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Perspective

Paper as a Sustainable Material for Smart Electrochemical (Bio)sensors with Unprecedented Features: A Perspective

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ABSTRACT: This perspective has the overriding goal of reporting the tipping points in the roadmap of electrochemical paper-based analytical devices by harnessing the multiple paper characteristics such as cost-effectiveness, widespread accessibility, mechanical strength, porosity, and capability to be easily cut, folded, modified, and assembled. The use of paper in electrochemical devices not only provides additional features to the electrochemical devices such as the environmentally friendless, ease multiplexed analysis, and three tridimensional structures by folding and unfolding operations but has broken down barriers for delivering measurement without (i) addition of reagents, (ii) sample treatment for liquid, aerosol, and solid samples, and (iii) any additional pump for microfluidics. I lay out the advantages of using paper for the design of multifarious electrochemical devices, underlying the next steps in the paper-based electrochemical device roadmap.

■ INTRODUCTION

The history of paper-based devices started with litmus paper, a paper strip loaded with chemicals and used to visualize the different pH values easily and quickly. The easiness of use, the cost-effectiveness, and the rapidity of analyses have fostered its use until nowadays in different fields,[1] such as the pH analyses using litmus paper as a quantitative indicator of reaction already reported by Walpole in 1913.[2] Following the vision of Escarpa,[3] which highlighted how the use of nanomaterials in electrochemical (bio)sensors has moved the electroanalysis in a true Renaissance period, the introduction of paper-based microfluidics by the Whitesides research group in 2007[4] paved the way for a true Renaissance period in paper-based devices, giving the start to the microfluidic paper-based analytical devices (μPAD) and creating an avalanche in this field.[5]

What are the reasons for this growing trend? In my opinion, this behavior is ascribed to the capabilities of this type of device in supplying answers to the following three requirements.

1. Main view/requirement: The Sustainable Development set by UN Agenda 2030 and focused on 17 Sustainable Development Goals[6] has had an impact not only in the environmental, economic, and social sectors but also in the scientific field. In analytical chemistry, the sustainability vision has already started from the 12 Principles of Green Chemistry established by Anastas and Warner in 1998,[7] in which they set the rules for partaking in a green route. In detail, the 11th Principle reports the need to develop analytical methodologies based on real-time analysis for pollution prevention. The improvement of the sustainability approach in analytical chemistry was then further enlarged, setting the 12 Principles of Green Analytical Chemistry[8] followed by the further rationalization of the concept in White Analytical Chemistry,[9] which is an extension and complement to Green Analytical Chemistry, encompassing the ecological, analytical, and practical aspects of the analytical methodologies. In this vein, answering to the sustainability vision and considering the White Analytical Chemistry aspects, analytical chemistry has to (i) reduce chemicals, (ii) develop analytical tools for on-site analyses, (iii) reduce the energy for the measurement, and (iv) use ecodesigned materials.

2. Main view/requirement: The COVID-19 pandemic has demonstrated the utility of rapid diagnostic devices because these analytical tools furnish qualitative information about the presence of infection quickly by not specialized personnel and using cost-effective setups.[10] Considering the feedback of this event from the diagnostic point of view, the device needs to be (i) robust, (ii) easy to use, and (iii) accurate, maintaining all

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reagents inside the device without any liquid waste to manage.

3. Main view/requirement: The World Health Organization (WHO) introduced in 2003 the ASSURED criteria to delineate the characteristics needed for effective point-of-care diagnostic devices, which are analytical devices to furnish diagnostic results close to the patient. ASSURED means Affordable, Sensitive, Specific, User-friendly, Rapid/Robust, Equipment-free, and Deliverable to those who need it. Recently, ASSURED criteria have been updated to RE-ASSURED ones, where real-time connectivity for digital healthcare and ease of specimen collection have been added to answer the current requirements of digital healthcare and at-home analyses.[11]

Paper-based devices face these three main points because their features answer the sustainability requirements and the RE-ASSURED criteria. It is worthy of note that in 2010 the Whitesides research group[12] reported a feature in the *Analytical Chemistry* journal entitled "Diagnostics for the Developing World: Microfluidic Paper-Based Analytical Devices" which highlighted the potentiality of μPADs as a new class of point-of-care diagnostic devices for developing countries. Nowadays, we can say that these devices have features that are useful not only for developing countries but also for answering ongoing needs because they are easily integrated into the advanced tele-medicine model.

This perspective aims to highlight the main features of the paper harnessed for designing smart electrochemical paper-based analytical devices (ePAD), demonstrating that the use of paper in electrochemical devices not only provides additional features but is also capable of overcoming the limitation of polyester/alumina-based printed electrodes. I aim to highlight the more recent applications of electrochemical paper-based devices and inspire new ones to face ongoing challenges in analytical chemistry with the overriding goal of delivering smart and sustainable analytical tools.

■ SELECTION OF PAPER TYPE TO FABRICATE PAPER-BASED ELECTROCHEMICAL DEVICES

The main reasons for the hit of paper use in the development of electrochemical (bio)sensors encompass paper's (i) low cost, (ii) widespread accessibility, (iii) resistance to heat, solvents, and chemicals, (iv) mechanical strength, (v) porosity, (vi) capacity to manage fluids without any external pump, and (vii) capability to be easily cut, folded, modified, and assembled, as well. In this perspective, I highlight how it is possible to harness the previously reported features of the paper to design and develop smart and ecodesigned electrochemical (bio)sensors.

Office Paper as a Sustainable Substrate. Polyester and alumina-printed electrochemical (bio)sensors have characteristics for measuring the target analyte using a drop of solution, thus reducing the volume of the sample to analyze. Among the different paper types, office paper is a type of paper[13] which allows for drop measurement like polyester-based printed electrodes (Figure 1A), with the advantages of being low cost and environmentally friendly, and it can be incinerated after use, reducing waste. If we think about how many polyester-based printed electrochemical biosensors for glucose detection in capillary blood are used every day all over the world for diabetes management, we can easily realize how the simple replacement of the support can reduce not only the cost of production but also the waste management. For the fabrication of printed electrochemical sensors, treated polyesters, such as Autostat HT5 or other supports for appropriate ink adherence during the printing and sintering processes, are needed. Therefore, this requirement is the first one to assess the reliability of the support in printing manufacturing. As an example of the suitability of office paper for ePAD fabrication, de Araujo and Paixão[14] used HP Office Paper 8.5 in. × 11 in. as support to print the whole electrochemical cell using silver ink for the manufacturing of pseudoreference, working, and reference electrodes. The office paper-based electrochemical sensor was first tested with $[Ru(NH_3)_6]Cl_3$ as a redox probe using cyclic voltammetry as technique, observing the typical behavior and demonstrating the functionality of the silver ink-based office paper-based electrode. This device was tested for detecting picric acid and lead ions in acetate buffer. Additional chloride ions were detected in the sulfuric acid solution, demonstrating the versatility in terms of the analyte detected and the working solution used. Office paper was also selected as support to print the electrochemical cell using silver ink for the pseudoreference electrode and graphite ink for the working and counter electrodes on Fabriano Copy 2, 80 g/m^2 office paper. The wax-inks with solid-ink printer Xerox ColorQube 8580 were chosen to print the hydrophobic zone for delimiting the electrochemical, with thermal curing at 100 °C for 4 min.[15] To evaluate the adherence of the ink on this support, the office paper-based electrode was subjected to 50 bendings, and the electrochemical response was evaluated in the presence of ferricyanide as a redox probe, without observing any significant variation of ferricyanide response using cyclic voltammetry as a technique. The office paper-based electrochemical sensor was then modified with bismuth film to detect Zn(II) using anodic stripping voltammetry, to also underline the capability to work as a support in which the printed working electrode was further modified with bismuth film, maintaining enough sensitivity.

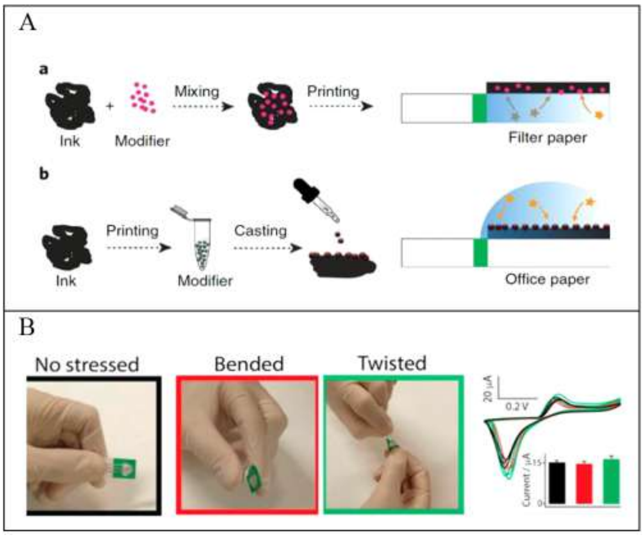

Figure 1. (A) Modification procedures and electrochemical detection using filter paper (a) or office paper (b) as support to print the electrodes. Reproduced with permission from ref 13. Copyright 2025 Springer. (B) Cyclic voltammetric responses in the case of no mechanical stress and after 100 repeated bending tests and 100 repeated twisting tests using silver electrodes printed on filter paper. Reproduced with permission from ref 18. Copyright 2025 Elsevier.

Filter Paper as Smart Support to Load the Reagents. If the office paper-based printed electrode works as the polyester-or alumina-based printed electrode measuring the target analyte in a drop solution, when porous support is used, the target analyte does not interact with the surface of the working electrode exposed to the air but with the working electrode in contact with the paper (Figure 1A). In fact, by adding the solution to porous paper like Whatman grade 1 filter paper (which is the most used[16]), the solution flows through the cellulose network of the paper, wetting the working electrode in contact with the paper. In this way, when the nanomaterial is used, it preferable to be added to the ink during the printing process, because if the nanomaterial remains on the working electrode surface, the target analyte will not interact with it. In this regard, the filter paper-based sensor to detect butyrylcholinesterase in serum by adding a Prussian Blue/Carbon Black nanocomposite in the graphite ink during the screen-printing procedure was reported in the literature.[17] Using filter paper, with respect to office paper, the curation of wax after the printing procedure requires only 2 min at 100 °C in an oven, demonstrating, however, the resistance to heat but with a different permeability of the wax in the filter paper compared to office paper. The filter paper as an office paper also demonstrated mechanical stability. Filter paper-based silver-printed electrochemical sensors were subjected to several mechanical tests,[18] namely, 100 repeated bending tests and 100 repeated twisting tests, demonstrating any evidence of physical damage and no difference between the electrochemical responses of the mechanically stressed and unstressed sensors (Figure 1B).

The porosity of the paper was also used to load the reagent, delivering reagent-free devices. In this way, the end user needs to add only the sample without any further sample treatment, including the addition of the reagents and pH adjustment. For instance, in the case of filter paper used for reagent loading, the Whitesides research group[19] designed an electrochemical immunosensor constituted of two zones, the detection zone where the electrochemical cell is printed and an embossed microwell in which the antibody is immobilized; thus, the reaction between antigen and antibody occurs with only the addition of the sample which contains the antigen because the antibody is already present on embossed microwell. Regarding also pH adjustment, we loaded all reagents for phosphate detection, namely, heptamolybdate and sulfuric acid on ePAD.[20] In this case, the phosphate is detected using the same principle of the colorimetric reference method based on the formation of phosphomolybdate complex in strong acid condition; thus, sulfuric acid is needed for the measurement. In respect to the reference method, the ascorbic acid is avoided, thanks to the electrochemical reaction that happens at the electrode surface. Thus, the chemical reagent ascorbic acid is replaced by the electrons generated at the electrode surface, and the heptamolybdate together with sulfuric acid was loaded on porous paper for a reagent-free measurement.

In this vein, the filter paper demonstrated an additional feature compared with office paper having the function of a reagent reservoir but, at the same time, introduced the reaction of the target analyte at the working electrode close to the cellulose network. The different diffusions of the target analyte in the solution film entrapped in the cellulose network can affect the sensitivity. However, it is very important to highlight that the porosity of the paper can also be used to preconcentrate the target analyte by consequently adding several drops of samples and waiting for the solvent volatilization. By redissolution of the target analyte with only one drop, an easy preconcentration step is achieved.[21] Furthermore, the preconcentration is quickly customizable by selecting the sample volume to load and the volume for the redissolution of the target analyte.

■ PUMP-FREE MICROFLUIDICS

The filter paper, beyond its use as a reagent reservoir, fosters microfluidics in ePADs without any external pump, facing the issue of microbubbles without a bubble trap or any additional device.[22] Additionally, the paper capillarity action, foldability, mechanical strength, and capability to be easily cut, folded, modified, and assembled have enabled the design and fabrication of novel printed electrochemical devices moving from lateral flow to unprecedented vertical flow.

Lateral Flow Configurations. The first lateral flow μPAD configuration combined with electrochemical detection was reported by the Henry research group in 2009[23] by joining photolithography to pattern the hydrophobic zone and Whatman grade 1 filter paper as the paper source. The three electrochemical cells were designed in lateral flow configuration for the detection of glucose, lactate, and uric acid by modifying the working electrode with the glucose oxidase, lactate oxidase, and uricase to produce hydrogen peroxide as the enzymatic byproduct, which was detected at Prussian Blue-modified working electrodes. After this configuration, many other lateral flow ePADs have been designed and fabricated to detect different types of analytes. For instance, a paper-based lateral flow in which the electrochemical cell was printed in the revealing zone to detect carbamic pesticides, namely, carbofuran and carbaryl, was reported by Kunpatee et al.[24] In detail, silica-gel paper chromatography Whatman SG81 was selected as a stationary phase for separating these pesticides based on the distribution coefficient. The graphene paper-based screen-printed electrode was used for the sensitive amperometric detection of these target analytes by combining it with the paper-based microfluidics via lamination, requiring low sample volume, i.e., 2 μL. Another flow configuration was reported by the deMello research group[25] which designed two-electrode detectors for a continuous flow assay of creatinine in urine samples, harnessing ferricyanide-mediated electrochemical quantification of creatinine (Figure 2A). The analysis of 19 clinical urine samples collected compared to commercial colorimetric assay sheds light on the reliability of this cost-effective diagnostic tool.

For customizing the flow rate and the electrochemical response, the designed paper-based microfluidics is used. In this regard, interesting works were reported by the Henry research group for the detection of microorganisms such as viruses[26] or organic compounds such as caffeic acid.[27] In the latter case, they reported a lateral flow ePAD by adding, at the end of the device, a fan-shaped pumping reservoir. The different dimensions of the fan-shaped pumping reservoir gave better resolution of the peaks and faster analysis. If the configuration of the adsorbent pad can manage the flow rate with an accelerated flow rate, another approach to managing the fluids and avoiding the manual addition of the reagents relies on creating waxed barriers. The Chailapakul research group[28] has joined the lateral flow to avoid the washing steps and the addition of several reagents by decreasing the flow rate of some reagents and introducing waxed barriers (Figure 2B). The time-delay strategy enabled DNA detection of the Hepatitis B virus in serum samples within 7 min.

These examples highlighted the huge capillary properties of the paper, which foster microfluidics without external pumps

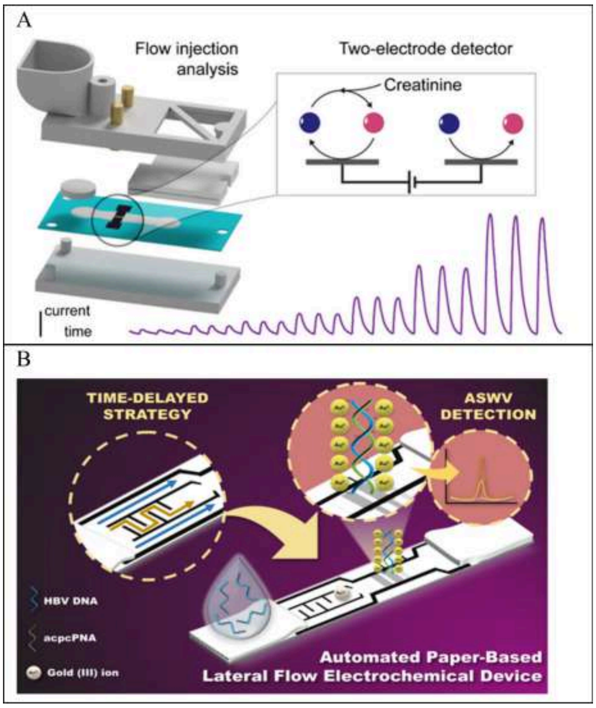

Figure 2. (A) ePAD based on the lateral flow configuration for detecting creatinine. Reproduced with permission from ref 25. Copyright 2025 American Chemical Society. (B) Waxed barriers in the lateral flow system to avoid adding the reagents manually. Reproduced with permission from ref 28. Copyright 2025 American Chemical Society.

with the capability to manage the flow rate by customizing the pumping reservoir or by introducing components such as waxed barriers.

Vertical Flow Configurations. The vertical flow configuration is mainly peculiar to paper-based electrochemical devices, which paves the way for three-dimensional ePADs. In the vertical configuration, the printed electrochemical sensor is usually the last layer due to the impermeability of the silver and graphite inks used in the screen-printing process. Recently, the Richards research group[29] has demonstrated that the graphite paper-based electrode fabricated through laser-induced cellulose pyrolysis has been characterized by both porosity and wettability, allowing the capillary-driven flow through the electrochemical biosensing system.

The easy cut and assembly of paper were used to fabricate programmable devices in which different layers of paper accomplish different tasks in the three-dimensional origami configuration, such as the clip one.[30−32] For instance, Khaliliazar et al.[33] designed an oSlip ePAD constituted of seven different layers, in which the first layer contains the working electrode functionalized with a capture probe in a wax-printed filter paper with a hollow. The second layer consists of a wax-printed filter paper with a hydrophilic paper channel to facilitate the capillary flow to the glass fiber absorbent pad. The third layer is a movable wax-barrier layer which works to stop or activate the fluid flow for the incubation time of the sample. The fourth layer is a glass fiber which has to absorb the sample fluid in the washing step. The fifth layer is the second movable wax-barrier layer. The sixth layer is a wax-printed filter paper with a hollow channel, which provides depth to the detection zone to hinder contamination of thread electrodes on the subsequent layer, and at the end, the seventh layer contains the counter and pseudoreference electrodes (Figure 3A). The authors used this configuration for toxic microalgae *Ostreopsis* cf. *ovata* genomic DNA detection via a nucleic acid amplification test.

Beyond the oSlip approach, the harnessing of foldability of the paper has opened a new approach to the fabrication of functionalized and programmable analytical tools using folded origami, plug-and-play, and pop-up configurations.

The Crooks research group[34] reported in 2012 a self-powered folded origami ePAD using an aptamer as a recognition element to detect adenosine. After that, several origami devices were reported.[35] For instance, we designed an ePAD to detect different classes of pesticides by folding and unfolding, cutting, and embedding operations.[36] The organophosphorus insecticides, phenoxy acid herbicides, and triazine herbicides were quantified by harnessing their capability to inhibit butyrylcholinesterase, alkaline phosphatase, and tyrosinase enzymes, respectively. The measurement of each class of pesticides took place by adding distilled water after that the pad containing the enzyme (red pad) was folded close to the substrate pad (green pad, step 1) and to paper-based electrochemical sensor (step 2) (Figure 3B). After the measurement (step 3), the pads used are unfolded (step 4) and cut (step 5). For the sample measurement, the sample was added to the second enzymatic pad (red pad) for 5 min (incubation time, step 6) followed by folding it close to the substrate pad (green pad) and paper-based electrochemical sensor (step 7) and the addition of distelled water; then, the residual current was measured (step 8). The degree of inhibition was evaluated by the chronoamperometric mode, and the response was compared with the measurement carried out in the absence of the pesticide. The measurement is repeated for each strip, which is customized for each class of pesticides. This device demonstrated the harnessing of paper-based pads to be folded, cut, and embedded for cost-effective smart screening tools.

The combination of vertical flow with a rotational approach is another configuration of the origami device. For instance, Yakoh et al.[37] combined the vertical and rotational flow to design an immunosensor for α-fetoprotein detection. The convective component of fluid motion was used to remove interference and augment the analytical performances of the biosensor compared to the nonrotating approach. For the analysis, the end users freely transfer, switch, and stop fluid flows by manually rotating the paper disk.

The Henry and Coltro groups[38] reported the first plug-and-play configuration coupled with colorimetric μPAD and an ePAD using vertical flow and reversible foldable mechanism for the colorimetric detection of Fe, Ni, and Cu and electrochemical detection of Zn, Cd, and Pb in river water samples (Figure 3C).

By folding a single paper sheet into a three-dimensional device to change shape, fluidic, and electrical connectivity, a pop-up configuration is designed. The first pop-up ePAD was reported by the Whitesides research group[39] for the detection of beta-hydroxybutyrate in whole blood by combining an ePAD with a commercial glucometer (Figure 3D). The pop-up configuration has been able to accomplish (i) dual-mode amplified signal read-out systems (i.e., differential pulse voltammetry and super-capacitor) as demonstrated by the Yu research group in the detection of adenosine 5'-triphosphate,[40] (ii) an easily multistep operation by simple folding as reported by the Chailapakul research group for the detection of hepatitis B virus DNA,[41] and by the Compagnone research group for the detection of carbaryl in different grains.[42]

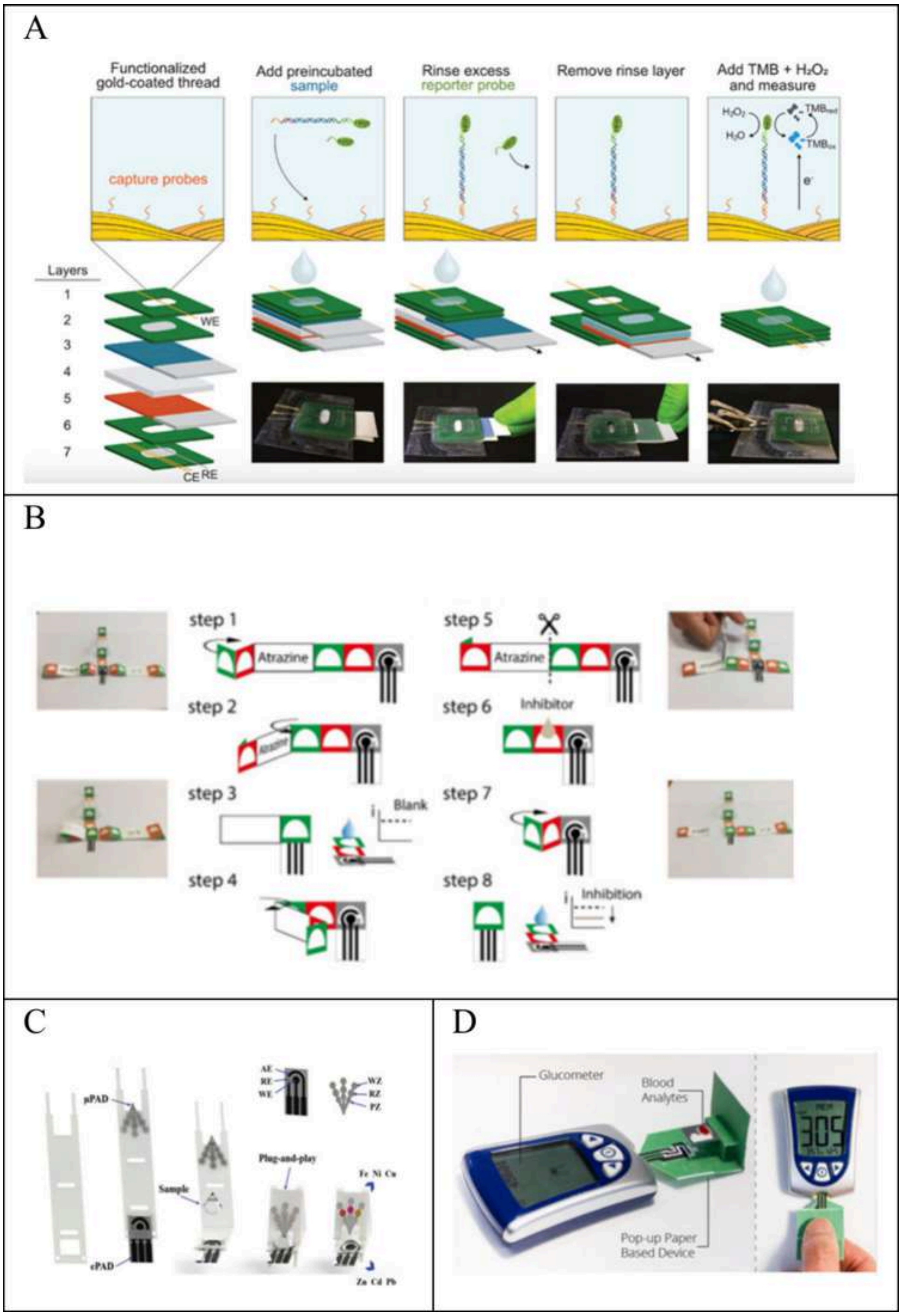

Figure 3. ePAD based on vertical microfluidics with (A) oSlip configuration. Reproduced with permission from ref 33. Copyright 2025 American Chemical Society. (B) folding, unfolding, and cutting procedure in origami ePAD. Reproduced with permission from ref 36. Copyright 2025 Elsevier. (C) Plug-and-play configuration. Reproduced with permission from ref 38. Copyright 2025 The Royal Society of Chemistry. (D) Pop-up configuration. Reproduced with permission from ref 39. Copyright 2025 American Chemical Society.

The ePADs have paved the way for the vertical flow configuration; furthermore, the foldability of the paper boosted the development of smart configurations such as origami, pop-up, and plug-and-play to deliver multitasking devices by the ease of folding, unfolding, and cutting.

■ MULTIPLEXED ANALYSIS

The challenge of the analytical methodologies relies on a low detection limit, robustness, wide linear range, and no matrix effect. In the vein of furnishing advanced analytical tools, multiplexed analysis is an additional feature for quantifying several target analytes. Different configurations of ePADs enable the accomplishment of this task by making the analysis using (i) a modified working electrode able to detect multiple markers, (ii) multiple working electrodes and one reference and counter electrode, and (iii) different embedded electrochemical cells.

In the case of the first approach, i.e., a modified working electrode, the Lieberzeit research group[43] reported an ePAD

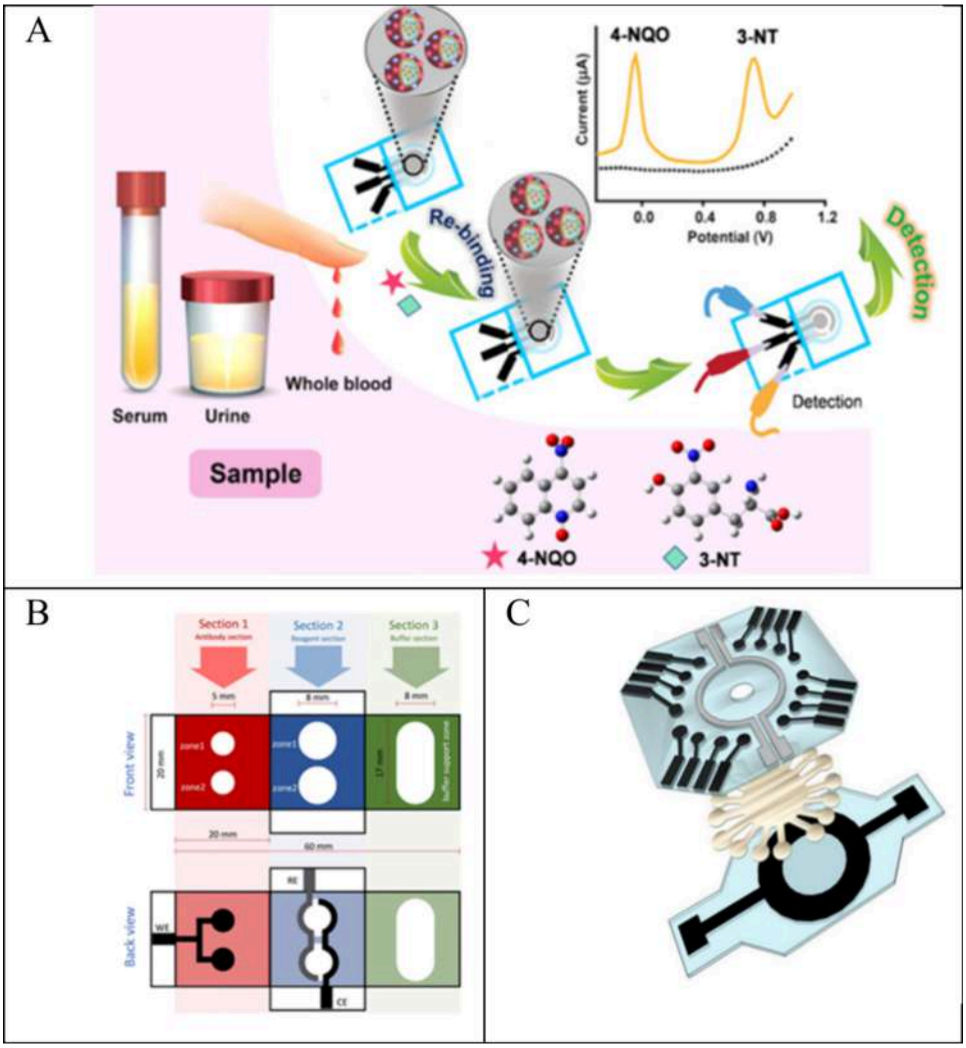

Figure 4. (A) Multiplexed analysis using dual molecularly imprinted polymer for the carcinogen oxidative stress biomarkers 3-nitrotyrosine (3-NT) and 4-nitroquinolin-N-oxide (4-NQO). Reproduced with permission from ref 43. Copyright 2025 American Chemical Society. (B) Origami configuration with two working electrodes for the detection of orfloxacin and enrofloxacin. Reproduced with permission from ref 45. Copyright 2025 Elsevier. (C) Multiplex analyses using 16 channels constituted of 16 working electrodes, in which each set encompasses four working electrodes and one reference electrode. Reproduced with permission from ref 48. Copyright 2025 Elsevier.

modified with a dual molecularly imprinted polymer for the carcinogen oxidative stress biomarkers 3-nitrotyrosine and 4-nitroquinolin-N-oxide (Figure 4A). The layer of dual molecularly imprinted polymer was able to bind 4-nitroquinolin-N-oxide and 3-nitrotyrosine, which were subsequently oxidated at −0.10 V and +0.78 V, respectively, with detection limits in nanomolar levels and effectiveness in urine, serum, or whole blood samples.

In the case of the second approach, i.e., the use of multiple working electrodes, the multiplexed analysis happens at the different working electrodes of the same electrochemical cell. For instance, the three working electrodes with only one reference and counter electrode were reported by Gu et al.[44] In this case, two working electrodes were functionalized with antibodies for the quantification of β-amyloid protein and Fetuin B. The third electrode was used as an internal reference electrode, with ferrocene as the electrochemical probe. This device successfully quantified β-amyloid protein and Fetuin B in the serum and brain tissue of transgenic AD mice. The same approach with origami configuration was reported by Chomthong et al.[45] for detecting norfloxacin and enrofloxacin using a label-free electrochemical immunosensor. This device was fabricated with two zones loaded with two different types of antibodies and another two zones loaded with the redox probes, namely, thionine and ferrocenecarboxylic acid for the current signal generation; indeed, in the presence of the target analytes, the redox probe signal decreases proportionally, obtaining a limit of detection equal to 2.02 and 1.70 ng/mL for norfloxacin and enrofloxacin, respectively (Figure 4B). The effectiveness of the simultaneous quantification of norfloxacin and enrofloxacin was assessed in milk, honey, and fish samples, demonstrating the reliability of this configuration also in complex matrices.

In the case of the third approach (i.e., multiplexed analysis using different embedded electrochemical cells), the device merged different electrochemical cells with fluidics to manage the sample toward the different electrochemical cells. For instance, the Henry research group[46] reported an ePAD to detect simultaneously C-reactive protein, troponin I, and procalcitonin in serum samples, using a configuration which encompasses a transparency film with three separate electrochemical cells containing reference and counter electrodes, a double-sided adhesive layer, a wax patterned paper with three separate electrochemical cells containing working electrode for the detection of each analyte, and a trasparent tape. By addition of the sample to the inlet, the fluidic channels allow the sample to be transported to the detection zones, which consist of graphene-modified stencil-printed carbon electrodes modified with the selected antibody for the corresponding biomarker. The quantification was done by monitoring the change in the peak current of ferro/ferricyanide with square wave voltammetry, owing to the binding of analytes to their respective immobilized antibodies. Following the same approach, Lomae et al.[47] developed the paper-based biosensing platform for the detection in three different electrochemical cells of SARS-CoV-2, influenza H1N1, and respiratory syncytial virus. Three acpcPNA probes specific for simultaneous analyses of the three viruses were selected as biorecognition elements, and the measurement was carried out by monitoring the DNA hybridization, demonstrating that this configuration is reliable for both immuno- and DNA-based sensors.

An interesting strategy which combined the second and third approaches was reported by the Fatibello-Filho research group.[48] They designed and fabricated a device with 16 channels (16 working electrodes, each set consisting of 4 working electrodes and 1 reference electrode) (Figure 4C). This ePAD was tested using the same target analyte, namely, glucose, but the functionalization of the working electrodes with different biocomponents can deliver a high throughput multiplexed analysis for different target analytes.

In this way, the origami ePADs allow for the multiplexed analysis not only by inserting additional working electrodes, as in the case of polyester/alumina printed electrochemical sensors, but also by using microfluidics to manage the sample toward different working electrodes and/or different electrochemical cells, rendering more effective the multiplexed analyses.

PAPER-BASED HYBRID DEVICES

The world of printed electronics well highlights the need to produce an entire device by using sequential and/or parallel material additive technologies such as screen printing, inkjet printing, or direct writing. Furthermore, for the mass production of electronic devices, a hybrid technology approach is usually selected, in which discrete electronic components are attached to the printed conductive traces, demonstrating the choice of hybrid devices for delivering robust electronic tools for market entry. Following this approach, in the last decades, the paper components have also been mingled with polyethene terephthalate (PET), polyvinyl chloride (PVC), or polydimethylsiloxane (PDMS) layers to deliver robust electrochemical paper-based devices. The Henry research group demonstrated the utility of stacked layers of polyester and double-sided adhesive films to create an effective capillary-flow microfluidic circuit.[49] As an example, they developed[50] an ePAD with stencil-printed carbon electrodes (SPCE) and 7 layers of polyester and double-sided adhesive films in which pad components were integrated including a blood-filtration membrane for on-board plasma extraction, nitrocellulose membrane (NCM) modified with capturing agents specific to the target analyte namely anti-SARS-CoV-2 nucleocapsid protein, bare glass fiber pad and a vent hole to prevent air from being trapped, and waste pad grade 1 CHR, Whatman PLC (Figure 5A). A 10 μL sample of whole blood on the blood-filtration membrane was added followed by the buffer addition, which filled all the device channels by capillary action, providing sequential delivery of the reagents. A polyester film was added to cover the system and avoid solution evaporation. This device was successfully tested for the quantification of anti-SARS-CoV-2 nucleocapsid protein antibodies in blood.

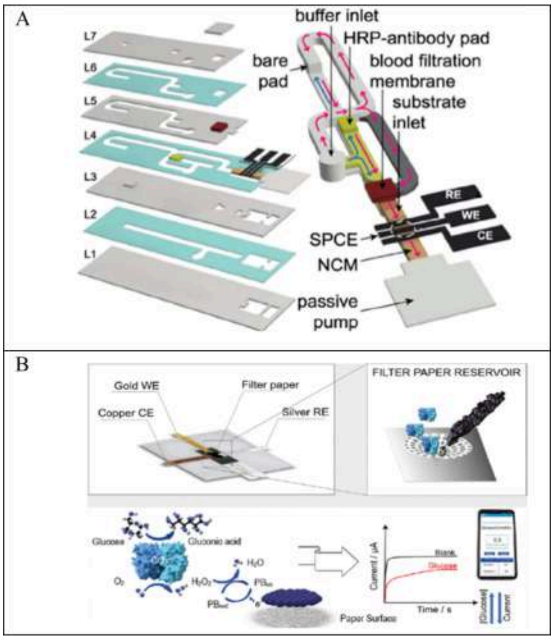

Figure 5. Hybrid systems constituted of (A) 7 layers of polyester and double-sided adhesive films in which pads are integrated. Reproduced with permission from ref 50. Copyright 2025 American Chemical Society. (B) PVC-based electrochemical in which a paper card-like pad functionalized with Prussian Blue/Carbon nanocomposite, glucose oxidase, and phosphate salts is inserted. Reproduced with permission from ref 51. Copyright 2025 The Royal Society of Chemistry.

We designed[51] a paper card-like pad previously functionalized with the Prussian Blue/Carbon Black nanocomposite, glucose oxidase enzyme, and phosphate salts to be inserted in a PVC-based electrochemical cell for the detection of glucose in artificial tears (Figure 5B). The paper card-like pad worked as a disposable component of this hybrid device, which was replaced for each measurement while the PVC-based electrochemical cell was reused. This paper-based card when loaded with glucose oxidase, lactate oxidase, or uricase enabled the detection of glucose, lactate, or uric acid, respectively, using the same PVC-based electrochemical cell. The Feng research group[52] developed a paper-based sandwich structured sensor to accurately evaluate pH in sweat, reducing the influence of sebum. The sandwich configuration encompasses five layers: a PDMS layer as a cover layer, a microfluidic snake channel for the sebum adsorption consisting of a filter paper layer and two oil adsorption layers, and finally, an adhesive layer composed of a double-sided medical adhesive tape used to fix the sensor on human skin. This paper-based device merged with a PDMS-based potentiometric sensor was successfully tested in on-body trials, confirming its feasibility.

In this way, the literature demonstrated the ease of the integration of the paper-based components with different material layers, proving their versatility in solving some requirements such as air bubble prevention, the sequential delivery of the reagents, the cost-effective customization of a PVC cell, and the integrated sample treatment.

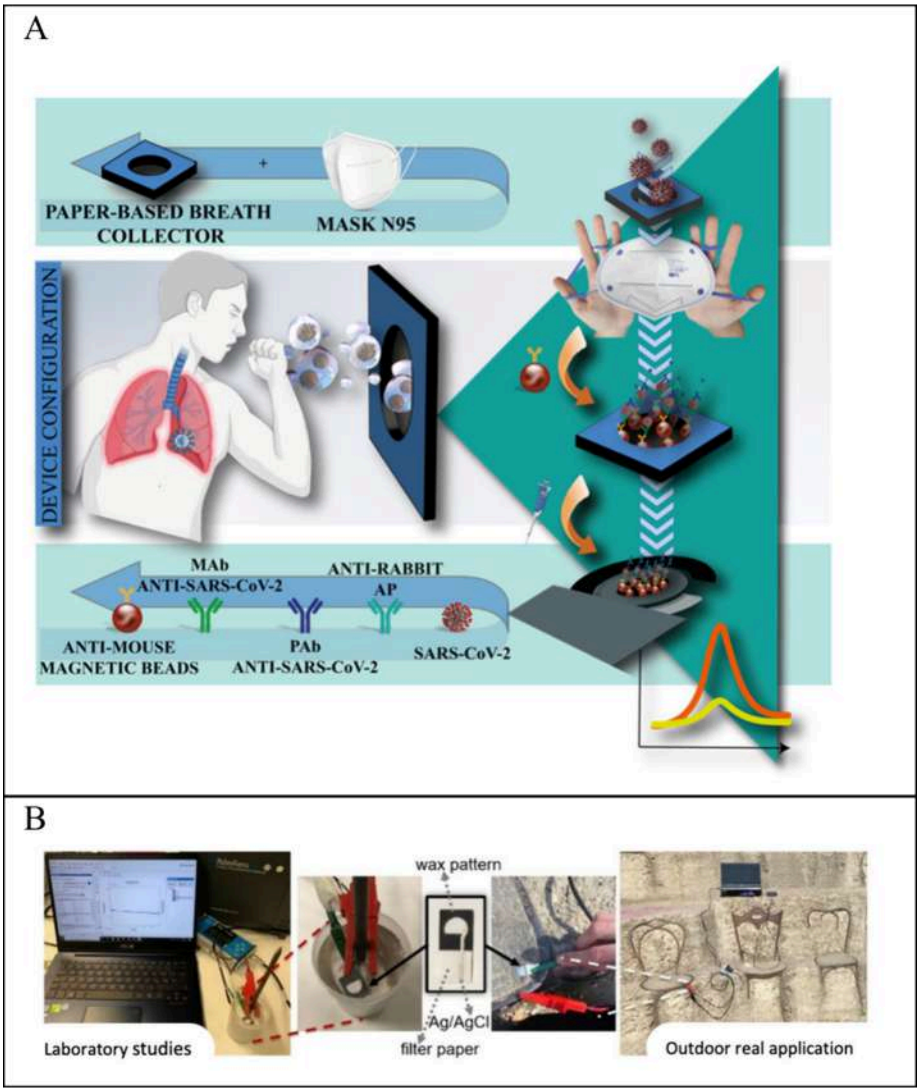

Figure 6. (A) ePAD for the detection of SARS-CoV-2 in breath using a paper-based device sampling system embedded in N95 face mask. Reproduced with permission from ref 55. Copyright 2025 American Chemical Society. (B) Paper-based sensor for corrosion monitoring in a solid concrete structure. Reproduced with permission from ref 57. Copyright 2025 Wiley.

■ PAPER-BASED ELECTROCHEMICAL (BIO)SENSORS FOR THE DETECTION OF TARGET ANALYTES IN AEROSOL AND SOLID SAMPLES

The polyester- and alumina-based printed electrochemical (bio)sensors have been developed to detect the target analytes in liquid samples by adding a drop of solution. When the target analyte is present in an aerosol sample, an additional sampling system is required, while in the case of the target analyte in a solid sample, sample treatment is needed before the analysis. The ePADs can go beyond the state of the art and break down these barriers, delivering analytical tools for detecting target analytes in aerosol and solid samples without any additional sampling system. In 2019, we designed[53] an origami ePAD for mustard agents in the aerosol phase by loading the biocomponent choline oxidase, enzymatic substrate choline, and phosphate buffer salts on porous paper-pads, and only humidity was used to wet the preloaded pads and to start the measurement. In this way, the humidity of the aerosol worked as an actuator, because, in its presence, there was the dissolution of the reagents, the start of the reaction between the enzyme and the target analyte in the aerosol phase, and the start of the reaction between the enzyme and its substrate. In the same year, the Dincer research group[54] designed an ePAD printed using an ink modified with Prussian Blue to quantify hydrogen peroxide in simulated breath. Likewise, in the case of mustard agent aerosol, breath worked as an actuator because it contained the target analyte and the breath relative humidity dissolved the salts (the paper-based sensor was pretreated with 1 M KCl) for electrochemical analysis. Following these pioneering works of using paper-based devices for electrochemical sensing of the target analyte in the aerosol phase, other studies are reported. For instance, we developed[55] a comfortable paper-based collector into an N95 face mask as a universal solution for analyzing several biomarkers, avoiding any contact between humans and the chemicals for a facile market entry. This paper-based device worked as a sampling system, and the target analyte (i.e., SARS-CoV-2) was detected out of the N95 face mask (Figure 6A). Recently, Fiori et al.[56] fabricated a working electrode by laser-induced carbon nanofibers decorated with Ni nanocatalysts for aerosolized glucose detection, inserting the paper-based device in the external side of the plastic breathing mask lateral hole. Target analyte was sampled in the aerosol

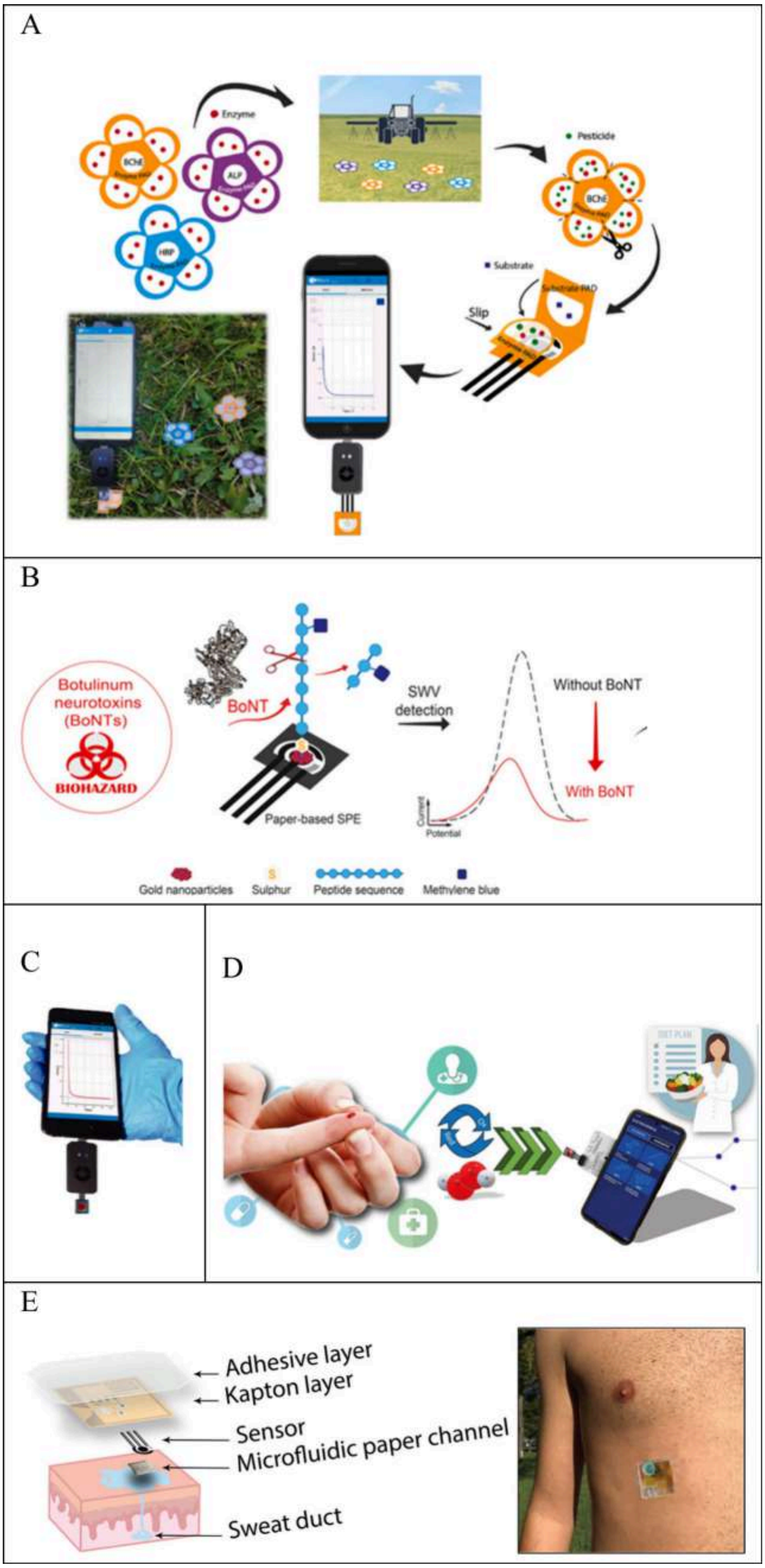

Figure 7. (A) Flower-like origami ePADs for pesticide customization in agrifood practices. Reproduced with permission from ref 61. Copyright 2025 Elsevier. (B) Peptide-based ePAD for botulinum neurotoxins A and C detection. Reproduced with permission from ref 70. Copyright 2025 Elsevier. (C) ePAD combined with smartphone-assisted potentiostat for precision medicine in Alzheimer's disease. Reproduced with permission from ref 84. Copyright 2025 Elsevier. (D) NFC-assisted ePADs for precision nutrition. Reproduced with permission from ref 85. Copyright 2025 Elsevier. (E)

Figure 7. continued

RFID-patch sensor with sampling cotton pad for potentiometric pH monitoring in sweat. Reproduced with permission from ref 88. Copyright 2025 Elsevier.

phase and successively analyzed out of the mask by dropping 0.1 M NaOH solution onto the paper-based electrochemical sensor.

If detecting the target analyte in the aerosol phase has been a relevant pillar for demonstrating an unprecedented feature of the ePADs, the use of this device for the detection of the target analyte in a solid sample has given an additional unprecedented feature to these analytical tools. We demonstrated the applicability and solving issue properties of ePADs in concrete-based structures.[57−59] Starting from the first work in which we demonstrated the reliability of the pattern of a polyester-based potentiometric electrochemical sensor with electrolyte gel to evaluate the corrosion of the iron bars inserted in the concrete structure (in which the iron bar worked as working electrode and the silver-based printed electrode combined with electrolyte gel as reference electrode),[60] paper has entered in this context by replacing the combined reference electrode (polyester printed sensor and electrolyte gel) with the filter paper-based silver ink reference electrode.[57] The addition of distilled water dissolves the electrolyte preloaded on the paper, rendering this simple ePAD a useful tool (Figure 6B) compared with the ASTM standard C876 method, which uses a classical Cu/$CuSO_4$ solid reference electrode and a wet sponge for the corrosion evaluation. If in this case of corrosion monitoring the paper furnished a cost-effective system, in the case of potentiometric measurement of pH monitoring and chloride content evaluation on the surface, ePADs supplied unprecedented electrochemical tools for the monitoring of these important parameters. Indeed, state-of-the-art research reports on the use of phenolphthalein in the case of pH evaluation without the possibility of punctual pH measurement and in the case of chloride content, invasive sampling and lab-based analyses.

Using these ePADs, the end users need to only put on the surface the potentiometric paper-based device functionalized with iridium oxide in the case of pH measurement[58] and an origami potentiometric paper-based device for chloride content[59] with drop(s) of distilled water and/or KCl, furnishing a cost-effective, noninvasive, easy to use, and rapid analytical tools.

■ PAPER-BASED ELECTROCHEMICAL (BIO)SENSORS FOR THE AGRIFOOD SECTOR

The electrochemical (bio)sensors are well-established analytical tools for on-site analyses for the evaluation of the safety and the quality of food, including during food manufacturing processes developed in both academic and industrial sectors. The concept of precision agriculture has further boosted the use of miniaturized and robust electrochemical sensors for on-site analysis. In this regard, we reported the first flower-like origami ePAD to put on the soil to evaluate the overuse of pesticides, with the overriding goal of customizing the use of pesticides during agrifood practices (Figure 7A).[61] Recently, wearable plant sensors were listed as among the Top 10 Emerging Technologies of 2023 in the World Economic Forum,[62] catching the attention of these devices. In this overall scenario, Sun et al.[63] have already developed in 2014 a wearable carbon tape-based electrochemical sensor for in situ salicylic acid measurement using, beyond carbon tape-based working electrode, a layer of filter paper in contact with the counter and reference electrodes and the tomato leaf, measuring the oxidation of salicylic acid at +0.7 V. Recently, in the same year of the World Economic Forum communication, Martins et al. developed[64] a kraft-based paper electrochemical to monitor the presence of pesticide carbendazim on the skin of apples and cabbages. The measurement relied on placing the porous ePAD on the selected fruit and vegetable to evaluate the oxidation of carbendazim at +0.57 V on the kraft paper-based sensor.

Consider the following:

i. easier market entry of the (bio)sensors in the agrifood sector compared with medical diagnostic devices that require the certification as In Vitro Diagnostic Devices (IVD) Regulation;[65]
ii. increasing interest in wearable devices for plants, fruits, and vegetables;
iii. it is expected that there will be a growing development of ePADs in this field in the future.

■ PAPER-BASED ELECTROCHEMICAL (BIO)SENSORS FOR ENVIRONMENTAL AND SECURITY SECTORS

At the start of ePADs development, the ePADs were largely developed for the detection of several pollutants, such as heavy metals, pesticides, and phenolic compounds. In fact already in 2016, a review entitled “Paper-Based Analytical Devices for Environmental Analysis” was published by the Henry research group.[66] After that, many other ePADs were developed mainly to detect the target analytes in water samples, and fewer applications were reported in more complex matrices such as soil and aerosol/air.[67] It is worth noting that recently greenness metrics on paper-based electrochemical (bio)sensors were assessed;[68] for instance, a greenness and whiteness assessment of different electrochemical devices for phosphate detection was made using the RGBfast model, demonstrating that ePAD was the most consistent within the Green Analytical Chemistry and White Analytical Chemistry principles, because of the combined savings in the use of hazardous reagents, energy, and practical utility together with satisfactory analytical performances.[69]

In the security field, ePADs were used for both chemical and biological warfare agents. Several cholinesterase-inhibitive biosensors which detect organophosphates are suitable for detecting nerve agents (e.g. ref 36), and an ePAD choline oxidase-based inhibitive biosensor was reported for mustard agent detection.[53] In the case of biological warfare agents, we developed[70] an office paper-based electrochemical biosensor for the detection of botulinum neurotoxin serotype A (BoNT/A) and C (BoNT/C) using a synthetic peptide as a biocomponent to deliver an antibody-free and fast analysis, when compared with the reference method which employs the mice (Figure 7B). Park et al. fabricated a peptide-based ePAD for the detection of airborne *Bacillus subtilis* spores as a *Bacillus anthracis* simulant in an air sample using electrolyte gel under the ePAD to detect the biological warfare agents in aerosol phase.[71]

The main advantage of using ePADs in the security field is the possibility of being incinerated after use, decreasing the cost of decontamination. Additional efforts are required to deliver multiplexed analysis with robust devices for use in the military context. Thus, the next activities should be focused in this direction.

PAPER-BASED ELECTROCHEMICAL (BIO)SENSORS IN THE BIOMEDICAL SECTOR

The global market size of paper-based point-of-care diagnostics was estimated at USD 16.39 billion in 2022, with a compound annual growth rate of 6.0% from 2023 to 2030.[72] The growing behavior is due to the increased concept of telemedicine and precision medicine. Furthermore, as reported in the Introduction, the COVID-19 pandemic further boosted the development of paper-based diagnostic devices. It is worth noting that professors such as Prof. Henry and I, who work with paper-based analytical devices in academia, are also founders of companies with a market core in paper-based point-of-care diagnostics.[73,74] The key values of ePAD for market entry are easy production and versatility at low cost. We developed[75] the first electrochemical immunosensor for SARS-CoV-2 detection in saliva using a polyester-based printed sensor and magnetic beads to load the immunological chain.

When the issue of the management of the washing solution waste for the market entry was encountered, the combination of this system with a paper-based pad in a cassette where the paper-based component works as a waste reservoir, loading reagent zone, and passive pump, has enabled the quickly resolution of the issue and the augmentation of the Technology Readiness Levels (TRL) of the diagnostic device.[76] Another added value is the capability of the ePADs to easily detect different biomarkers ranging from organic molecules to viruses in different matrices such as capillary blood,[77] serum,[78] urine,[79] saliva,[80] wound fluid extracted,[81] nasal swab,[82] and sweat.[83]

In the case of capillary blood, serum, urine, saliva, and nasal swab, several point-of-care diagnostic devices have been developed using smartphone-assisted, RFID-, or NFC-based potentiostats, which are well integrated into the telemedicine model.

The origami configuration with several layers for sample treatment, reagent reservoir, and electrochemical analysis furnishes an ecodesigned lab on a chip on paper to apply in different biomedical subsectors. In Figure 7C, a smartphone-assisted origami-ePAD for precision medicine in patients affected by Alzheimer's disease is shown, based on the measurement of the residual butyrylcholinesterase enzymatic activity in the absence and in the presence of drugs used by Alzheimer's patients, namely, rivastigmine and donepezil.[84] In Figure 7D, an NFC-assisted office paper-based potentiometric sensing tool for precision nutrition is illustrated based on evaluating the postprandial oxidative stress in capillary blood in the case of Mediterranean and western diet meals.[85]

ePADs have demonstrated reliability and advantages in the next market diagnostics, namely, breath analysis and wearable sensors.

In the case of the breath analysis, after the pioneering work of the Dincer research group,[54] a growing interest has been gathered[86] considering that the World Economic Forum has listed disease-diagnosing breath sensors as one of the Top 10 Emerging Technologies of 2021.[87]

In the case of wearable sensors, paper-based microfluidics allows for the easy management of sweat to monitor the biomarkers as the media of the concentration, by single analysis, or by punctual concentration monitoring over time, as we demonstrated in the case of an RFID patch for pH measurement of sweat for the media concentration analysis using a sampling cotton pad[88] (Figure 7E), an ePAD for cortisol detection in sweat for a single analysis using an origami system,[89] and punctual monitoring of pH and Na ions using a hybrid wearable ePAD based on paper-based butterfly like microfluidics.[90]

The different configurations of the ePADs to sample the sweat and carry out the analyses gave a reliable chance for market entry, considering the growing interest in sweat analysis at the molecular level.[91]

CONCLUSIONS

Paper-based devices were rediscovered by the Whitesides research group in 2007[4] developing the first colorimetric μPAD, followed by the designing of ePAD in 2009 by the Henry research group.[23] If paper was initially used to fabricate sustainable devices, being paper cost-effective and environmentally friendly, during the last years, paper has been used to deliver the following:

i) pump-free microfluidic ePADs, harnessing the capillarity of the paper
ii) reagent-free ePADs, by loading reagents on a porous paper network to ask to an end user for only the addition of the liquid sample, which redissolves the reagents
iii) ePAD with customized sensitivity by preconcentrating the sample with several additions of the sample in the same ePAD and waiting for the solvent volatilization, followed by the redissolution of the sample with lower volume
iv) ePAD with unconventional configurations like origami and pop-ups to accomplish several tasks, namely, pH adjustment, sample filtration, and multiplexed electrochemical detection by folding, unfolding, and cutting
v) robust ePADs by combining several features of the paper with the robustness of polyester or 3D printed devices
vi) versatile ePADs by demonstrating their reliability in the detection of several target analytes in different matrices belonging to various sectors, namely, agrifood, environmental, security, and biomedical ones

ePADs have also broken several barriers in printed electrochemical devices, demonstrating the reliability of detecting target analytes in the aerosol phase and on the solid surface without any additional sampling device.

Actually, the main challenge is to boost the mass production on the industrial scale of these sustainable analytical tools.

Which barrier will be broken by the ePADs in the next feature together with the industrial scale production?

We are working to break down the next barrier, namely, organ-on-a-chip on paper devices within the Horizon Europe Pathfinder Project Phoenix-OoC, to deliver the next advanced and sustainable origami paper-based organ-on-a-chip device,[92] with the overriding goal to harness the multifarious features of paper to deliver a pump, bubble-issue, and reagent-free organ-on-a-chip with the further advantage of embedding a multiplexed sensing system.

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Notes

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