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Review Article

Microfluidic devices for photo-and spectroelectrochemical applications

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Abstract

The review presents recent developments in electrochemical devices for photo- and spectroelectrochemical investigations, with the emphasis on miniaturization (i.e., nanointerdigitated complementary metal-oxide-semiconductor devices, micro- and nano-porous silicon membranes or micro-optoelectromechanical systems), silica glass/microreactors (i.e., plasmonic, Raman spectroscopy or optical microcavities) or polymer-based devices (i.e., 3D-printed, laser-engraved channels). Furthermore, we have evaluated *inter alia* the efficiency of various fabrication approaches for bioelectrochemical systems, biocatalysis, photochemical synthesis, or single nanoparticle spectroelectrochemistry. We envisioned the miniaturization of applied techniques such as cathodoluminescence, surface plasmon resonance, surface-enhanced Raman spectroscopy, voltametric and amperometric methods in the spectroelectrochemical microdevices. The research challenges and development perspectives of microfluidic, and spectroelectrochemical devices were also elaborated on.

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Photoelectrochemistry, Spectroelectrochemistry, Microfluidics, Silicon technology, Lab-on-chip.

Introduction: why combine microfluidics with electrochemistry?

Nowadays, miniaturized analytical devices, which provide features such as simplicity, automation, portability, cost effectiveness, and ease of operation, are developed and employed for various applications. Microfluidic devices have been attracting interest in numerous applications as offer rapid manipulation of solutions, minimum consumption of reagents, low cost, ease of mechanization, and the ability to perform a wide range of chemical and biological reactions with a small and portable form factor [1–3]. Compared to standard fluidic systems, microfluidics (defined by a channel size of less than 1 mm) operate in the laminar regime due to their small channel dimensions. The higher surface-to-volume ratio in microfluidics facilitates rapid heat transfer between the device and the liquid, ensuring homogenous temperature across the stream. Electrochemical detection methods benefit from the characteristics of microfluidic systems, since the electrode surface is in contact with a larger fraction of the sample. Further, electrochemical parameters, such as applied potential and current response, can be easily adjusted to improve selectivity in synthesis applications. Microfluidic flow cells have therefore also been employed as a production method in the industrial field for large-scale electrosynthesis. The integration of flow chemistry in electrosynthesis improves many of the issues with typical electrochemical cells. The use of disposal of hazardous, toxic oxidising and reducing agents can be drastically reduced, thereby making processes milder, safer, and more cost-effective [4].

Metal and carbon microelectrodes are the dominant electrodes in microsystems. Among metal electrodes, the leading materials are those that combine high conductivity and chemical stability, such as gold and platinum. Carbon pastes and noble metals facilitate mass production as they can be deposited directly on the substrate, although their high price must be considered. In addition, metal electrodes often show a narrow working potential window in aqueous electrolytes. Also, their relatively high background currents and tendency towards fouling significantly limit their use in some applications. Different carbon allotropes, such as graphene, carbon nanotubes, carbon fibre, graphite, and diamond can be used as electrodes in microfluidic systems. Furthermore, pyrolyzed photoresist film (PPF) carbon, screen-printed carbon, carbon paste, and carbon ink can also be found in microfluidic systems [5]. Another crucial component for microfluidic EC devices is the substrate, where electrodes with multiple microchannels or microchambers are integrated. The substrate should be inexpensive, non-conductive, resistant to the operating conditions, and compatible with the electrode materials employed. Transparency is crucial for optical techniques. The most frequently used substrates are therefore glass and polymeric materials (e.g., polydimethylsiloxane − PDMS, polymethyl methacrylate − PMMA, cyclic olefin copolymer − COC). Another increasingly popular substrate material is paper. Microfluidic paper-based analytical devices (μPADs) have proved themselves especially for pregnancy and SARS-CoV-2 antigen detection [6,7]. The use of paper is especially attractive due to its low cost, flexibility, availability, and biodegradability. An extremely cost effective solution is to generate a graphite electrode on a paper substrate with a pencil [8].

Electrochemical detection techniques are well suited for miniaturized systems due to their compatibility with microfabrication technologies, rapid analyses, cost effectiveness, and simplicity [9]. Therefore, voltammetric, amperometric, impedimetric, and potentiometric electrochemical techniques are widely used as detection techniques under flow-through conditions. However, electrochemical methods may not be sufficient to determine the exact reaction products and by-products. Thus, combined techniques, such as spectro- and photoelectrochemistry, which merge electrochemistry and optical methods, have attracted great research attention due to the possibility of more precise qualitative and quantitative analysis of the processes taking place at the electrode/electrolyte interface. Here, spectroelectrochemistry refers to systems where light is used to investigate electrochemical reactions, whereas photoelectrochemistry describes systems where light is used to affect the electrochemistry.

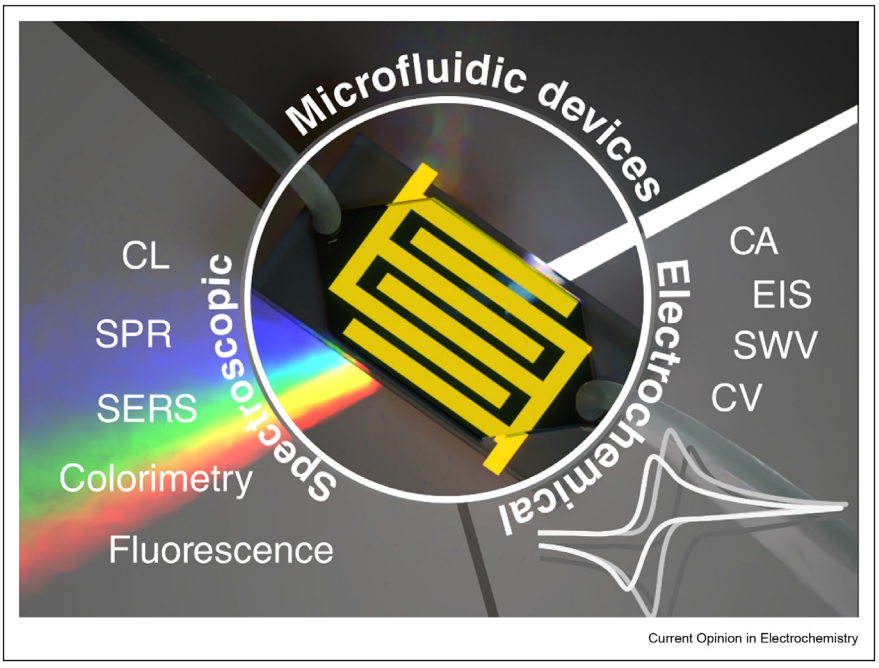
Here, we present an overview of general concepts of flow chemistry coupled with photo- and spectroelectrochemical techniques. The review begins with a discussion of design and fabrication of microfluidics that can be implemented with electrochemical electrodes. Next, we report how photoelectrochemistry is used for investigations on such devices. Finally, the review shows the recent designs before disclosing the discussion of example applications of the microfluidic devices in the photo- and spectroelectrochemical fields (see overview in Figure 1).

Design and fabrication of microfluidics integrated with electrochemical electrodes

The choice of design and fabrication method for microfluidics with integrated electrodes, is strongly dependent on the application, user settings, constraints from materials and type of samples (wetting properties and viscosity), with designs often not directly transferable between applications [10,11] (see Figure 2**ab**). Commonly, a straightforward single channel design, aiming at accurate flow control, is used. Multiplexing, in the design of both electrodes and fluidic channels, leads to higher throughput and testing capability [10]. Microfluidic sample pretreatment (e.g., by filtration or mixing, dilution, and enrichment) minimizes interference during analysis. Integrated, electrochemically (EC) inactive electrodes have been extensively used in various microfluidic applications requiring homogeneous electric field—electro-driven separation, electroosmotic flow, electrical actuation, dielectrophoresis and electrowetting with some integration approaches also relevant for the EC active electrodes. In EC devices, electrodes with higher surface area, leading to the increased contact with sample per square centimeter of geometric surface area, are of advantage. This section discusses selected publications reporting microfluidic design, fabrication of electrodes, and approaches for integration with microfluidics relevant for the development of EC devices. Other recent reviews provide insights into the design [12] and fabrication [13−17].

In the choice of technology, rapid prototyping of microfluidics can be achieved by using consumer-grade off-the-shelf tools and materials [18], and by using relatively simple techniques, such as xerography, micromilling, 3D-manufacturing, screen printing, and thermal lamination process. Due to lower costs and short turnaround time in prototyping, cleanroom-free fabrication methods are often used, with PDMS moulding dominating. Efforts have been made to develop flexible electrodes, pumpless liquid delivery and mixing [19], spectro-electrochemical cells [20], controlled sample manipulation [21], mitigation of bubble formation [22], and improvement in the reliability of bonding over electrodes [23]. Also, an organ-on-a-chip system with EC analysis, venting, and sequential reagents delivery capabilities was fabricated in PDMS [24] (see Figures 2**d**−2**f**). Electrodes were integrated with droplet

Figure 1



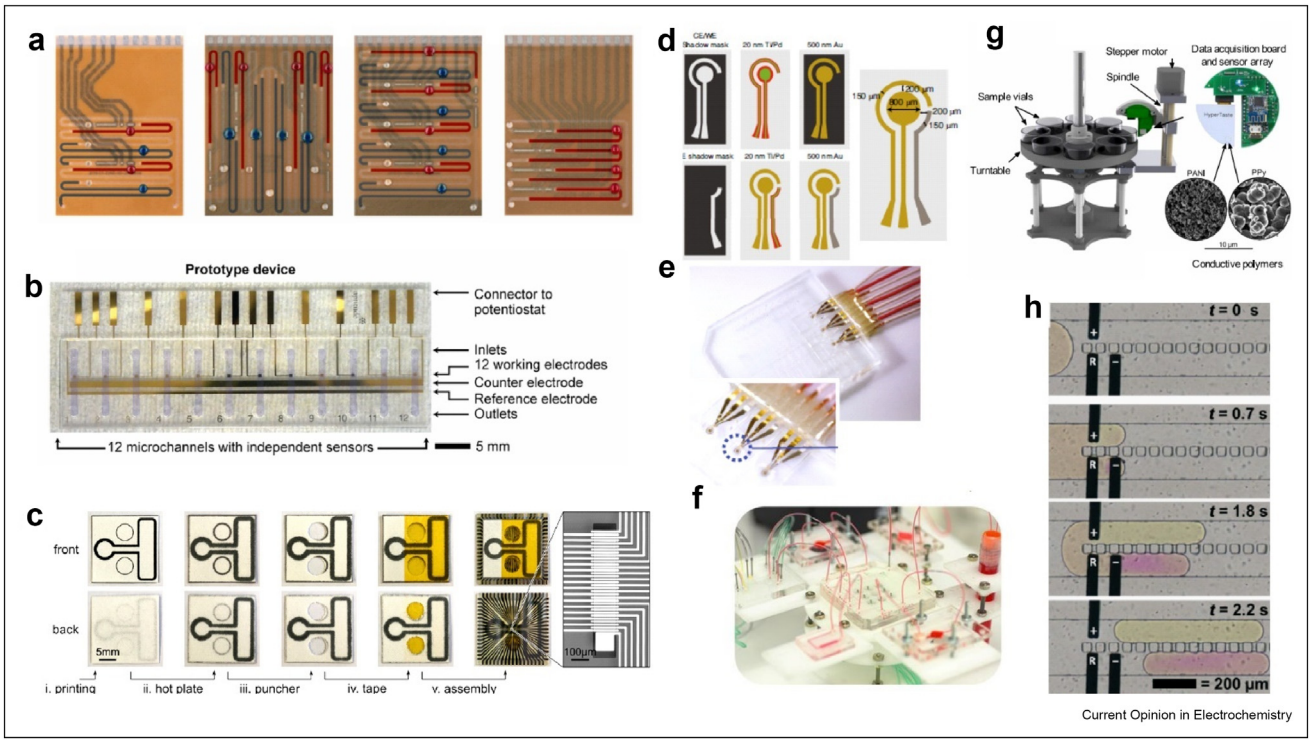
Overview of techniques applied in microfluidic devices for photo- and spectroelectrochemical studies (Attn.: CL – Cathodoluminescence, SPR – Surface Plasmon Resonance, SERS – Surface Enhanced Raman Spectroscopy, CA - Chronoamperometry, EIS – Electrochemical Impedance Spectroscopy, SWV – Square-Wave Voltammetry, and CV – Cyclic Voltammetry).

generating structures in PDMS for EC analysis of droplet content [25] and temporal pH regulation (Figure 2**h**) [26]. In pumpless microfluidic devices, such as wearables, the water contact angle of the channel plays a crucial role in capillary-driven fluid transport; for this reason, lowering the contact angle can be temporarily achieved by a simple O_2-plasma treatment, or permanently, by silanization [27].

Polymer rapid prototyping technologies are frequently applied for the fabrication of fluidic cartridges, mechanical and assembly parts for EC electrodes with a flexible gasket for liquid-tight operation [28]. These technologies typically cover dimensions ranging from hundreds of micrometers to centimeters, sufficient for many integrated electrodes' applications with pumpless liquid transport and limited multiplexing. Foils of functional electrode materials and adhesives were cut for layer-by-layer assembly using a knife plotter [29]. A larger scale, automated setups, i.e. for the exposure of arrays of EC sensors [30] (see Figure 2**e**) and flow-through EC cells for synthesis with exchangeable electrodes [31] are the examples of system level integration. Paper is a common material for EC-integrated microfluidics. To overcome limitations in EC electrode sensing performance arising from Ag nanoparticle (AgNP) agglomeration, a paper microfluidic device with a wax-patterned microchannel with a microelectrode array, capable of resolving individual AgNP was developed [6] (see Figure 2**c**).

Microelectromechanical systems (MEMS) technology offers control over the dimensions in the range from tens of nanometers to micrometers, reproducibility, and mass production. An overview of relevant fabrication steps in Si/glass can be found elsewhere [32]. Microfluidic features as small as 50 nm (by nanoimprint lithography (NIL) and electron-beam lithography (EBL)) and 2 μm (by UV lithography), through holes for sample delivery, and functional integrated materials for sensing and actuation (electrical isolation films, thin metal films, piezoelectric films, etc.) are feasible. Wafer-level fabrication of 2- and 3- wafer stacks [33], electrically actuated valves with the capillary flow, and self-venting microstructures for programmable, bubble-free liquid operations on-a-chip were demonstrated [34]. Another example, based on dry film resist technology on polyimide, shows multiplexed microfluidic EC biosensing platform for amplification-free, parallel detection of miRNAs using thin film Pt and Ag/AgCl electrodes (Figure 2**a**) [10]. MEMS-based EC microfluidics also faces some challenges, i.e., restrictions on materials in CMOS compatible labs and incompatibility between the desired EC electrode material and available fabrication technologies (e.g. due to processing temperatures during steps such as bonding or passivation of

Figure 2



(a) CRISPR-multiplexed sensor designs with electrochemical cells for detection (Reproduced with permission from Bruch et al. [10], Copyright 2021, Elsevier.); **(b)** Prototype of an electrochemical microfluidic device for vaccine quantitation with 12 microchannels, each having an independent gold working electrode (Reproduced with permission from Chozinski et al.[11], Copyright 2021, American Chemical Society); **(c)** Fabrication steps of an electrochemical μPAD sensor: hydrophobic barriers and alignment markers (i-ii), the alignment and attachment between the chip and the paper (iii-iv) (Reproduced with permission from Weiß et al. [6], Copyright 2021, American Chemical Society); **(d)** Diagram of the two-stage fabrication steps of the microelectrode with the use of two shadow masks (CE/WE and RE). A 20 nm layer of Ti is deposited, followed by Pd. For the CE/WE mask, a 500 nm layer of Au is deposited, and a 500 nm Ag for the RE mask (Reproduced with permission from Aleman et al. [24], Copyright 2021, Springer); **(e)** EC biosensor cell comprising Au WE, Au CE, and Ag RE for antibody-based and aptamer-based biosensing and monitoring of organ-on-a-chip devices (Reproduced with permission from Aleman et al. [24], Copyright 2021, Springer); **(f)** A multisensor-integrated multi-organ-on-chips platform. The red color shows medium circulation, and the green color indicates the valve connections. **(g)** Custom-built for automated measurement of liquids with data acquisition board for readout from the polymeric sensor array (example of morphologies characterized by SEM are shown) with 16 electrodes on a double-sided PCB. (Reproduced with permission from Gabrieli et al.[30], Copyright 2021, American Chemical Society); **(h)** Electrochemical pH regulation achieved in microdroplets in a microfluidic device: series of micrographs showing splitting of an aqueous microdroplet (top images). The microelectrodes consisted of a Ti (10 nm) layer, a Pt layer (100 nm) and an Ag layer (300 nm). (Reproduced with permission from Srikanth et al. [25], Copyright 2022, Royal Chemical Society).

electrodes). Fabrication permitting post-processing e.g. by drop casting or (chemical or physical) surface modification in a flow mode to complete the EC cell with additional functional materials is often required. This allows to achieve higher selectivity (specificity) or regeneration of electrodes. Reversible bonding techniques for access to electrodes may therefore be used. Recently, alternative room temperature bonding methods, which can also be applied to EC devices, have been demonstrated [35]. For size critical applications, the total footprint including contact pads can be an issue. This can be overcome by allocating electrodes and contact pads on both sides of the substrate and connect them by vias, and by 3D integration of multiple substrates. Antifouling coatings (for life-sciences and medical applications) and coatings modifying wettability of microfluidic channels often challenge the optimal performance requiring additional development [36]. Over time, electrodes may also deteriorate leading to changes in material and EC active area. Microfluidic designs and materials compatible with electrode cleaning methods, either chemical or EC, are of high importance. Integration with microfluidics allows to automate cleaning steps with solvents (e.g., to remove deposits) in between the measurements, thus prolonging the lifetime of electrodes.

Microfluidic devices in spectroelectrochemical applications

The high surface-to-volume ratio of microfluidic systems together with the short optical path that limits attenuation of incoming light makes them ideal for

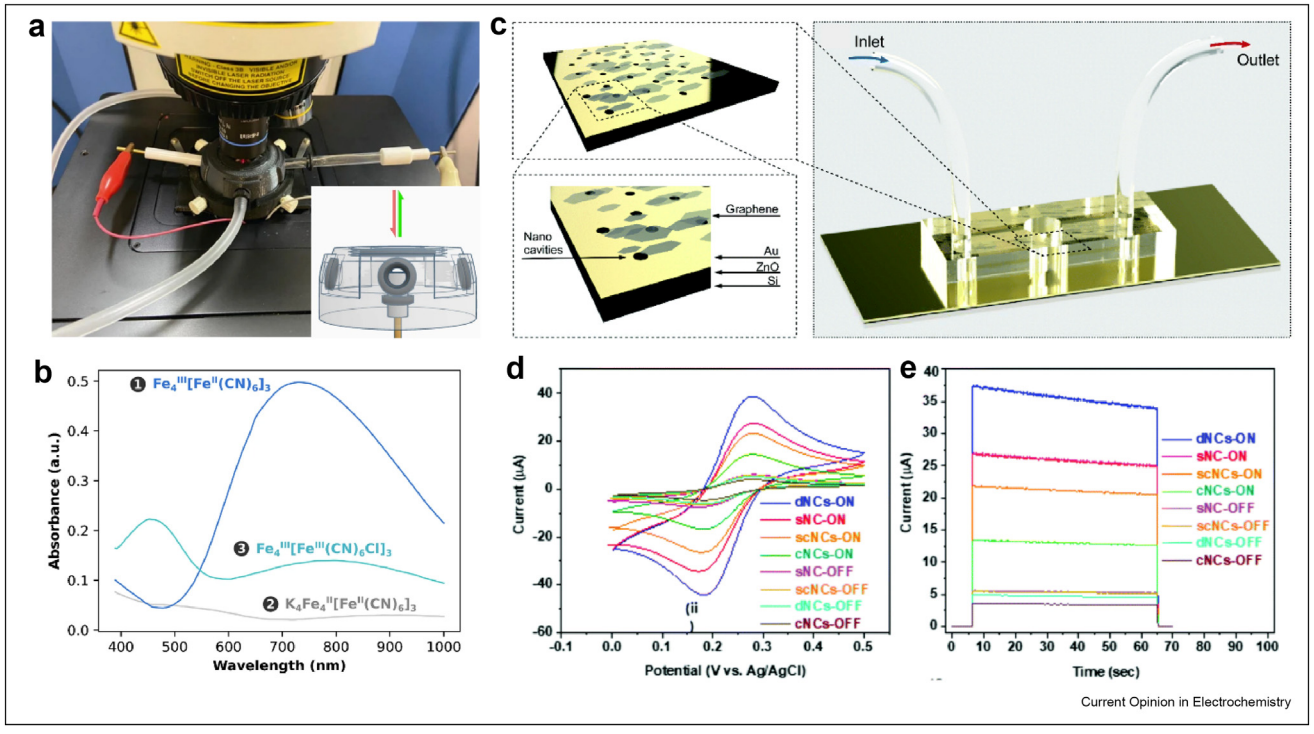
heterogeneous photochemical processes and has been exploited for a long time. The photoelectrochemical applications also require the efficient transfer of electrons between the reactants and the electrode surface. With standard microband electrodes, a large proportion of the reactant can pass over the electrodes without interacting with them [37]. This limitation can be overcome by the development of 3D structured or flow-through electrodes with paper- or carbon-cloth-based electrodes and microflow systems. Guima et al. reveal a low-cost 3D-printed microflow cell for water treatment and energy harvesting [38]. In a paper on photoelectrochemical CO_2 conversion, Kalamaras et al. show the improvements that can be reached with microflow systems over batch reactors [39]. The state of photocatalytic fuel cells was recently reviewed by Queiroz et al. [40].

In photoelectrochemical (PEC) analysis the microfluidic system is often used as a convenient delivery system of small volumes of the analyte, rather than used for enhancing the efficiency as in energy applications [41]. Cheng et al. [42] developed a PEC sensor for a specific antigen. In this and other similar cases [43], ascorbic acid is used as a hole scavenger that is oxidized at the photoelectrode to create a photocurrent when illuminated. The sensing is based on a sandwich-type structure where the target antigen binds to the photoanode and a secondary antibody marker to the bonded antigen. This secondary marker quenches the photocurrent if the target is available. The reaction takes place in a small reaction chamber instead of in the microchannel itself. This is also common among many of the available sensors [43–46]. In the latter two cases [45,46], Feng et al. use a photocathode instead of an anode to detect H_2O_2, the production of which is enhanced in the presence of the analyte, a model biomolecule attached to a nanoparticle. They explain that there is less interference at a cathode rather than an anode.

Light stimuli and readout could be utilized in microfluidic devices inducing specific spectroelectrochemical interactions. The most of studies are devoted to UV–Visible Spectroscopy, Fourier Transformed Infrared (FTIR) Spectroscopy, or Raman Spectroscopy allowing for a quantitative or qualitative investigation of electrode/electrolyte interfaces and as well as information on the species in the electrolyte.

An alternative way of coupling light into microchannels is by embedding an optical fiber with a manipulated cladding to let the light interact with the liquid in the channel, a technique pioneered by the Śmietana group. The dual-domain (optical and EC) label-free sensing

Figure 3



(a) Spectroelectrochemical cell for *in situ* Raman microspectroscopy installed in a Horiba LabRAM, **(b)** V-VIS reflection-absorption spectra (Reproduced with permission from da Silva Junior et al. [50], Copyright 2021, Springer-Verlag); **(c)** Schematic of the nanostructured microfluidic device for PEC detection of H_2O_2, **(d)** current responses CV and **(e)** chronoamperometry for both under dark and visible light illumination conditions at self-organized gold nanocavities, enhanced with graphene nanosheets (Reproduced with permission from Del R. Mata et al. [51], Copyright 2021, Royal Chemical Society).

Table 1

Electrochemical, photo- and spectroelectrochemical device designs using a microfluidic approach.

Sensing electrode	Working principle	Fabrication	Performance	Reference
Biotin-functionalized ITO-coated optical fibers	Transmission + CV	RF magnetron sputtering	Avidin detection LOD = 0.1 μg/mL Range = 0.1–100 μg/mL	[47]
Optical fiber microcavities	Transmission + CA	Micromachining + chemical etching + 3D-printing + laser engraving + sputtering	–	[48]
Filter paper-based PAD	Colorimetric (high concentrations) + DPV	Screen printing + laser engraving	Thiocyanate detection LOD (EC) 0.006 mmol L–1. Range = 0.025–100 mmol L–1	[56]
Carbon-ink	CA	Xerography + lamination	–	[18]
Au	PCR + SWV	Soft lithography + photolithography + e-beam	E. coli LOD = 10^2 CFU/mL Range = 10^2–10^6 CFU/mL	[19]
Enzyme-based lactate sensors + ion-selective sensors – functionalized carbon ink	CA	Xerography + screen printing	Lactate LOD = 0.2 mM Range = 1–25 m M Na = 0.02–200 mM K = 0.01–100 mM	[27]
Laser-induced flexible graphene (LIFG)	LIFG bioelectrode	Laser-induced carbonization + screen printing	Power density of 13 μW/cm^2 (52 μA/cm^2)	[23]
Conductive carbon ink	CV	Direct laser writing + maskless lithography + ink jet printing	Ascorbic acid–	[25]
Carbon black/polycaprolactone	SWV	Screen printing	Tryptamine Range = 10–75 μmol L^{-1} LOD =3.2 μmol L^{-1}	[41]
poly (dimethyl diadly ammonium chloride-functionalized) MWCNTs + CdS QDs	PC	Screen printing	Glucose Range 0.05–1000 μM LOD = 15.99 nM	[57]

*CV: Cyclic Voltammetry; CA: Chronoamperometry; DPV: Differential Pulse Voltammetry: SWV: Square-wave Voltammetry, PC: Photocurrent.

experiment was reported on the ITO-coated optical fiber probe revealing interactions using a lossy-mode resonance (LMR) along with cyclic voltammetry [47,48]. The electrochemical properties of the ITO film allowed for the application of the sensor as a working electrode in an EC domain simultaneously controlled by optical resonance spectra readout. The approach allowed for a biotin/avidin incubation procedure monitoring. It was manifested that an increase in avidin concentration induces a decrease in redox couple oxidation current and an increase in LMR resonance shift. Both optical and EC readouts go along with the protein binding procedure. Extensive data has been attained relating to exclusively EC studies.

Raman spectroelectrochemistry has been recently expanded to an advanced classification tool delivering knowledge on the electrode / electrolyte boundary along with regulated adsorption of targeted analytes and improved reproducibility. Miniaturized microfluidic devices enable the fabrication of portable and integrated spectroelectrochemical systems (EC and Raman) outperforming the current EC or surface-enhanced Raman spectroscopy instruments supplying cross-check validation [32]. Huang et al. [49] reported an integrated EC-SERS microfluidic device combining a three-electrode printed circuit board for the determination of uric acid. The devices were fabricated utilizing magnetron sputtering of gold nanospheres at the nanocone array hot embossed with a microfluidic channel. This approach enabled an enhancement factor of up to 8.5×10^6 of uric acid detection revealing a linear relationship. 3D additive manufacturing technology allows to design of dedicated integrating parts for electrochemical and spectroscopic methods (see Figure 3**ab**) [50]. PET or ABS-based printouts reveal high chemical and impact resistance along with the durability of rapid prototypes or Raman or UV—Vis supplied electrochemistry.

A photoresist, nanostructured microfluidic device was applied by del Real Mata et al. [51] for amperometric detection of H_2O_2 released from human cells under simulated visible light illumination in PDMS channel (see Figure 3**cd**). They utilized self-organized gold nanocavities improved with graphene sheets revealing an excellent LOD of 1 pM (see Figure 3**e**). The synergistic effect of a carbon-based microelectromechanical array of interdigitated electrodes (down to 20 μm of spacing) and photopatterned SU-8 photoresist channel was also applied for resistive sensing applications (avg. resistivity of 1.412 ± 0.011 mΩ cm) [52]. Recently, it was manifested that microcavities in optical fibers could serve as highly functional spectroelectrochemical microanalytical devices [53]. The microchannel forms Mach-Zehnder Interferometer in a single-mode optical fiber supported by a microfluidic system. The working ITO electrodes tailored the electrochemical performance monitored simultaneously by optical readout revealing a comprehensive approach for extremely sensitive opto-electroanalysis. Sobaszek et al. [54] applied the Mach-Zehnder interferometer methodology for spectroelectrochemical investigations of *in-situ* monitoring of electropolymerization at the transparent boron-doped diamond electrode. The measurement of optical phase change allowed for precise estimation of refractive index of the deposited polymeric layer using an optical setup with dedicated EC cells. The cells could work in flow mode allowing for monitoring of surface functionalization required for biosensors and energy harvesting devices.

Electrochemical cells were designed to conduct parallel optical and amperometric measurements in a droplet traveling in PDMS- glass systems [55]. The glass slide was bonded with PDMS utilizing plasma treatment. The device enables reliable investigations of droplet velocity, size, and composition estimated from the chronoamperometric curve and numerical simulations. Pungjunun et al. [56] utilized laser engraving to fabricate microcapillary pump paper-based for the analysis of saliva. The sensing device relies on the dual sensing mode: colorimetric and electrochemical approach. It was used for rapid detection of SCN manifesting rapid visible color and high oxidation current resulting in low LOD of 6 μmol L^{-1} with a RSD of less than 5%. The recent developments in the microfluidic devices for electrochemical, photo- and spectroelectrochemistry were listed and compared in Table 1.

Concluding remarks and future trends

Summarizing, this review provides the recent progress and state-of-art achievements focused on the application of various designs of electrochemical microfluidic systems. In general, the limit of detection could be boosted by raising the flow rate of the analyte in sensing device channels. Recently, shaping channel geometry or multiplying them provide unique electrochemical responses and improved electrode performance. Silicon and glass showed significant application in the initial stages of microfluidic systems, and recently polymeric and paper-based devices have become increasingly popular particularly due to their disposable and low-cost nature. Electrochemistry presents a capable option to cross the boundaries of biosensors toward a rapid detection of ultra-low concentration species or investigations of single—molecule processes in fuel, and electrolysis cells. Whereas multiplex detection is becoming a major analytical sensing and monitoring approach in studies of living cells, tissues, or pathogens. The integration of functional materials in microfluidic devices allows for achieving miniature actuators withdrawing the need for external components. The most important scientific and technical challenges of electrochemical microfluidic devices include chemical and

physiological variation in the properties of real analytes (i.e. wastewater or biofluids) and discrepancies in terms of transposable elements.

Miniaturization of electrodes, integration with microfluidics and upscaling for high-throughput analyses continue to be important trends. Miniaturized electrodes (tens of micrometers and less), enabled by advances in technologies, are sought in electroanalytical and energy conversion application. They put higher demands on measurement techniques and instrumentation for noise cancellation. Besides the majority of electroanalytical applications, the electrochemical energy conversion studies utilize also microfluidic approaches to raise the efficiency and rate of energy conversion thanks to the enhanced mass transport, flexible cell design, and ability to eliminate high-cost ion-exchange membranes. Overall, microfluidic spectroelectrochemical designs are complex systems that require time-consuming optimization procedures to guarantee their accuracy and reproducibility.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this article.

Data availability

No data was used for the research described in the article.

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** of outstanding interest

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