED on an a-Si:H fluorescence sensor. Kang et al. (2016) developed a fabrication methodology (see Fig. 6b) for building mechanically flexible microfluidic fluorescence sensors. They managed to integrate microscale vertical cavity surface-emitting lasers (micro VCSELs) and silicon photodiodes on a flexible substrate of polyethylene terephthalate (PET). This substrate integrated with elastomeric fluidic chips on plastics demonstrated potential for multiplexed, real-time operation.

Polymers or silicon-based materials with refractive indexes varying between 1.4 and 3.5 are usually used for the fabrication of optofluidic integrated systems. Since the refractive index of water is 1.33, the total internal reflection condition required to confine the light when hollow-core optical waveguides are used simply cannot be satisfied for this particular case. Antiresonant reflecting optical waveguides (ARROWs), based on the thin-film interference principle and the conventional silicon microfabrication techniques, propose a solution for this inconvenient. A particular solution is represented by the aerogel waveguides. A series of alternating dielectric layers creates the conditions for interference-based guidance of leaky modes (Parks et al. 2014). This technique proved to be very suitable for very sensitive fluorescence detection. Parks et al. (2014) used this technology for developing a programmable microfluidic chip with on-chip detection of fluorescence. The active control of the biologic solutions was realized using programmable microvalve arrays (see Figs. 6a, 7). Measor et al. (2011) introduced a methodology for the fabrication of on-chip

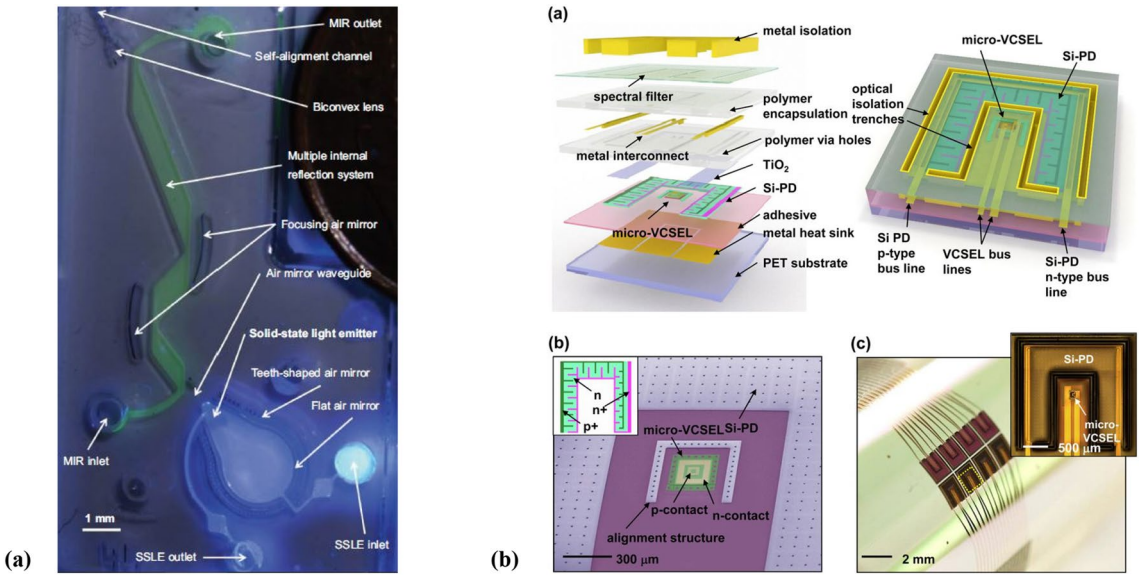

Fig. 6 **a** Photonic lab-on-a-chip with the solid-state light emitter, air mirrors, multiple internal refection system, biconvex lens, and the channel for fiber optics integration. (**b**) (a) Illustration of the flexible sensor design and fabrication methodology. (b) Scanning electron microscopy view of the VCSEL and the 3 μm thick Si-Photodiode. (c) Image of an array of sensors wrapped around a cylindrical bar. (a) Reproduced from (Llobera et al. 2015), Copyright 2015, with permission from Springer Nature. (b) Reprinted with permission from (Kang et al. 2016), Copyright 2016, American Chemical Society

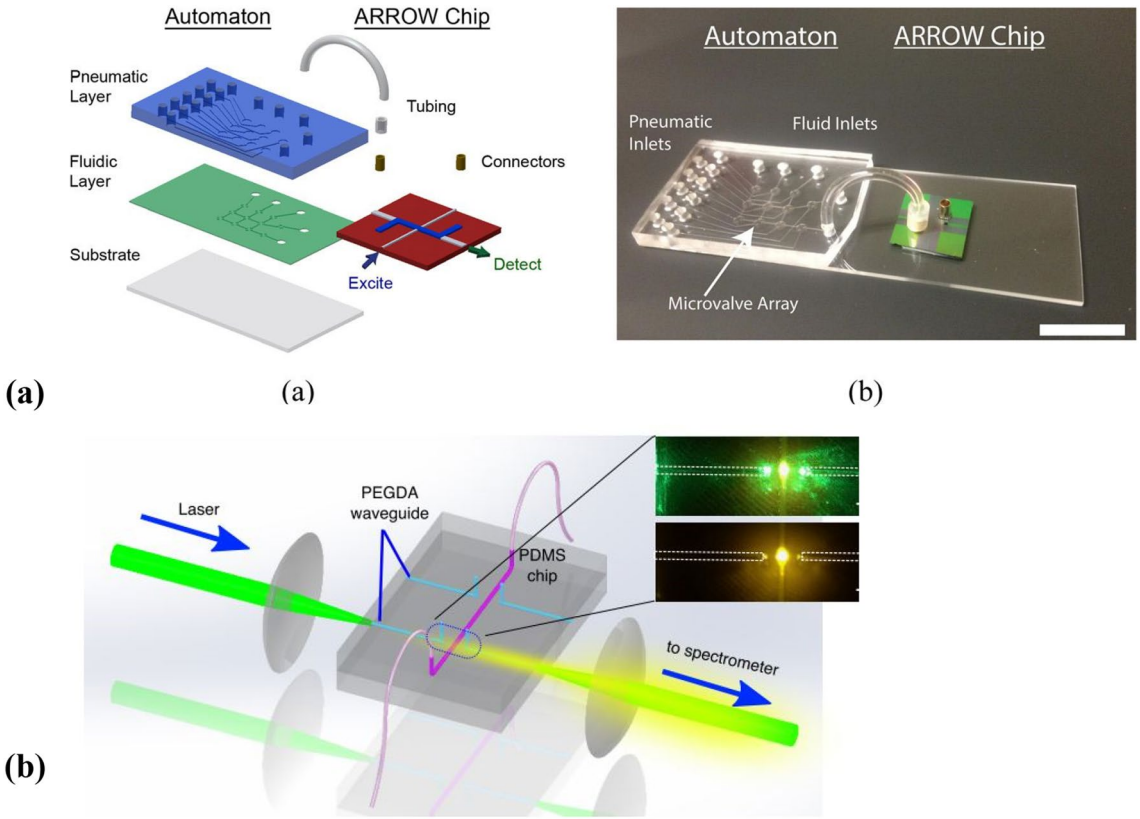

Fig. 7 **a** Hybrid chip-scale system combining the automated microfluidic processing (automaton) and on-chip optical detection based on the ARROW principle. Scale in the figure—1 cm. **b** Optical device schematic with a PEGDA waveguide used for excitation light coming from a 532 nm laser and another PEGDA waveguide used to collect the fluorescence emission from the interrogation volume. (a) Reproduced from (Parks et al. 2014), Copyright 2014, with permission from AIP Publishing. (b) CC-BY 4.0

interference filters with multiple high and low loss regions. Interference filters, compatible with the silicon microfabrication techniques, possess lower autofluorescence when compared with absorbance filters. In this work, they managed to decrease the number of dielectric layers requested for efficient working of the interference filter from more than 30 down to 3. Aerogels are materials with low-refractive indexes, making them suitable for solid-cladding in liquid-core optofluidic waveguides based on the principle of total internal reflection. A comprehensive review of aerogels used for optofluidic waveguides is presented in Özbakır et al. (2017).

Following the trend of scaling down by 3D integration of various heterogeneous components, a SU-8 polymer-based methodology was developed by Nittala and Sen (2018). The cost-effective reported methodology allowed integration of commercially available components in a relatively simple way. The key element of this approach was planarization of the layers with correctly chosen SU-8 parameters in such a way that the next layer could be stacked using epoxy-based bonding. This method allowed packaging a photon detector, the filters, the microfluidic chip, and a LED. On the other hand, a low-cost master mold fabrication process based on a dry film photoresist for soft lithography, and operated in standard laboratory conditions was reported in Rodríguez-Ruiz et al. (2017). This protocol managed to reduce by ten times the material costs and reduced considerably the fabrication time compared with standardized SU-8 master mold techniques. The methodology initialized a simpler fabrication methodology of photonic devices. Integrated hydrogel waveguides potential for developing wearable and implantable lab-on-a-chip devices was evaluated by Torres-mapa et al. (2019). They used self-aligned polyethylene glycol diacrylate (PEGDA) waveguides, which present tunable mechanical and optical properties, integrated via micro-molding technique into a PDMS structure to evaluate the fluorescence response from a rhodamine 6G solution. The PEGDA waveguides integrated into the PDMS showed high transmission, minimal absorption in the visible spectrum, and propagations losses lower than 1.1 dB/cm. Further investigations on mechanical and light guiding properties during stretching/bending are requested (see Fig. 7b).

3.3 CMOS-based fluorescence sensing

CMOS technology revolutionized the field of micro-electronics (Shakoor et al. 2018) and it holds the promise to do so for micro-optical sensing as well. On-chip CMOS-integration, coupled to microfluidics for detection at the micro-scale, was increasingly observed in the recent literature (Nakazawa et al. 2011; Choi et al. 2016; Tanaka et al. 2017; Wei et al. 2017), especially for the development of filterless prototypes (see Table 4). The focusing and the filtration optics represent a barrier in the miniaturization process (Papageorgiou et al. 2017), alternative techniques replacing them being envisaged. The filterless discrimination between the excitation light and the generated fluorescence light emerged as a cost-effective, compact, and lightweight miniaturization method. CMOS technology introduced advantages such as reduced dimensions, high sensitivity, coupled with filtration algorithms, very low unit prices, low-power consumption, and integrated signal processing, making it compatible with the targeted goals of fluorescence detection device miniaturization. Until recently, charged-coupled devices (CCDs) were largely used in image sensing, but now CMOS image sensors seem to be more used, due to their superior features. A CMOS image sensor is an integrated circuit with an array of pixel sensors. Each pixel sensor contains its own light sensor, an amplifier, and a pixel select switch. The main components of a CMOS sensor are color filters, a pixel array, a digital controller and an analog-to-digital converter (see Fig. 8a).

Different models are available for gathering information from pixels: RGB; hue, saturation, value (HSV); hue, intensity, saturation (HIS); CIELab or CIExyY (Sudhakaran 2020), all implemented at the system level. There is an increased interest in employing the RGB model combined with an image sensor or a camera to determine the concentration of analytes (Bueno Hernández et al. 2017). The commercially available CMOS image sensors are usually equipped with integrated filters. Generally, the performance of these filters is not sufficient and different filtration algorithms are implemented, to eliminate parasitic light. CMOS-based contact sensing coupled with time-correlated photon counting (TCSPC) has proven to be a sound methodology (Wei et al. 2017). Different strategies implementing CMOS image sensors have been recently proposed Măriuța et al. (2019) with good results and enough space for further improvements. The challenges existing in combining the integrated circuits with biological or chemical components in lab-on-a-CMOS concept, such as thermal effects, floorplanning, signal coupling, electrochemical effects, surface treatments, sterilization, and microfluidic integration were detailed by Datta-Chaudhuri et al. (2016).

One of the most critical challenges in lab-on-a-CMOS design and fabrication represents the interaction between the fluid samples and the chip surface, traditional wire-bonding packaging being not compatible with the planar microfluidic concept. Lindsay et al. (2018) developed a heterogeneous integration solution of a CMOS sensor and a fluidic network using wafer-level molding process. A technology enabling monolithic integration of the read-out system within the sensor for general label-free miniaturized optical detection by integrating nanophotonic structures with CMOS photodiodes was reported in Shakoor et al. (2018). One-dimension grating structures with a CMOS integrated image sensor arrayed with photodiodes. The gratings were made of silicon nitride and refractive index changes were induced when different analytes were applied. Pang et al. (2011) developed a CMOS based detection system by integrating Fresnel zone lenses (above described) (see Fig. 8b).

Tanaka et al. (2017) proposed a system based on charge accumulation techniques that simultaneously allowed filterless measurement of multiple low-intensity fluorescence wavelengths (five in this work). The charge accumulation technique involves fluorescence detection by measuring the voltage change of a capacitor, which is proportional to the accumulated signal charge quantity. This technique has the capability to increase the output signal level, reducing the noise induced by the incident light. From experiments, the dynamic range obtained was 100:1. The filter was fabricated by an older 2-poly, triple-well, 5 µm CMOS process.

A lens-free system for breast cancer cell detection was developed by Papageorgiou et al. (2017). It integrated stacked CMOS metal layers above each photodiode to form angle-selective gratings, rejecting background light. Choi et al. (2016) presented a filterless method for the suppression of forward scattering in silicon by surface planarization, resulting in a separation efficiency improving from 550:1 to 1250:1. This was achieved mainly due to the low roughness of the polysilicon surface.

Plasmon enhanced fluorescence or metal enhanced fluorescence, is a powerful amplification method used to increase the sensitivity and shorten detection times, and is based on the interaction between fluorophore labels that are coupled with the confined field of surface plasmons. A comprehensive review of this topic can be obtained from Bauch et al. (2014) and a detailed overview is presented in the book of Geddes (2017). The integration of nano-plasmonics with CMOS technology, without any other post-processing, enabled the possibility to integrate large multiplexed assays on the same chip. A detailed theoretical description of plasmon-enhanced fluorescence coupled with CMOS technology is found in Hong et al. (2017a).

3D copper-based nanoplasmonics components were integrated within standard CMOS devices through sub-wavelength copper-based electrical interconnect lithography features by Hong et al. (2017a), developing a bio-sensor with a nano-waveguide array-based filter. The sensor was

Table 4 Microfluidic systems using CMOS-based designs towards-on-chip approaches for fluorescence detection

References	Achievements	Applications	LOD	Analyte	Further improvements [Author's suggestions]
Hong et al. (2017a)	Fully integrated bio-molecular fluorescence sensor in 65-nm CMOS with integrated nanoplasmonic waveguide-based filters capable of more than 50 dB of rejection ratio across a wide range of incident angles	Enable parallelized sensing on a single chip	48 zeptomoles	Quantum-dots	–
Tanaka et al. (2017)	Developed a low-detection-limit filterless fluorescence sensor by a charge accumulation technique Sensor was fabricated with a photogate and a triple-well process	Implementation of filterless design strategies	0.1 nW		Dynamic range was obtained to be 100:1, which could be improved by the optimization of FD capacitance
Choi et al. (2016)	Suppressing forward scattering in silicon by surface planarization; improvement of a filter-less fluorescence sensor Separation ability of the filter-less fluorescence sensor was increased from 550:1 to 1250:1	Implementation of filterless design strategies	–	–	–
Bueno Hernández et al. (2017)	MATLAB interface developed for reading-out florescence signals with RGB model in CMOS sensor First application of the use of RGB model with CMOS sensor to detect OTA in wine and beer samples	Portable detection of mycotoxins	2 µg/L	Ochratoxin A (OTA)	–
Lindsay et al. (2018)	Methodology developed for heterogeneous integration of microfluidics and silicon-integrated circuits using compression molding with a commercial fan-out wafer-level packaging approach Electrical, fluidic routing made in 0.18-µm CMOS optical sensor integrated circuit Rapid prototyping fabrication methodologies for fluidic integration, resulting in millimeter-scale fluidic channels (a stacked laser-cut fluidic assembly) and sub-millimeter-scale fluidic channels (the fabrication of monolithic SU-8 microchannels over the integrated circuit surface)	Optofluidic lab-on-a-CMOS	− 2.5 nA	Quantum-dots	Long-term adhesion and material compatibility to be studied for liquid contact

Table 4 (continued)

References	Achievements	Applications	LOD	Analyte	Further improvements [Author's suggestions]
Hong et al. (2017b)	Design methodology based on CMOS integrated nanoplasmonic filters, exploiting the sub-wavelength lithographic features of on-chip interconnects, eliminating the need for any post-fabrication, or external optical elements First fully-integrated fluorescence-based CMOS bio-molecular sensor with integrated nano-plasmonic sensor	Low-cost, fully integrated, high performance, and fully scalable biosensor for point-of-care applications	47 zeptomoles	Quantum-dots	–

developed by implementing a 65 nm process, managing to diminish the noise by 50 dB for a large variety of incident angles. It comprised an assay platform, a sensor, and readout circuitry, making the integration of external optical components and any other post-fabrication techniques unnecessary, except for the light source that was a micro-laser diode or a LED. The optical fields could be manipulated in a controllable manner. Within the same team, the work of Lu et al. (2018) analyzed the possibility of photonic crystal integration on a CMOS sensor, exploiting optical physical unclonable functions (PUF) for a better management of the background noise.

In Varsanik and Bernstein (2013), a plasmonic resonator was designed, fabricated, and tested, proving both field enhancement and localization to nano dimensions. The proposed architecture enabled a solution for high-resolution and low-noise detection of fluorescence within an integrated microfluidic optical detection device. The microfluidic channel was built in a polymer on top of a glass substrate wafer. A diffused waveguide was embedded within the glass substrate, crossing the fluidic microchannel in the interrogation region. The width and the depth of the microchannel were 8 μm and 200 nm, respectively, enabling an extremely reduced interrogation volume and, by consequence, reduced noise. Finally, the system was capable to successfully detect 20 nm sized fluorescent particles.

CMOS-based fluorescence sensing field did not benefit from high-performance integrated optical filters until recently. This situation led to the implementation of either time-resolved techniques with synchronized sources (Samouda et al. 2015), or externally located optical filters and focusing optics (Lu et al. 2018). The above-mentioned methodologies, that were recently reported, enlarged the horizons toward more robust and compact fully-integrated solutions aiming to solve the chip-in-the-lab dilemma (Shakoor et al. 2018) with further improvements. The Internet-of-Things (IoT) field of applications requires low-power and low-cost sensors, and here CMOS based fluorescence detection is expected to play a major role (Lu et al. 2018).

3.4 Organic electronic-based designs

Organic light-emitting diodes (OLEDs) and organic photon detectors (OPDs) are the subject of significant research efforts and continuous improvements (see Table 5) due to their multiple applications and advantages compared to their inorganic counterparts (Krujatz et al. 2016). Organic electronics introduced some unbeatable advantages, such as direct on-chip integration, easy emission and detection, and compatibility with flexible substrates. An OLED is a solid-state device composed of flexible thin films of organic molecules that emit light when subject to electricity, using less power than current available LEDs.

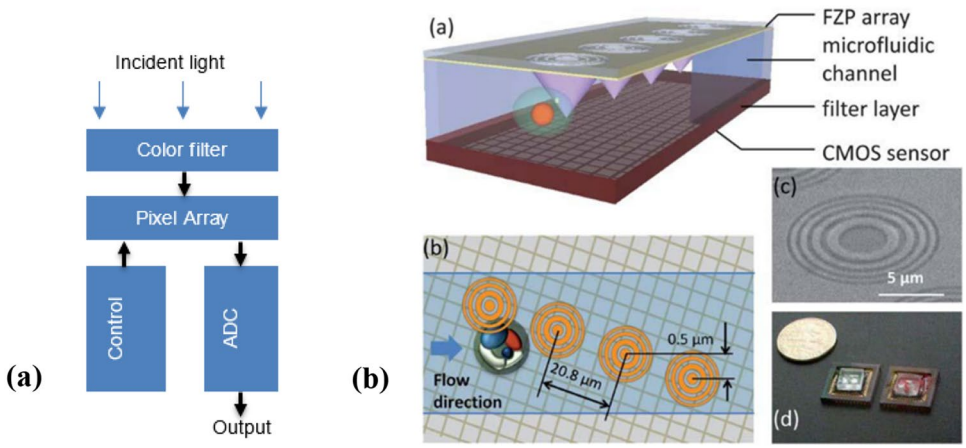

Fig. 8 **a** CMOS image sensors in-depth working principle. **b** (a) CMOS image sensor with thin layer filter coated on top, the microfluidic channel, and the Fresnel zone plate (FZP) array. (b) Top view schematic of the device with the FZP array configuration and its design parameters. (c) Scanning electron microscopy image of the fabricated Fresnel lens. (d) Images of the fabricated laboratory devices. Reproduced from (Pang et al. 2011), Copyright 2011, with permission from The Royal Society of Chemistry

Currently, the OLEDs are largely used in commercially available electronics (TVs, smartphones, etc.), being available in a large bandwidth emission spectrum. However, the OLEDs possess lower efficiencies (around 80 lm/W) than inorganic LEDs (higher than 200 lm/W) (Krujatz et al. 2016). For enhancing widespread OLED implementation, the PI-SCALE project (pi-scale.eu) aims to integrate existing European infrastructures into an "European flexible OLED pilot line", operating in an open access mode and serving customers with individual product designs, validation of upscaling concepts, and system-level flexible OLED integration. Comprehensive reviews of the latest achievements in OLEDs used for fluorescence sensing may be found in Williams et al. (2014), Jeong et al. (2015), Krujatz et al. (2016) and Yersin (2018). In Jansen-van Vuuren et al. (2016), recent achievements in the field of OPDs were described, while the last comprehensive review about the integration of fluorescence sensors using organic optoeletronics with microfluidics (see Fig. 9a) is presented by Lefèvre et al. (2015).

A fluorescence light detector combining both an organic electrochemical cell (OLEC) and an organic photodiode (OPD) within one microchip (see Fig. 9b, c) was introduced and tested by Shu et al. (2017). Moreover, linear polarizers were used as emission and excitation filters, enabling the possibility to detect fluorescent targets with emission and absorbing peaks very close to each other. The organic layers were manufactured using solution deposition processing, considerably decreasing the fabrications costs. The emission light peak of the OLEC was modified by choosing different light-emitting polymers, enabling multiplexing. The OLEC was used in pulsed mode to detect fluorescein amidite, reaching a 1 μM limit of detection. The brightness of the OLEC was up to 2800 cd/m^2 at a driving voltage of 50 V. The brightness was not altered up to 10,000 pulses for a 30 ms pulse width, resulting in an autonomy of 10 min. The proposed solution proved stability and high commercialization potential. Organic optoelectronics for building compact lab-on-a-chip applications was used by Jahns et al. (2017) who introduced two devices. For the first device, four 5 mm^2 OLEDs and four 5 mm^2 OPDs were manufactured separately on two 25 × 25 mm^2 glass substrates. A dichroic filter was used, to decrease the noise. The second device had a cylindrical form and used a reflection system, to facilitate the decrease of the noise and avoid additional filters.

A detailed description of the integration process of an organic optoelectronic system within a microfluidic platform has been presented in Poorahong et al. (2016). A system comprising a series of blue and green OLEDs, OPDs, and optical filters was designed, to develop a detection system for a PDMS multi-chambered structure with 9 μL detection volumes. The 480 nm and 515 nm OLEDs, OPD, and optical filters were manufactured individually and then integrated within the microfluidic structure. The spectral width of the OLEDs was around 87–90 nm. Their durability was tested by applying pulses of different voltages (12 V for a blue OLED and 18 V for a green OLED) and after some tens of pulses, the emission intensity stayed constant. The limited lifetime of the organic materials, especially when high voltages are implied, limits the long-term usability. An innovative OPD manufacturing solution, enabling a 14,000 h lifetime under continuous operation was presented by Kielar et al. (2016).

Thin film transistor array technology, inspired by the flat panel display and X-ray image industry, is a new approach used to enable low-cost multi-biomarker detection. Smith et al. (2014) introduced a miniaturized fluorescence-based

Table 5 Microfluidic systems using organic electronic based-designs towards-on-chip approaches for fluorescence detection

References	Achievements	Applications	LOD	Analyte	Further improvements [Author's suggestions]
Shu et al. (2017)	Microfluidic fluorescent sensing system, with a fully solution processed light source, and a fully solution processed photodetector The blue OLEC was first introduced and demonstrated as a low-cost excitation light source The emission light peak could be relatively easily modified by selecting different light emitting polymers Two orthogonally oriented linear polarizers were included onto the micro fluidic glass chip Demonstration of successful integration of solution processed organic light emitting diode and organic photon detector with a microfluidic fluorescent detection device	Low cost, portable and disposable fluorescence sensors with a high sensitivity	1 μM FAM in water (S/N > 1.1)	Fluorescein amidite (FAM)	–
Jahns et al. (2017)	Two organic lab-on-a-chip fluorescence detection designs and their fabrication methodologies described and demonstrated First system: OLED and OPD integrated on separate substrates Second system: OLED and OPD integrated into a cylindrical geometry on a single substrate. It avoided usage of filters, it was scalable and promising for miniaturized, multi-agent lab-on-a-chip systems		520 nM (first system)	Acid Yellow 73	For the second system, performing further analysis to determine the behavior of the signal and the limit of detection

Table 5 (continued)

References	Achievements	Applications	LOD	Analyte	Further improvements [Author's suggestions]
Poorahong et al. (2016)	Fabrication methodology of OLEDs and OPDs for fluorescence detection demonstrated, integrated with microfluidic chips fabricated using standard soft lithography techniques in PDMS	Water pollution detection	0.5 nM	Diuron	-
Kielar et al. (2016)	Demonstrate organic photodetectors as possessing a competitive level of stability for successful commercialization of this promising technology, approaching the performance of silicon-based photodiodes Three solution-processed layers and two low-temperature annealing steps used suring the fabrication, resulted in a dark current density as low as 0.31 nA cm^{-2}, a responsivity of 0.32 A W^{-1}, and a detectivity of 3.21×10^{13} Jones at − 2 V Photodiode with lifetime of over 14,000 h under continuous operation	Cost-effective fully-integrated excitation light source	–	–	–
Venkatraman and Steckl (2015)	Thin film phosphorescent green OLEDs fabricated on plastic substrates integrated on-chip OLEDs were fabricated by sequential deposition of organic thin films (100 nm) onto ITO-coated PET substrates	Low-cost, disposable lab-on-a-chip point-of-care (POC) diagnosis system	3 nM (S/N = 3)	Quantum dot	–

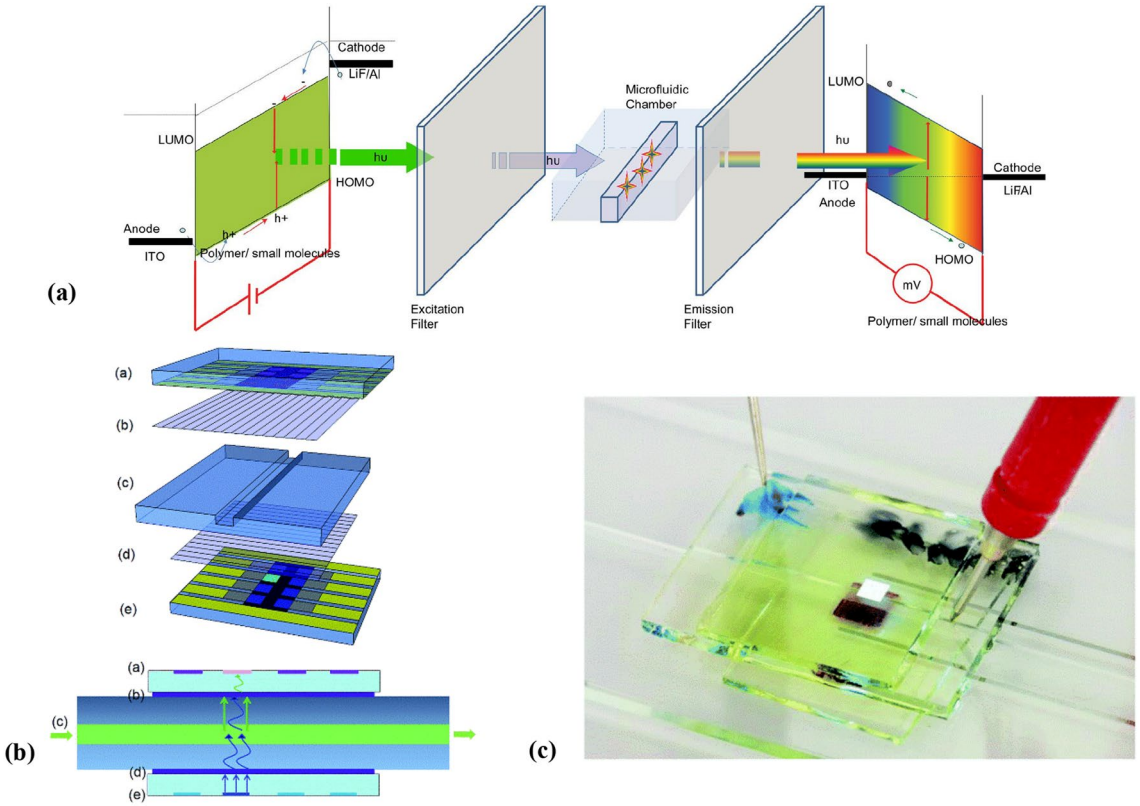

Fig. 9 **a** Generic illustration of the fluorescence optofluidic detection based on organic electronics. **b** Schematic representation of OLEC excitation and OPD detection system. (a) OPD. (b) Linear polarizer filter. (c) Glass microfluidic chip. (d) Blue OLEC. (e) fully-processed blue OLEC. **c** Fabricated optofluidic system. (a) Reproduced from (Lefèvre et al. 2015), Copyright 2015, with permission from Elsevier. (b) and (c) Reproduced from (Shu et al. 2017), Copyright 2017, with permission from The Royal Society of Chemistry

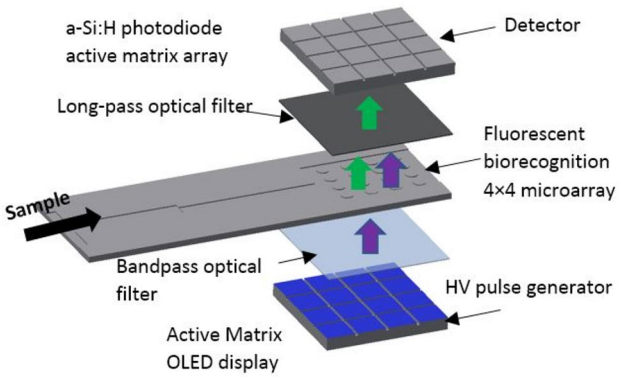

Fig. 10 Lab-on-a-chip sensing architecture based on OLED display and photodiode active matrix technology for point-of-use diagnosis of multiple diseases (Smith et al. 2014)

lab-on-a-chip sensing architecture (see Fig. 10) based on an OLED display and photodiode active matrix technology for point-of-use diagnosis of multiple diseases or pathogen markers in a cost-efficient disposable configuration. A straightforward concept, enabling a new approach using matrix active OLED and photodiode array technology for the multi-target analysis was implemented and tested. The 8×8 biorecognition array of 64 pixels based on this technology had an area lower than 2×2 mm^2 and was able to work with a 100 µL volume of fluid. The array-based OLED was formed from multiple light-emitting elements (pixels) which were individually activated, to emit light at specific wavelengths and to enable multiple target detection. The same group proposed in Katchman et al. (2016) a high-density fluorescence, programmable, multiplexed recognition compact miniaturized device for point-of-care molecular diagnostics. The OLED technology was combined with protein microarray technology and 10 pg/mL limit of detection was achieved for human IgG.

4 From current challenges to a possibly ideal concept: discussion

It has been suggested that one of the reasons for which micro total analysis systems failed yet to cross the border from research to commercial application is the lack of a

well-established design methodology (Volpatti and Yetisen 2014). Therefore, microfluidic devices still deploy complicated and sophisticated optical equipment to enhance fluorescence detection (Matteucci et al. 2015). This has partly been due to the reliability of detection still being too inadequate for meaningful results to be interpreted. Successful translation of micro-total-analysis systems from the laboratory to the market rely on the ability to integrate the detection components on-chip (Watts et al. 2012; Mohammed et al. 2015). The efficiency of the microfluidic processes taking place within the microchannels is often strictly related to the precise control of specific parameters, such as hydraulic diameter, and the memory effects (molecule adsorption within the walls structure affects the sensitivity and reliability of the sensor). Thus, working with fluids at microscale for sensing applications involves complexity. By consequence, there are still many issues which have to be solved regarding the repeatability, the portability, the ease of use and the sensitivity, the fabrication time, and the cost, before making these systems more advantageous than the classical world spread analysis systems (Wolfbeis 2013; Babikian et al. 2017). Currently, it can be emphasized that the optical and fluidic circuits were successfully miniaturized, while the entire system miniaturization is still challenging, more attention having to be focused on the system integration.

Some general parameters can be used for the quantification of the performances of a fluorescence-based sensor: fabrication cost, sensitivity, repeatability, multiplexing, auto-calibration, selectivity, response time, long-term stability, and autonomy. Among all the presented prototypes, some perform in one or several of these above-mentioned criteria, but none in all. While off-chip approaches achieved a high degree of maturity, very low prices and good performance, a multitude of methods are still tested for strategies towards on-chip integration. The microstructured optical fibers involving hollow core Bragg fibers refreshed the way optical fibers are implemented within fluorescence detection systems, proposing a design strategy integrating into one fiber the interrogation area, denoted the collector, the delivery channel, and the filter. The microfluidics-PCB concept managed to integrate microfluidics with optics and electronics in a monolithic manner, opening a promising development path. The printed circuit boards were used for both support of electronic components and microfluidic parts. Broad implementation of CMOS sensors, coupled with signal processing algorithms to filtrate and improve the sensitivity, could be observed in the recent literature. The CMOS technology coupled with contact sensing and time-correlated photon counting (TCSPC) emerged as a sound technology. It avoids usage of filtration and focusing optics. Nano-plasmonics coupled with CMOS technology managed to create enhanced fluorescence quantification on platforms with multiplexing capabilities. Organic electronics possess a huge potential, which is not fully exploited, both light emitting sources and photon detectors being already largely developed and commercially available. It offers unique advantages for fluorescence detection, such as flexibility of the emitting and detection layers, providing the possibility to develop flexible sensors. The tuning of different layers allows readout of a multitude of different wavelengths, enabling multiplex detection. Compared with LEDs, organic light-emitting diodes still possess lower efficiency, but recent achievements promise to improve this aspect (Krujatz et al. 2016).

It is obvious that further miniaturization strategies should focus on simplification of the traditional detection approach by identifying micro-fabrication and design architectures to replace/simplify the implementation of the intermediate light manipulation steps. A possible solution addressing this topic is the implementation of an advanced pattern recognition algorithm and/or selecting a more advanced photon detector, as some authors are suggesting (Babikian et al. 2017; Shin et al. 2017). Further development of fluorescence optical sensors should envisage strategies involving all the elements as they are illustrated in Fig. 11. This is mandatory

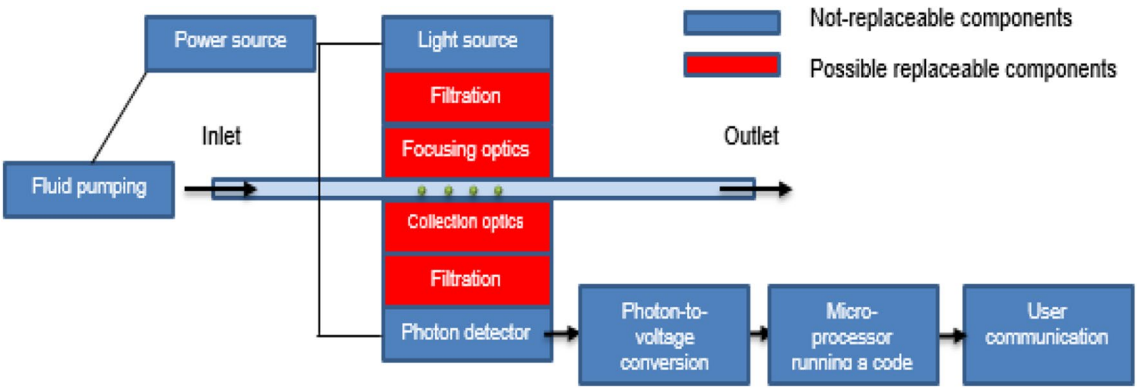

Fig. 11 Fluorescence sensing: general integration scheme

for solving the chip-in-the-lab dilemma that refers to the lack of portability, operation simplicity, and reliability outside of the laboratory of the majority of the miniaturized analytical systems.

Once the miniaturization dream of chemical and biological sensing would be achieved, the following step is easy to be anticipated. Large sensing networks coupled with AI and IoT would allow rapid and in-time measurement of the presence of specific indicators identified in small amounts of body fluids, better monitoring pollution, and many other applications.

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Availability of data and material (data transparency) All data generated or analysed during this study are included in this published article.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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