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Electrochemical Paper-Based Microfluidics: Harnessing Capillary Flow for Advanced Diagnostics

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Electrochemical paper-based microfluidics has attracted much attention due to the promise of transforming point-of-care diagnostics by facilitating quantitative analysis with low-cost and portable analyzers. Such devices harness capillary flow to transport samples and reagents, enabling bioassays to be executed passively. Despite exciting demonstrations of capillary-driven electrochemical tests, conventional methods for fabricating electrodes on paper impede capillary flow, limit fluidic pathways, and constrain accessible device architectures. This account reviews recent developments in paper-based electroanalytical devices and offers perspective by revisiting key milestones in lateral flow tests and paper-based microfluidics engineering. The study highlights the benefits associated with electrochemical sensing and discusses how the detection modality can be leveraged to unlock novel functionalities. Particular focus is given to electrofluidic platforms that embed electrodes into paper for enhanced biosensing applications. Together, these innovations pave the way for diagnostic technologies that offer portability, quantitative analysis, and seamless integration with digital healthcare, all without compromising the simplicity of commercially available rapid diagnostic tests.

1. Introduction

Diagnostics are a central pillar of the modern healthcare system, playing a critical role in the early detection of disease and effective patient management. Over the past three decades, we have witnessed a paradigm shift from centralized laboratory testing to point-of-care diagnostics, driven by the advent of miniaturized and portable sensing technologies. This shift has been particularly influential in the fight against infectious diseases, which are among the leading causes of death globally.[1]

Infectious diseases disproportionately affect resource-constrained and low-income regions with limited access to centralized diagnostics.[2] It is therefore unsurprising that point-of-care diagnostics have had a profound impact on containing the spread of infectious diseases. For example, during the Ebola outbreak in Liberia in 2015, the widespread use of testing reduced the time it took to identify cases from 6 days after infection to just 1.5 days.[3,4] This, in turn, led to a significant reduction in the reproduction number (the average number of secondary infections caused by a single case) from five to almost zero. It has been shown that the rapid results provided by point-of-care tests, although often less accurate than their laboratory counterparts, improved the timely delivery of targeted treatment[5] ultimately saving lives and providing socioeconomic benefits.[6] Beyond infectious diseases, point-of-care diagnostics are extending their utility to noncommunicable diseases such as cardiovascular disease and diabetes, and more generally to personal health monitoring.[7]

In 2003, the World Health Organization (WHO) introduced the "ASSURED" criteria to define the ideal features of point-of-care diagnostic tests.[8,9] Such tests should be affordable, sensitive, specific, user-friendly, rapid and robust, equipment-free, and deliverable to end-users.[10] More recently, real-time connectivity for digital healthcare and ease of sample collection have been added to this set to reflect current development efforts, resulting in the "REASSURED" guidelines for point-of-care tests.[10]

The Coronavirus Disease 2019 pandemic demonstrated the utility of rapid diagnostic tests, with antigen testing playing a central role in informing the community about their personal health and guiding pandemic management at the population level.[11] The success of lateral flow tests is the result of more than six decades of continual development, culminating in a device that allows us to detect disease biomarkers without equipment, whilst being affordable and easy to use.[12]

Inspired by capillary-driven lateral flow tests, paper-based microfluidics has been a focus of intense research over the past decade, with the goal of diversifying the type and number of operations that can be performed on a single, disposable

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device. Such devices have the potential to create complex diagnostic tests at a low cost while maintaining the ease of operation of commercial rapid tests.[13] Most contemporary paper-based devices rely on colorimetric readouts, allowing them to be easily interpreted by the naked eye. However, simplicity comes at a cost, with colorimetric tests often being qualitative or at best semi-quantitative.[14]

The growing demand for fully quantitative rapid testing has fueled the recent momentum behind electrochemical signaling. This approach brings a new dimension to paper-based microfluidics, promising unambiguous results and direct interfacing with digital technologies. The unique properties of paper have reshaped the conventional approach to electroanalysis and spawned new sensing principles at the crossroads with capillary fluidics. In addition, fabrication on and in this unconventional material has presented challenges for electrode implementation and its full potential has yet to be realized.

Here, we review recent developments in electrochemical paper-based microfluidics from the lens of capillary flow. By revisiting the origins of lateral flow tests and paper-based microfluidics, we illustrate how capillarity has been ingeniously harnessed to produce simple yet powerful diagnostic tools. From there, we highlight how electrochemical detection has been leveraged to bring quantitative testing to the point of need. In particular, we focus on the challenges and efforts to integrate electrodes into paper substrates and to exploit their synergy with capillary effects to create new integrated devices.

2. Paper-Based Microfluidics: Endless Possibilities?

The term "paper-based microfluidics" was coined by Martinez et al. in 2008,[15] with the motivation of improving lateral flow tests and translating recent advances in microfluidics for diagnostic applications into more affordable and portable formats.[16,17] Cellulose paper was chosen because of its negligible cost and widespread availability, as well as its ability to wick fluid by capillary action. In particular, cellulose paper is mechanically robust (unlike nitrocellulose, which is brittle when cast into thin sheets), and resistant to heat, solvents, and chemicals.[18,19] These properties allow cellulose paper to be cut, folded, treated, and assembled with minimal constraints, facilitating the creation of intricate flow paths and operations for advanced bioassays.[20] Additionally, it is worth noting that in the context of paper-based microfluidics, the term "paper"—traditionally defined as a network of cellulose fibers mechanically pressed into a thin sheet—is expanded to encompass any porous membrane material that wicks fluids by capillary action.[21] In fact, many of the concepts and technologies developed in this field are not exclusive to cellulose-based materials, and multiple materials (such as cellulose, nitrocellulose, or polyethersulfone) are often combined in a single device.

To fully appreciate the current state and utility of paper-based microfluidics and the merits of electroanalysis, it is instructive to examine the rich historical evolution of lateral flow immunoassays, which has been driven by the convergence of several scientific disciplines.

2.1. Historical Development of the Lateral Flow Test: Success Driven by Capillary Flow

Lateral flow immunoassays (LFIA) have undoubtedly established themselves as the most popular point-of-care test and have become synonymous with rapid testing due to their ability to screen for the presence of an antigen, antibody, or other target protein in a timely manner. As such, they are often deployed as a first line of defense during infectious disease epidemics.[11,22] In LFIAs (or the less commonly used vertical flow assays), the target of interest is typically labeled with nanoparticles and directed through a nitrocellulose membrane to a capture test line, driven by an absorbent pad (**Figure 1**).

The advent of LFIAs can be traced back to the late 1950s with the development of the immunoassay,[12] initially using radioisotope labels (later replaced by enzymes).[24,25] Within a short period of time, immunoassays were combined with paper-based electrophoresis to differentiate between labeled and unlabeled target analytes using electric fields.[26] Although initially performed on cellulose paper, electrophoretic analysis on nitrocellulose garnered traction due to the uniform microporous structure of the material.[27] As nitrocellulose made its way into laboratories, it found use as a solid-state immobilization platform for proteins and nucleic acids, laying the foundation for blotting techniques in biology.[28] Three principal properties of nitrocellulose, namely the facile adsorption of proteins for immobilization, homogeneous and reproducible capillary flow, and low nonspecific binding (especially in the presence of surfactant) made nitrocellulose the substrate of choice for LFIAs. Around the same time, protein-particle conjugates were being developed for latex agglutination assays.[29] Here, antigen-coated micron-sized particles aggregated in the presence of target antibodies, offering a visual indicator for antibody detection, and setting the stage for particle immunolabeling. Fast forwarding to the 1970s, the improved understanding of human chorionic gonadotropin (hCG), and its role as a reproductive hormone and biomarker for pregnancy, was a key driver behind the development of the first commercial LFIA.[30] However, translating this assay to a solid-state format on nitrocellulose and bringing it to the market required a variety of other enabling technologies. These ranged from nitrocellulose membrane manufacturing, antibody production, and precision liquid dispensing, to gold nanoparticle production and conjugation. Many of the seminal LFIA patents were filed by various companies during this period.[31–34] By 1985, Unilever had commercialized the first LFIA for pregnancy testing.

With the growing interest in the application of LFIAs for infectious disease diagnostics and the emergence of LFIA tests with disparate performance, evaluation methodologies had to evolve to properly assess and benchmark these products (similar to the implementation of randomized clinical trials for therapeutics)[35] This resulted in the creation of the "bench-to-bedside" pathway for diagnostics development, as well as the formation of nonprofit entities, such as the Foundation for Innovative New Diagnostics (FIND) in 2003, dedicated to guiding and assessing diagnostic development for diseases affecting low-income populations.[36] During this period, the prevailing vision was that point-of-care tests could approach the performance of reference laboratory standards.[37] This was reflected in the Rockefeller Foundation's offer of a $1 million prize for the

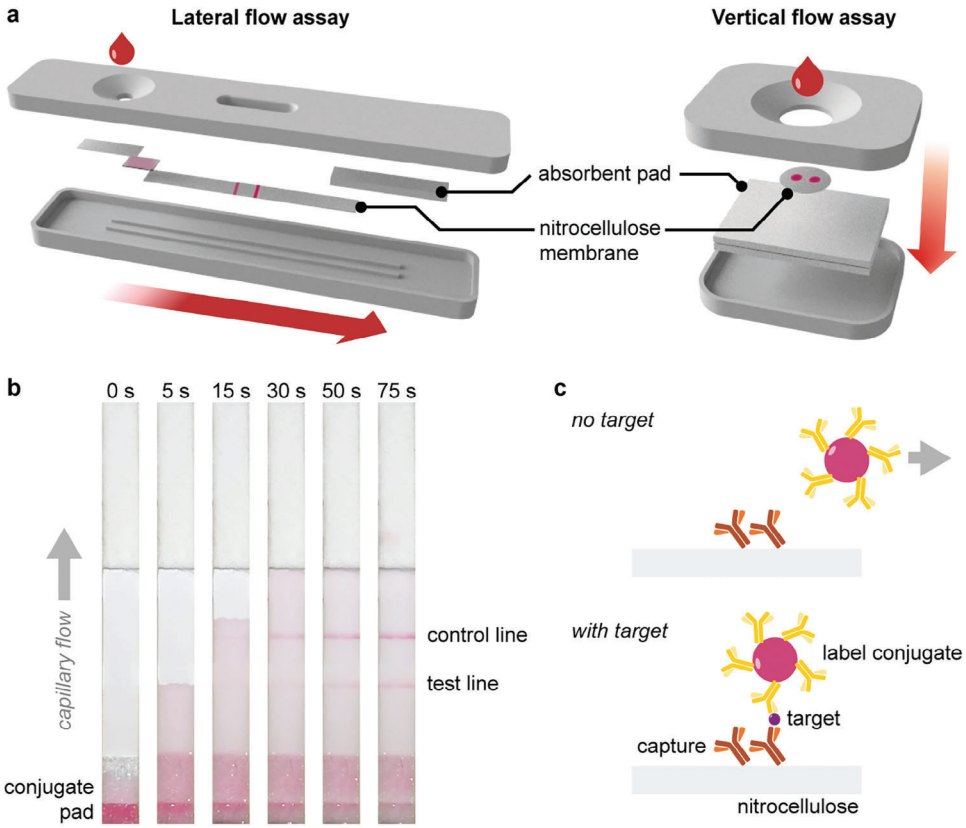

Figure 1. a) Architecture of commercial rapid tests. b) Sequential photographs reporting a reactive LFIA in action.[23] In the presence of the target, the test line captures the nanoparticle labels c).

development of a rapid test for a panel of STIs with stringent performance and cost requirements.[38] The prize was never claimed. The initial unrealistic expectations put on LFIAs eventually gave way to a more pragmatic view: these tests did not need to be perfect. Instead, their utility should be tailored to the situation and context in which they would be used. For example, rapid tests with lower sensitivity were shown to result in a higher number of treatments despite detecting fewer cases.[5] In this context, mathematical modeling has been instrumental in predicting and optimizing the impact and cost-effectiveness of rapid tests of varying levels of sensitivity and specificity depending on the settings.[37] For example, if treatment is inexpensive and side effects benign, or if isolation measures are easy to implement, high sensitivity prevails over high specificity. Conversely, high specificity is critical when the target disease has a low prevalence. In the 1990s, the first malaria LFIAs were being used by trained healthcare workers, although it took another two decades before World Health Organization (WHO) prequalification requirements were settled.[39] Since then, the WHO has recommended LFIAs for many diseases, including antigen tests for human immunodeficiency virus (HIV), malaria, and hepatitis C virus (HCV).[39]

The principle of capillary flow has been instrumental in the success of the lateral flow assays. Following the track, as the field of paper-based microfluidics progresses toward high-performance devices, their design requires a thorough understanding of fluid dynamics in porous materials.

2.2. The Physics and Engineering of Capillary Flow

Capillary action is a fundamental interfacial force that governs fluid movement through porous materials and has long been studied due to its ubiquity and importance in industrial processes such as textile dyeing and wood impregnation.[40]

Capillary-driven flow through paper-based microfluidic analytical devices (μPADs) is generally divided into two distinct phases: the wetting phase, driven by the flow front, and the fully wetted flow between the inlet and absorbent pad.[41] From a fluid dynamics standpoint, both of these regimes obey the same principles and are derived from the same set of equations.[19,41] Due to the micron scale domains within a wicking material, capillary flow is laminar (Reynolds numbers $\ll 1$) and follows a Stokes flow regime, with viscous forces dominating inertial forces.[42] In the case of a porous medium, the flow front velocity, v, is described by Darcy's law:[43,44]

$$v = \frac{Q}{A} = -\frac{\kappa}{\mu}\frac{\Delta p}{L} \tag{1}$$

Here Q and A are the volumetric flow rate and cross-section area of the channel, respectively. The flow is driven by a pressure drop, Δp, (in Pa) over length L, and depends on the dynamic viscosity of the fluid, μ, (in Pa·s) and the material permeability, κ, (in darcy unit; 1 darcy = 0.98 μm^2) that can be anisotropic. In an open system, the capillary pressure, p_c, typically dominates

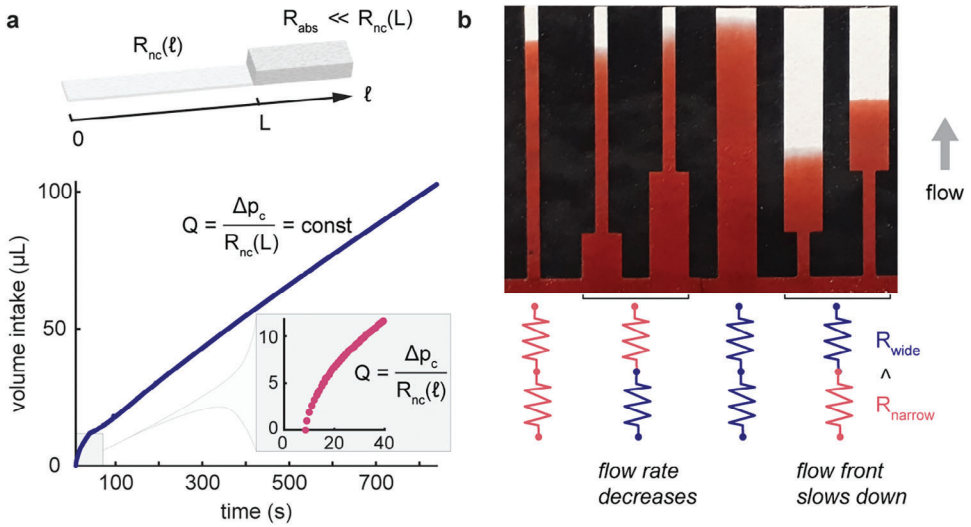

Figure 2. a) Dynamics of capillary flow through a dipstick comprising a nitrocellulose (nc) strip and an absorbent pad.[49] At early times, the flow rate, Q, follows the Washburn equation with an increasing flow resistance as the flow front progresses. After the front reaches the absorbent pad, the flow rate stabilizes, controlled by the (constant) resistance from the fully wetted nitrocellulose strip. b) Photographs of various channel geometries, highlighting the dynamics of the capillary front through variable channel cross-sections.

the pressure difference ($\Delta p = -p_c$). Assuming that the material's wetting properties are homogenous along its length (i.e., constant p_c), Equation (1) can be integrated to yield the general Washburn equation for the wetting phase[45]:

$$L^2 = D_w\, t \text{ with } D_w = \frac{2\kappa p_c}{\mu} \tag{2}$$

Here, the front position, L, at time, t, is governed by the general Washburn coefficient, D_w, (in $m^2\ s^{-1}$). To better understand the factors underpinning capillary pressure, we further simplify the problem by approximating the porous material as a bundle of uniform capillaries of radius r arranged in the flow direction ($\kappa = r^2/8$).[42] Inside a single pore, the capillary pressure across the front interface is given by the Young-Laplace equation,[45] $p_c = 2\,\gamma\, cos\theta / r$ (γ is the interfacial surface tension and θ the contact angle of the fluid on the solid phase), which results in a Washburn coefficient given by:

$$D_w = \frac{r\,\gamma\,\cos\theta}{2\mu} \tag{3}$$

From this analysis, we can see that the material must be hydrophilic ($\theta < 90°$) to generate a positive capillary driving force. In addition, the front position is proportional to the square root of time and is independent of the channel width. Also, larger pores (to a certain extent) will produce faster wicking rates.

The Washburn equation assumes a homogeneous material, with constant cross-section and no flow resistance.[45] Moving to multi-material systems, or multi-dimensional paper-based fluidic networks, multiple regimes are observed when the flow transitions from one material (or 1D) to another.[41] Since Darcy's law (Equation 1) is analogous to Ohm's law in the field of electrical networks, capillary flow rates can be viewed as "currents" and the capillary pressure as the applied "voltage." The flow path is considered to be a combination of "resistances" ($R_i = \mu/\kappa \cdot L/A$) arranged in series or parallel (**Figure 2**). The fluidic flow will then take the path of least resistance through the network, and the narrowest constriction (i.e., highest resistance) will dictate the overall flow rate. With that in mind, the fully-wetted flow (also referred to as the Darcy flow) occurs when the flow front reaches the absorbent pad, which acts as a capillary pump, with a large capacity and low fluidic resistance.[46] The fluid flow is thus theoretically steady and limited by the flow resistance of the channel itself ($Q = \Delta p_c / R_{channel}$).[47]

In summary, when designing µPADs with variable channel geometries, extending in multiple dimensions, or composed of multiple materials, it is critical to consider the resistance of each component and how the path of least resistance forms and guides the flow. Fluids often take unexpected paths, some of which are visually apparent (leaks), but which can also be "hidden" as localized dynamics, e.g., from inhomogeneous contact between pads.[48]

2.3. Harnessing Capillary Flow for Bioassays

Utilizing the capillary action of paper, numerous reports have demonstrated ingenious µPADs that can transport fluids, mix reagents, and perform complex biochemical assays without the need for external pumps or power sources for fluid actuation.[50] These operations are often inspired by advances in polymer microfluidics or standard laboratory flow-based techniques.[51] To achieve this, channels are patterned into paper layers for specific functions. Common fabrication methods include laser cutting of channels, or printing/lamination of hydrophobic wax barriers—a topic extensively covered in several reviews.[21,50,52] Below, we highlight capillary-driven assay operations and their integration into µPADs (**Figure 3**).

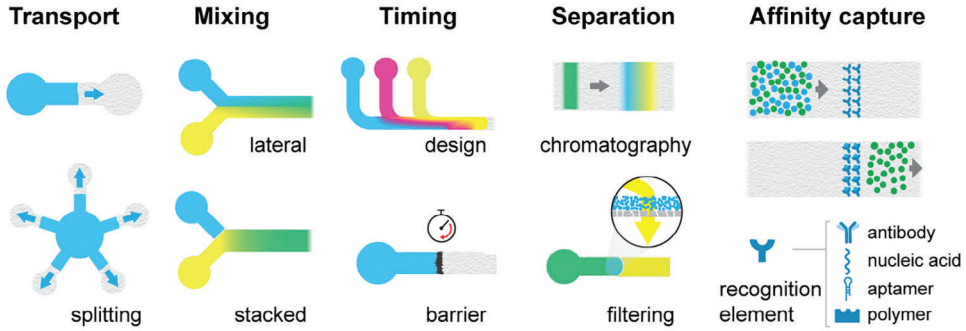

Figure 3. Overview of the toolbox available for harnessing capillary flow to perform bioassay operations on paper-based microfluidic analytical devices.

2.3.1. Transport

The primary function of capillary flow is to transport liquids, whether moving from a reagent reservoir to the detection zone,[51] or splitting the sample into multiple streams for multiplexed detection.[15,53] The advancing flow front also plays a critical role in the rehydration and transport of dried reagents to different parts of the fluidic network; a process that can occur either sequentially or in parallel.[54,55] The duration of transport is a critical factor in allowing reactions to occur. For example, introducing elements that alter flow dynamics in an immunoassay can significantly affect binding times, thereby affecting overall assay performance.[56]

2.3.2. Mixing

Combining different streams requires careful consideration of mixing, especially when considering the highly laminar nature of capillary flow. To address this, the hydrophobic walls defining channels can be patterned with inhomogeneous wall structures to enhance advective mixing.[57] An alternative approach to achieve rapid mixing is to superimpose channels. The increased contact area in a stacked configuration promotes more efficient mixing compared to lateral contact.[51,58]

2.3.3. Timing

Unlike pressure-driven flow, capillary flow operates passively and has no inherent interruption mechanisms. Various strategies have been developed to ensure precise reagent delivery for bioassays.[59] For example, 2D channel configurations with varying widths and lengths have been used to facilitate the sequential delivery of reagents essential for procedures such as enzyme-linked immunoassays.[60,61] Other passive mechanisms include delay loops or dissolvable barriers,[62] whilst some active approaches incorporate actuated valves to achieve total fluidic control.[59]

2.3.4. Separation

Capillary flow through paper can facilitate separation in three main ways: i) through solid-solute interactions (chromatography), which stands as one of the earliest applications of paper in analytical chemistry;[63] ii) by diffusion-based extraction, analogous to an H-filter in chip-based microfluidics;[51] iii) by filtering species on the basis of size or charge, which is applicable in areas such as blood plasma separation,[64] DNA extraction,[65,66] or isolation of microorganisms.[67]

2.3.5. Affinity Capture

Immunoassays are a primary application for μPADs, which are used to detect analytes via affinity capture on a solid phase. Capillary flow assists by transporting the sample through the capture zone and subsequently washing away unbound analytes. Although cellulose paper does not readily adsorb proteins or DNA, several strategies have been developed to immobilize biomolecules using chemical or photochemical treatments.[68,69] That said, the most common method remains the stacking of multiple layers, with one layer typically consisting of nitrocellulose decorated with the recognition elements. These operations collectively constitute a versatile toolbox. Through judicious assembly and combined with a signal transduction method, they enable the design and realization of advanced diagnostic μPADs.

2.4. Enabling Complex Flow Assays Through Innovative Device Architecture

Building upon the tools outlined above, we now turn our attention to the construction of integrated devices for diagnostics. Below, we highlight three innovative μPADs that have been recently introduced. These platform technologies are notable for their unique approach to performing complex assays, leveraging inventive device architectures that capitalize on capillary flow.

Joung et al. presented a vertical flow device for highly-multiplexed immunoassays (**Figure 4a**).[73] The device consists of 11 stacked layers, each with a specific function, including a flow diffuser, a conjugate pad, and a capture pad.[73] Parallel channels are patterned on the nitrocellulose membrane, and capture reagents are spotted in a microarray (with up to 81 capture zones).[70,73,74] After capture, the target analytes are labeled with colorimetric or fluorescent tags and detected using a smartphone-based microscope.[73,74] Notably, multiplexed detection is paired with machine learning to identify more

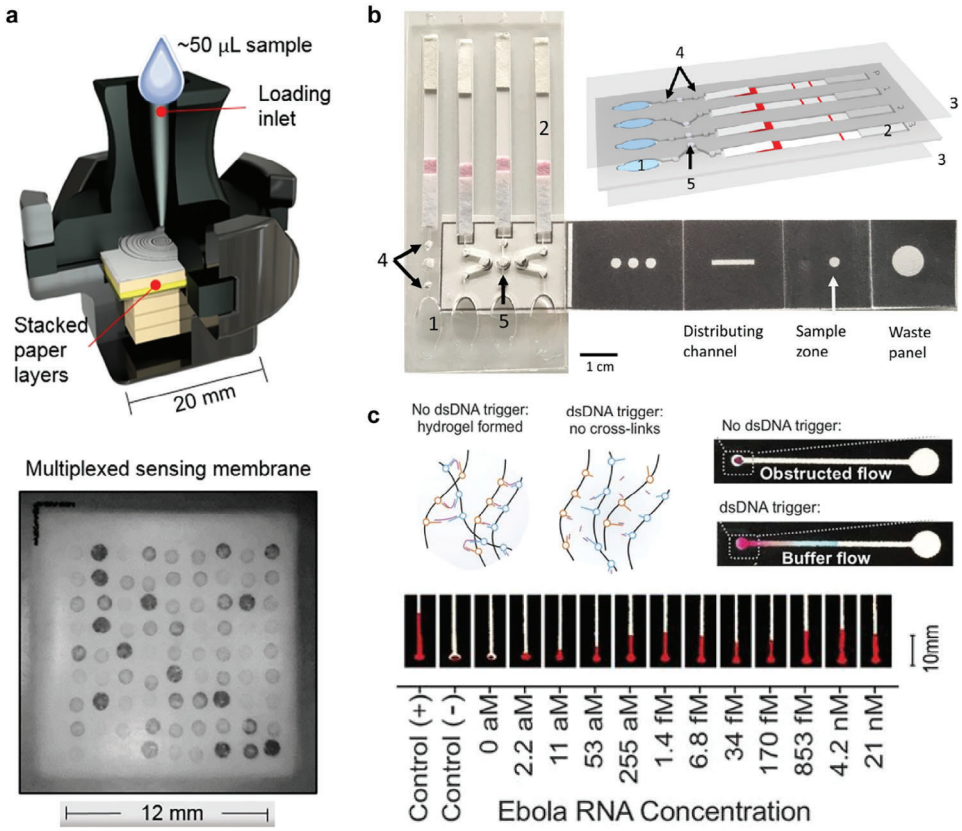

Figure 4. Harnessing capillary flow for advanced paper-based diagnostics with optical readout. a) A multiplexed vertical flow immunoassay with smartphone-based fluorescent readout. Adapted under the terms of the CC BY 4.0 license.[70] Copyright 2020, The Authors. b) An integrated device combining origami-assisted nucleic acid extraction, isothermal amplification, and lateral flow colorimetric readout. Adapted under the terms of the CC BY 4.0 license.[71] Copyright 2019, The Authors. c) A CRISPR-responsive device that degrades a paper-embedded hydrogen barrier upon DNA target recognition, resulting in a distance-based readout. Adapted with permission.[72] Copyright 2019, AAAS.

robust channels, improving quantification and minimizing cross-reaction.[75] This platform facilitates the diagnosis of complex disease biomarker panels in clinical samples, whilst also simplifying the interpretation of results via a dedicated reader. This platform exemplifies the evolution of lateral flow tests and the move toward multiplexed detection of biomarker patterns with digital result interpretation and communication.

Developing a point-of-care test for nucleic acids is challenging due to low target concentrations and the preparation and incubation steps required for amplification. To address this issue, Reboud et al. developed a device that streamlines nucleic acid purification, isothermal amplification, and amplicon detection on an inexpensive µPAD (Figure 4b).[71] The multi-chamber design was able to simultaneously test for two malaria parasites and a positive control. Within the device, a cellulose origami component is sequentially folded to filter and elute nucleic acids previously captured by micron-sized particles. The purified DNA is then directed into a chamber containing predried amplification reagents. After incubation, a finger pump transfers the liquid to integrated lateral flow strips for result reading. This process, which takes less than 40 min, matches the performance of traditional PCR and can be adapted to other diseases.[71,76] The authors also developed a mobile device for temperature control and readout, whilst providing decision support and data connectivity.[77] Although trained operators are required, they demonstrated the potential of this technology in resource-limited settings using finger-prick samples.[71,77] Recently, a similar approach has been used to integrate nucleic acid testing into wearables, such as face masks.[78] These platforms are encouraging examples of how we can move molecular diagnostics away from centralized laboratories to the point of need.

Recent advancements in synthetic biology have paved the way for novel bioassays in diagnostics.[78] Notably, endonucleases directed by clustered regularly interspaced short palindromic repeats (CRISPR) have demonstrated unparalleled specificity in targeted nucleic acid detection. This technology has rapidly found its way into µPADs for practical, field-deployable readouts.[79,80] A unique approach in this regard was presented by English et al., who combined a CRISPR-based assay with a µPAD that incorporates a stimuli-responsive hydrogel (Figure 4c).[72,81,82] When the target nucleic acid is present, the CRISPR-activated endonuclease triggers hydrogel degradation, promoting capillary flow.[72,81] Conversely, without a target, the hydrogel impedes this flow, resulting in an intuitive distance-based readout that showcases remarkable sensitivity. Although this is an early-stage demonstration with challenges like extensive sample preparation and long incubation times (>4 h), this ingenious design offers potential solutions to the qualitative limitations of naked-eye readouts. These

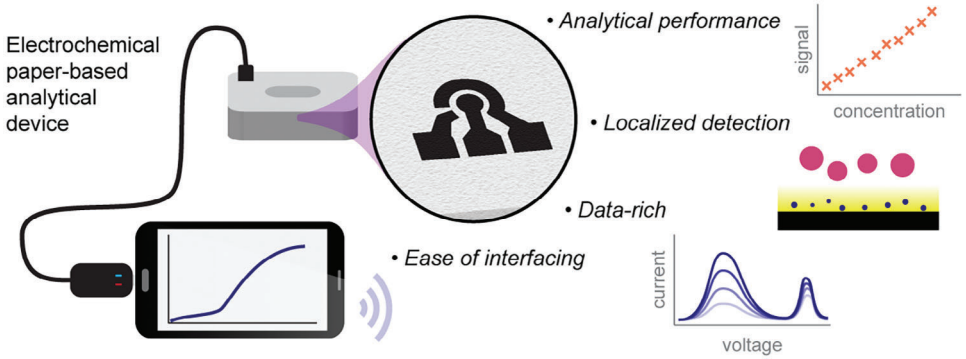

Figure 5. Benefits of incorporating electrochemical detection within paper-based electrochemical devices.

highlighted technologies underscore the versatility of μPADs in providing advanced diagnostic capabilities in user-friendly formats. Whilst integration with readers is driven by the demand for digital interpretation and increased accuracy, the use of optical (colorimetric or fluorescent) readouts inevitably requires the use of expensive and bulky optical components. Furthermore, the attempts to utilize smartphones for optical imaging introduce complications due to variations in the optical components across different smartphone manufacturers.[83,84]

3. Electrochemical Paper-Based Microfluidics: Pushing Boundaries

Cellulose-based materials, particularly in the form of paper electronics, have received increasing attention for their potential in green and flexible electronics.[85,86] In the realm of analytical devices, the appeal of electrodes lies primarily in their potential for electrochemical detection—a technique that quantifies chemical reactions based on electrical signals produced at an electrode interface.[87] The promise of electrochemical μPADs was quickly realized, with pioneering studies emerging shortly after the field's inception, featuring screen-printed electrodes deposited onto the paper surface.[88,89] Since then, the panel of electrode fabrication technologies has blossomed, with a wide variety of techniques, designs, and materials.[90] The driving force behind the adoption of electrochemical readout is the ambition i) to improve the performance of colorimetric assays and ii) to venture into sensing avenues beyond the reach of optical-based signal transduction.[91,92]

3.1. What Does Electrochemistry Bring to the Table?

The Clark Electrode Probe, introduced in 1962 for continuous blood oxygen monitoring, pioneered the use of biosensors.[93] This electrochemical probe laid the foundation for the emergence of glucose meters, which became the most successful point-of-care technologies ever developed.[94] Over the years, innovations in readout hardware, analytical methods, and manufacturing techniques have propelled electrochemical sensors as viable and affordable solutions for a wide variety of applications.[95] In the following discussion, we explore the predominant benefits of adopting electrochemical sensor technologies for in vitro diagnostics, particularly within paper-based analytical devices (**Figure 5**).

3.1.1. Analytical Performance

One of the outstanding advantages of electrochemical sensors is their inherent quantitative capabilities. For example, in voltammetric and amperometric measurements, the current readout correlates directly with the analyte concentration.[87] In addition, by exploiting the wide dynamic current ranges of modern transducers and readers—from picoamperes to milliamperes—wide dynamic response ranges can be achieved.[87] Thus, the defined upper and lower detection limits are usually due to inherent physicochemical processes, such as nonspecific binding and reaction kinetics, rather than limitations of the electrochemical readout hardware itself.[96] Beyond optical-based methods, electrochemical techniques also introduce novel capabilities, such as label-free detection made possible by impedance spectroscopy,[97] and in some cases may offer improved sensitivity compared to colorimetric readout.[98]

3.1.2. Ease of Interfacing

Electrochemical sensors integrate seamlessly with low-cost (and low-power) electronic readers,[99] streamlining data processing and wireless transmission.[53,100] Unlike colorimetry and spectrophotometry, electrochemical methods are unaffected by local lighting conditions. This eliminates the need for dedicated imaging chambers, allowing for more compact devices suitable for point-of-care testing. As a result, the strategic placement of electrodes can be fully exploited in multilayer devices, as they do not need to be in the line of sight. For example, optical-based vertical flow immunoassays typically require the disassembly of the device upon assay completion to analyze the capture layer.[73] In this context, electrodes could be strategically positioned to achieve optimal functionality, provide a direct readout, and improve usability.

3.1.3. Localized Detection

Unlike optical measurements, which are primarily sensitive to the bulk of a solution in the detection zone, electrochemical

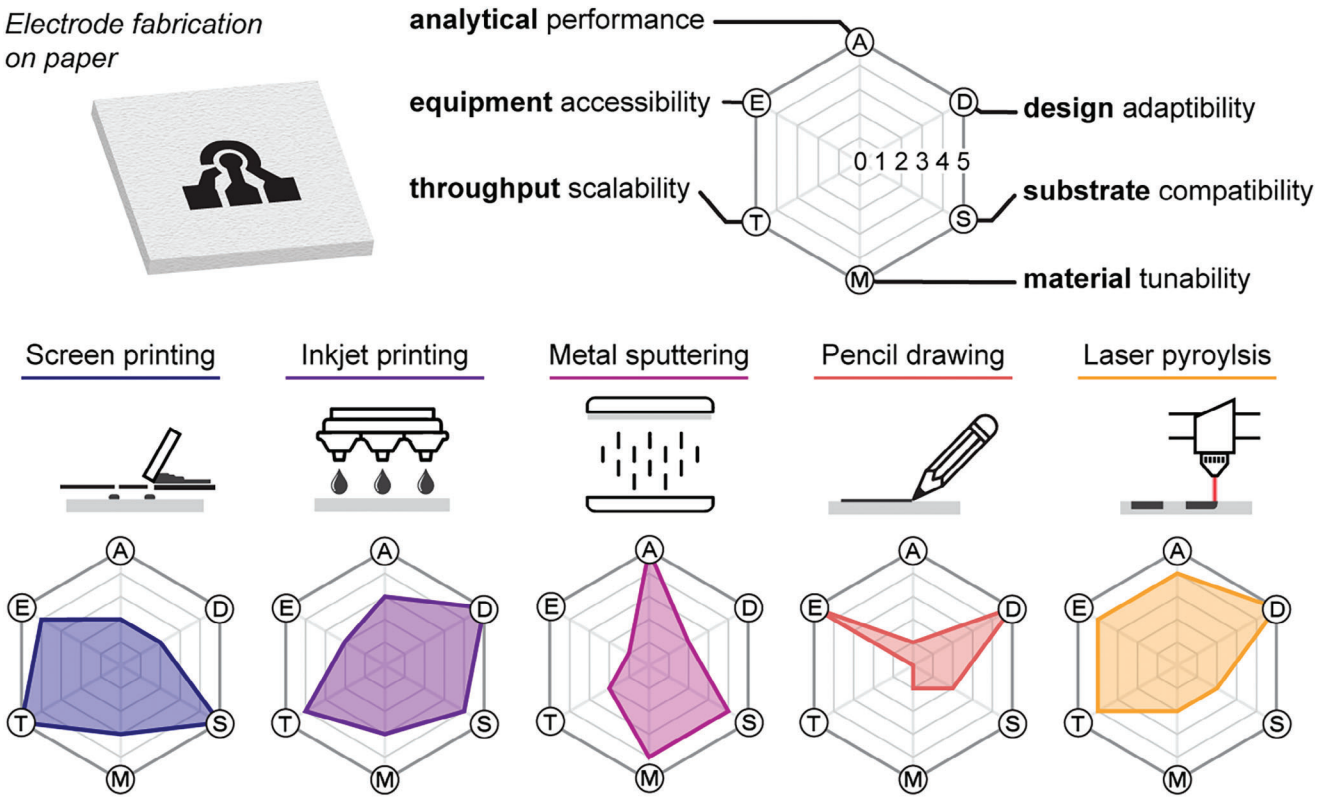

Figure 6. Comparison of the most popular and emerging technologies for electrode fabrication on paper using six selected criteria. The criteria are qualitatively assigned to each fabrication method and presented in radar charts for each fabrication technique (bottom).

reactions occur exclusively at the electrode-solution interface.[87] This surface-level detection is inherently localized, responding only to the immediate environment surrounding the electrode. Despite the smaller detection volume, electrochemical detection provides highly sensitive and accurate assessments of physicochemical processes occurring at the electrode site. As a result, electrochemical methods are largely unaffected by typical optical contaminants such as suspended solids or color-altering substances such as hemoglobin. This robustness proves invaluable in µPADs designed to process complex matrices such as whole blood, saliva, or environmental samples. However, careful consideration must be taken when choosing the placement of electrodes.[101]

3.1.4. Data-Rich

Electrochemical sensors, although lacking spatial resolution, provide a wealth of physiochemical information through the use of various interrogation techniques that can be performed on an electrochemical cell.[87,102] By varying the voltage, using time sampling, and performing frequency sweeps, chemical species can be distinguished based on their redox potentials[98] or different reaction mechanisms,[103,104] opening up the possibility of multiplexed detection.[105]

Having discussed the appealing features of electrochemical detection, it is important to acknowledge that the method is not without its own set of unique challenges. These include electrode surface fouling, the pronounced effects of nonspecific binding, and the intricacies of fabricating and modifying the electrodes themselves[106–108] (see Section 4).

3.2. Electrode Fabrication: A Benchmark of Current Technologies

Electrodes on paper are notoriously difficult to fabricate due to their porous and inherently rough texture.[109] Current fabrication methods mostly comprise techniques derived from printed electronics[110] and microfabrication,[111] although techniques specifically engineered for paper do exist[112] Below, we critically evaluate these technologies based on six factors (**Figure 6**): i) *Performance* of the electrode for electroanalytical sensing. High scores are given to materials with fast electron transfer kinetics or large porous electroactive surface areas. ii) A*ccessibility* of the equipment required for fabrication. Techniques requiring common and widely available tools score high. iii) S*calability* of the fabrication process for high-throughput manufacturing. iv) *Tunability* of the deposition method in terms of electrode materials, composition, surface properties, or morphology. This excludes the possibility of treating or modifying the material after deposition. v) *Compatibility* of the deposition process with different paper substrates, such as nitrocellulose or nanocellulose. vi) *Adaptability* of the deposition techniques to design changes, a key feature for rapid prototyping turnaround. It is worth noting that cost was not included as a standalone criterion, as its ranking is a combination of scalability and accessibility. A method that scores high

on either of these criteria typically ensures low fabrication costs. As an aside, the ecological impact of each fabrication technique is not discussed here but can be found elsewhere.[113]

3.2.1. Screen Printing

Involves pushing a paste or ink through a stencil pattern. Given its well-established use in the fabrication of disposable electrochemical sensors,[114] it emerged as the preferred method for the first electrochemical μPADs,[88,89] and remains the most widely used approach to date.[115–118] Whilst each design requires its own stencil, hindering rapid design exploration,[114] the method is highly scalable and applicable to a wide range of substrates.[119] The commercial availability of conductive pastes, including carbon,[88] gold,[120] platinum[121] or even Ag/AgCl,[122,123] coupled with the ability to incorporate additives,[118] makes screen-printing particularly appealing for multi-material electrode system in μPADs.[116] However, the presence of binder in the pastes can hinder electron transfer kinetics[124] and, unmodified, offer limited electroactive areas due to their planar structure.[125,126]

3.2.2. Inkjet Printing

Dispenses droplets of conductive inks from a piezoelectric printhead.[127] This method is feasible at an industrial scale, and also exists in benchtop formats, allowing rapid transfer of electrode design to physical devices.[110,128] Many ink materials have been developed, including gold,[109,129,130] silver,[109,129] and carbon nanotubes,[131] enabling fully-printed sensors[132] and the deposition of reagents and biomolecules.[127] However, ink formulation is challenging and laborious, requiring careful optimization of fluidic properties.[133] In addition, many materials require a sintering step,[129] which might be incompatible with the μPAD substrate. A significant limitation is that many inks are formulated primarily for plastic substrates, overlooking the unique properties of paper (such as wicking and porosity), as well as the specific requirements of electrochemical sensors, (e.g., avoiding the use of reactive silver inks). Typically, this results in moderate electrochemical performance,[109,129] but the development of dedicated inks could provide significant improvements.[131]

3.2.3. Metal Sputtering

Evaporates a metallic target onto paper via a mask. It allows the deposition of pure metallic gold, platinum, or silver electrodes, providing the high-performance and well-established functionalization pathways of traditional metal electrodes.[134–137] However, the high cost associated with sputtering equipment, as well as the limited throughput of low-pressure deposition and the need for masks limit the widespread adoption of this method for disposable μPADs, both in manufacturing and in academic environments for prototyping.[138]

3.2.4. Pencil Drawing

The practice of drawing with a pencil on paper is universal and allows for the creation of conductive graphite composite traces.[103,139] Despite the simplicity of the process, these electrodes are effective for the electrochemical detection of relevant small molecules,[140,141] and functional sensors can be conceived purely through multi-material drawing.[142] Although pencils offer little control over the graphitic electrode material, doping[143] and surface modifications that improve biosensing capabilities are possible.[141,144] Despite the pedagogical appeal of this method, its manual, poorly reproducible, and slow nature makes it unsuitable for sensor production, despite efforts to automate the process.[145]

3.2.5. Laser Pyrolysis

Employs a laser engraver to carbonize a substrate into a conductive graphitic material.[146] Originally developed for polyimide plastics, this highly scalable process has recently been extended to a wider range of materials,[147,148] including cellulose paper.[149–152] Electrodes fabricated by this method exhibit excellent electrochemical properties owing to their porous morphology and active graphene surface.[153–155] However, the method has limited control over material composition, which can only be modified by adjusting the laser atmosphere,[156] or by using metal-containing pretreatments.[157,158] In addition, its efficiency is closely tied to the substrate used, and it is not universally compatible; for example, nitrocellulose is unsuitable because it thermally decomposes at common carbonization temperatures.[159] The growing popularity of this fabrication method can be attributed to the widespread availability of CO_2 lasers, even in resource-constrained regions.[160] Moreover, its digital and reagent-free nature streamlines the pattern of electrode designs on demand.[161]

Among these methods, screen printing, inkjet printing, and laser pyrolysis stand out as being highly suitable for high-throughput manufacturing. The latter two are well suited for rapid prototyping. Laser pyrolysis, in particular, is attractive due to the wide availability of fabrication equipment and its potential for rapid scale-up. On the other hand, metal sputtering and pencil drawing are more niche-oriented, filling opposite ends of the spectrum regarding accessibility and electrode quality. In summary, each technology has its own set of advantages and limitations; there is no one-size-fits-all solution, and all have room for improvement. The ideal choice will ultimately be dictated by the specific application and the intended environment in which it will be used.

3.3. Selected Examples of Capillary-Driven Paper Electrochemical Assays

Innovations combining paper-based microfluidics and electrochemical detection are emerging and show consistent progress. A significant portion of this research has centered on creating devices for affinity-capture immunoassays,[97,135,162–168] with the aim of improving quantification. Multiplexed detection has also gained attention, leveraging the paper's capillarity to distribute the sample to sensors in parallel.[169–172] Notably, electrochemical detection has opened new applications beyond the reach of colorimetric readouts, finding use in continuous flow sensors for paper-based chromatography[137,173,174] and flow injection

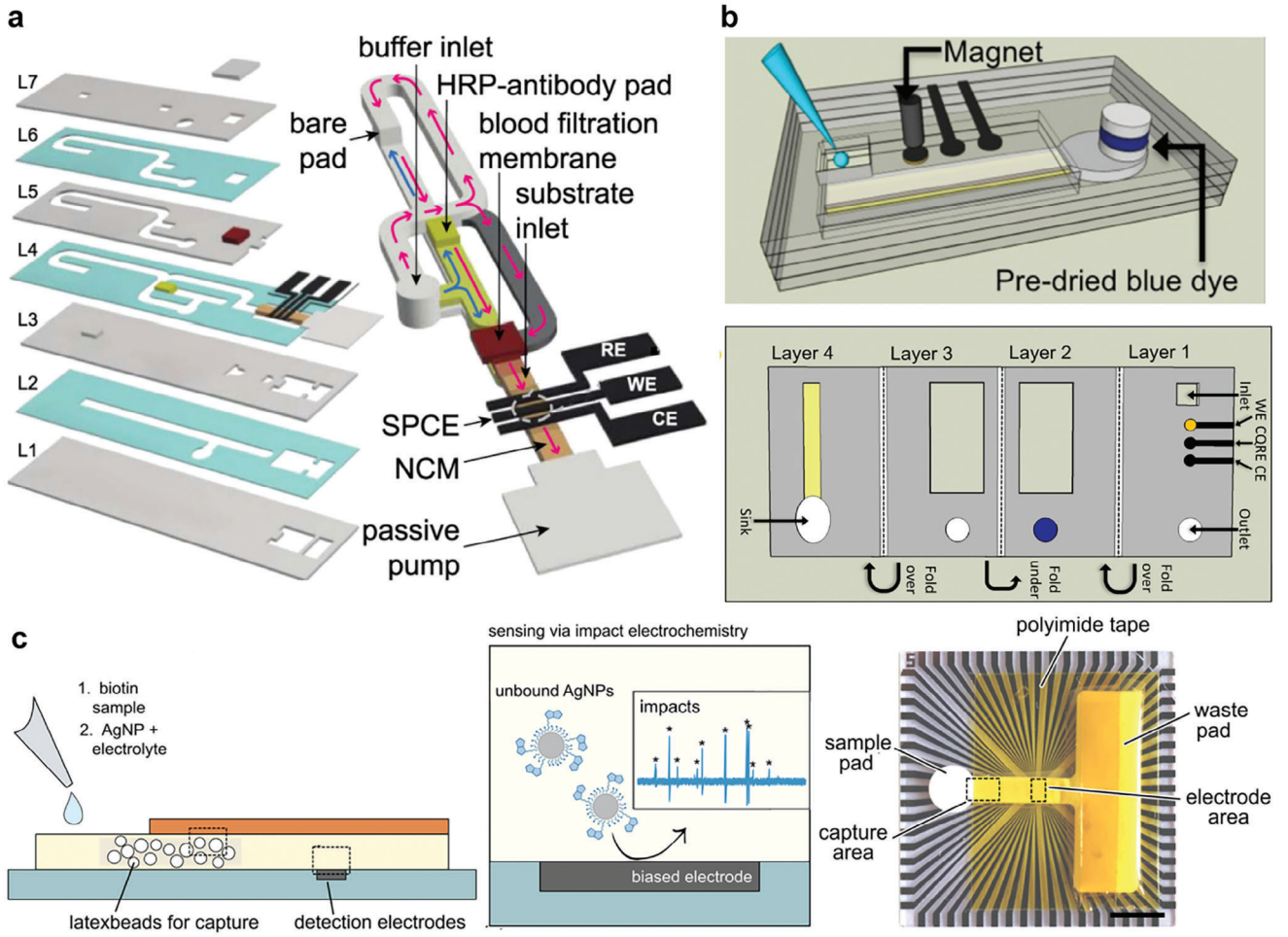

Figure 7. Selected examples of electrochemical μPADs. a) A serology test using a screen-printed electrode contacted with a nitrocellulose strip. The various reagents for the enzyme-linked immunoassay are delivered sequentially through the intricate design of paper channels. Adapted with permission.[178] Copyright 2021, American Chemical Society. b) An antigen immunoassay using magnetic capture and nanoparticle signal amplification. Adapted with permission.[179] Copyright 2016 American Chemical Society. c) A proof-of-concept device for quantification of unbound nanoparticles via single-impact electrochemistry. Detection is performed using micropatterned external Pt electrodes. Adapted with permission.[180] Copyright 2022, American Chemical Society.

analysis.[103,175–177] Below, we highlight some of the standout platforms that demonstrate the versatility and potential applications of these devices (**Figure 7**).

Recently, Klunder et al. introduced external electrodes made of conductive carbon particles mixed with binders and shaped by thermoforming or screen-printing for use in paper-based analytical devices.[126,181,182] They first performed electrochemical flow injection analysis of caffeic acid in beverages,[176] and then moved to a more sophisticated device tailored for immunoassays. Using a multilayer construction, they designed an intricate network of paper channels to filter the sample and deliver various reagents to a lateral flow strip in contact with the external electrodes above the capture zone (Figure 7a). They demonstrated their platform for antigen[183] or antibody[178] testing, with the sample, rinsing, and amplification reagents being delivered sequentially in a passive way, enabling an enzyme-linked immunoassay with electrochemical readout. While this platform represents a significant contribution toward integrated devices, its application has been limited to spiked or lab-cultured samples and has yet to be used with clinical samples.

In an effort to overcome some of the shortcomings of electrochemical μPADs used for immunoassays, Scida et al. created a foldable paper device with integrated screen-printed electrodes (Figure 7b).[184] Specifically, the target analytes were labeled with antibody-functionalized silver nanoparticles[185,186] and captured using magnetic particles. Capture was enabled by a magnet placed behind the electrode, which also served to concentrate the immunocomplex near the paper-electrode interface. The silver nanoparticles offered not only robust signaling (compared to enzymes[187]) but also strong signal amplification through passive galvanic dissolution, induced by a thin coating of gold over the screen-printed carbon electrodes.[179] This approach demonstrated low nanomolar sensitivity for the detection of heart failure biomarkers in undiluted clinical serum samples.[162] It is worth noting that while the detection pathway was highly sensitive to traces of serum, this could be mitigated by adequate washing.[188]

Nevertheless, the capture step presented challenges, as magnetic microparticles tended to clog the (micron-sized) pores of the paper.[189,190]

The coupling of capillary flow and electrodes also opens the door to transformative ways of quantifying nanoparticles. Weiss et al. showed that a paper channel contacted with external micropatterned Pt electrodes enabled the detection of nanoparticles by single-impact electrochemistry (Figure 7c).[134,180] By carefully monitoring the frequency of collision events, they were able to quantify the size or concentration of silver nanoparticles, even after rehydration of predried particles at the channel inlet.[134,191] Building on these promising results, they developed a competitive assay using biotin as a model analyte and incorporating a streptavidin capture zone, achieving detection limits below 10 pM in the buffer.[180] The same team also reported single-impact detection of nanoparticles using low-cost screen-printed technology.[192] Whilst experiments were performed under idealized conditions, their approach establishes the groundwork for an innovative approach to capillary-based electrochemical biosensing and demonstrates a remarkable application of single-impact electrochemistry, an electrochemical method traditionally limited to fundamental studies[193]

These platform technologies attest to the dynamic evolution of the field and highlight both the potential and challenges of developing electrochemical μPADs. Yet the construction and fabrication of these devices are significantly more complex than their colorimetric counterparts, and the benefits do not always warrant the added complexity. Most devices are built around a specific bioassay but often do not consider the interplay between the electrode and the capillary flow and how this might affect the design itself. To simplify device designs and take full advantage of electrochemical detection, a holistic approach that includes both electrode material engineering and bioassay development is essential.

3.4. Hitting a Brick Wall: Integrating Paper-Based Electrodes with Capillary Flow

A major challenge of integrated electrochemical μPADs is that some of the most common electrode fabrication technologies, such as screen printing, metal sputtering, and pencil drawing, impede capillary flow. Since they sit on the paper surface and remain in contact with only a fraction of the liquid flowing through the paper, impermeable electrodes restrict possible device architectures and result in reduced detection efficiencies.[154] As a result, most paper-based electrochemical devices do not leverage capillary-driven assays, and instead use paper simply as a low-cost and disposable substrate.[194] Alternatively, many have opted for the approach of using external electrodes pressed against a paper channel.[175,195] This offers a simpler approach compared to embedding impermeable electrodes since depositing electrodes on the paper substrate offers minimal benefit over external electrodes unless they seamlessly integrate into the paper's porous matrix. Given these practical limitations, the applications of electrochemical μPADs, especially in vertical flow (flow-through) formats, remain severely limited. Such configurations are highly valued in optical-based devices due to their simple construction, rapid operation, and multiplexing capabilities (see Section 2.4).[196] The attempts to realize electrochemical vertical flow assays with screen-printed or sputtered electrodes have relied on complex designs such as stacked rotating discs,[165] or hybrid systems combining lateral and vertical channels to bypass the electrodes.[164]

In an effort to improve the integration of electrodes with the capillary flow on paper, Hamedi et al. presented a platform combining wax-printed channels and drop-cast conductive inks (**Figure 8a**).[197] This method allows the electrode to be fully permeable to capillary flow, opening up novel electrofluidic applications. For example, they demonstrated a device where capillary flow triggered a resistive heater for a predetermined time by interconnecting electrodes.[197] However, a major drawback of this platform is the inability to pattern the electrodes, which are confined within the wax channels. This limitation prohibits the fabrication of electrochemical sensors on a single sheet of paper (Figure 8b), although we expect that inkjet printing may offer a solution here.

In a similar vein, recent advances in laser-induced pyrolysis of cellulose provide a unique pathway for the patterning of electrodes that integrate seamlessly with the paper matrix.[148,154] We have recently demonstrated the potential of combining wax lamination with laser-induced pyrolysis to fabricate paper-based electrofluidic devices, granting full control over fluidic and electronic patterns (Figure 8c).[154] A key aspect of this approach is that the pyrolyzed cellulose paper retains its fibrous and hydrophilic nature (Figure 8d), facilitating the fabrication of electrode materials capable of driving capillary flow.[154] This platform enables the construction of capillary-driven devices with electrochemical readout without the constraints commonly imposed by electrode placement. For instance, this versatility allows the development of flow-through electrochemical immunoassays that retain the simplicity of commercial vertical-flow colorimetric devices (Figure 8e).[154,196] However, while these proof-of-concept devices have demonstrated the applicability of these paper-like laser-pyrolyzed electrodes, further development is essential to optimize surface functionalization chemistry, extend shelf life, and validate these devices in clinical settings.[154,198]

Taken together, these platforms underscore the critical importance of integrating electrodes with capillary flow. This approach not only maximizes detection efficiency,[177] but also unlocks new device functionalities.[154,197] By taking full advantage of passive capillary-driven systems, it marks a shift toward simplified device construction, away from the need for actuation, and reimagining the electrode as a fundamental, integrated component of the device, rather than an add-on.

4. The Way Forward

Recent advances in the field of electrochemical paper-based microfluidics have introduced innovative and more efficient ways of conducting capillary-driven bioassays. Nevertheless, there remains considerable room for improvement and many untapped opportunities. The avenues for further development span multiple aspects across different length scales: from the molecular engineering of the surface to electrode-scale operation and signal transduction, all the way to device-scale considerations for the development of integrated, user-friendly diagnostic tests.

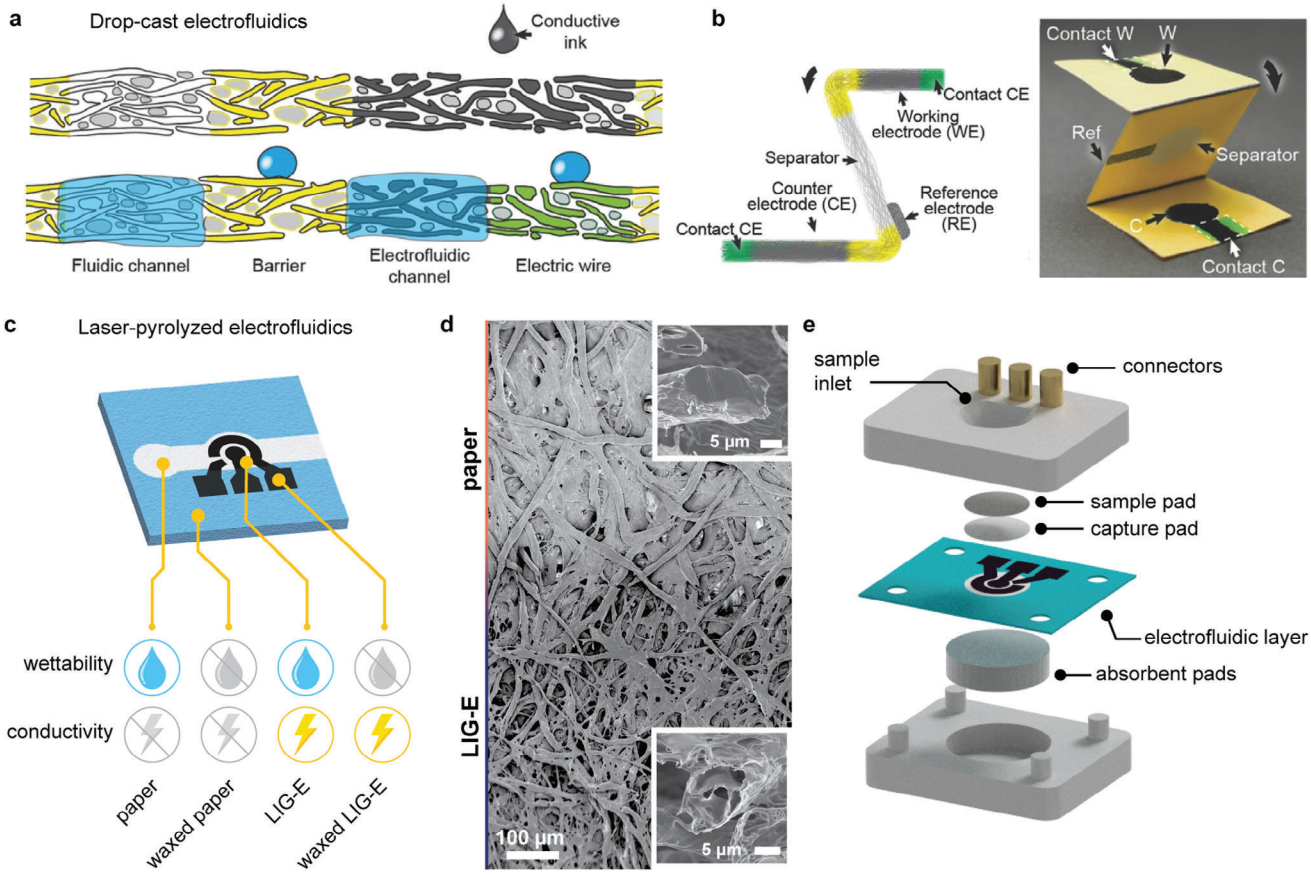

Figure 8. Paper-embedded electrofluidic platforms. a) Channels and electrodes are fabricated through a combination of wax printing and drop-cast conductive inks. b) Three-layer electrochemical sensor fabricated with drop-cast electrodes. Adapted with permission.[197] Copyright 2016, Wiley-VCH. c) Laser-pyrolyzed electrodes combined with wax channel lamination to pattern electrode and fluidic channel into cellulose paper. d) Scanning electron micrograph of cellulose paper (top) and the laser-pyrolyzed electrode (LIG-E, bottom), showing the top view and cross-section of the fibers (insets). e) Vertical flow immunoassay based on laser-pyrolyzed electrofluidic layer for electrochemical detection. Adapted under the terms of the CC BY-NC 4.0 license.[154] Copyright 2023, The Authors.

4.1. Boosting Performance Through Molecular Surface Engineering

Microfluidic systems rely on micrometer-scale fluidic networks for reagent transport and bioassay operations. In these systems, the large surface-to-volume ratios make surface engineering all the more critical, as it directly impacts capillary flow, surface-analyte interactions, and, in the case of electrochemical detection, signal transduction. In this context, moving toward electrodes embedded into paper means that the electrode becomes an integral part of the microfluidic network. As such, its surface properties, which influence wetting, capture, and detection, must be carefully considered throughout the assay development process.

4.1.1. Surface Fouling and Reactivity

The high surface area of porous and permeable electrodes is advantageous for enhancing electrochemical signals, but it also presents challenges. These include mitigating nonspecific binding and electrode fouling, which will affect the electrochemical performance. To address these challenges, researchers are continuously developing new methods, such as protein-nanoparticle composite coatings or electrochemical treatments, to mitigate fouling and improve the reliability of electrochemical sensors.[106,107,199]

Furthermore, highly reactive electrode surfaces are a double-edged sword: they benefit analyte detection through fast electron transfer rates but also act as an effective catalyst for water electrolysis. This catalytic activity narrows the working potential window and can be problematic when detecting analytes that require large oxidation or reduction potentials[200] However, the working potential window is not immutable and can be engineered by modifying surface topology and chemistry.[200,201]

Storage stability of the electrode, strongly influenced by its surface, is also an essential requirement for transitioning technology from the laboratory to the field. Although often overlooked in the scientific literature, loss of electrode performance is a significant concern and is particularly challenging for carbon-based electrodes that are highly prone to surface contamination.[198,202] Treatment with oxygen plasma prior to storage can help prolong activity retention;[154] however, further efforts are required to improve these figures to levels suitable for commercialization (typically >12 months).

4.1.2. Nanomaterial Composites

Surface engineering of an electrode involves more than just mitigating degradation or fouling effects; it can also be used to introduce new functionalities and improve performance. In particular, the incorporation of nanoparticles onto electrodes has had a transformative effect on the field of electrochemistry, leading to facilitated biofunctionalization, increased signal strength, or novel signal transduction pathways.[187,203] Post-treatment modifications, such as electrodeposition or drop-casting, have been traditionally applied to decorate electrodes with nanoparticles (e.g., gold), with the goal of boosting performance or acting as anchors for biofunctionalization.[204,205] However, such post-treatment approaches involve additional, complex steps that are poorly scalable. Therefore, the added benefits must be carefully weighed to justify the increased complexity. On the other hand, preincorporation of nanomaterials in the electrode precursor, e.g., in the conductive ink, offers an attractive path toward nanocomposites without compromising fabrication workflows.[130,131] For example, the addition of metal salts into polymer substrates forms graphitic electrodes with embedded metal or metal oxide nanoparticles upon laser-induced pyrolysis.[158,206] Still, these examples have thus far focused mostly on composite material formation, and their promise has not yet been demonstrated in complex biosensing assays.

4.1.3. Biofunctionalization

Biochemical functionalization of electrode surfaces is complex when applied to paper-based systems. This complexity arises primarily from the difficulties associated with rinsing unreacted reactants between each process step, affecting both the scalability of device fabrication and introducing variability across devices.[108] Current functionalization techniques remain labor-intensive and time-consuming, often requiring multiple steps and lengthy incubation times.[207] To overcome these limitations, a prevalent method involves using a separate nitrocellulose capture layer on top of or upstream from the electrode.[154,178,208] This approach is especially compelling for permeable electrodes, allowing for layer stacking and flow-through operation.[154] Nonetheless, direct electrode functionalization has its benefits, especially in the direction of label-free affinity biosensors. These biosensors require direct surface binding for accurate quantification, which is achieved by assessing electrode surface crowding.[97,209] Accordingly, simplified, one-pot functionalization methods are urgently needed to bring the capabilities of paper-based transducers to the forefront of electrochemical detection schemes.

4.2. Exploiting Electrodes to Their Full Potential

Surface engineering is crucial but not the only determinant of electrochemical biosensor performance. Of equal importance is how the electrode is used and how it operates within the biochemical environment to generate a signal that is specific and sensitive to a target analyte.

4.2.1. Assay and Signal Generation

Current electrochemical sensor technologies excel at detecting small molecules or enzymes, as exemplified by the glucose sensor.[94] However, beyond the detection of redox-active small molecules or enzymatic substrates, the translation of affinity-based assays (for protein or nucleic acid sensing) into electrochemical formats has proven to be a formidable challenge.[210,211] Currently, most electrochemical signaling methods are derived directly from established colorimetric assays, such as those using enzyme labels[212] or gold nanoparticles,[213] and are often difficult or unsuitable for translation to paper-based sensors. This is mainly due to long incubation times and low detection efficiencies. With the need for additional detection or amplification reagents, current electrochemical immunoassays still represent a significant increase in operational complexity compared to rapid diagnostic tests.[105,187]

There is a need for labeling and signal transduction strategies that are not only tailored for electrochemical readout but are also compatible with the inexpensive electrode materials found in paper-based devices. This is a significant challenge since detection chemistries are often limited to specific electrode materials, limiting their broader applicability. However, improved methods are emerging, such as harnessing the catalytic potential of gold nanoparticles in tandem with ferricyanide reporters,[208] both of which are well-established components of low-cost biosensors[96] On the other hand, label-free methods based on impedance, whilst providing ultralow detection limits, have not yet been translated into clinical environments.[209,214] Nonspecific binding and surface blocking remain significant limitations as they directly affect signals, especially in complex matrices. The integration of label-free sensing with flow-based devices, which has not yet been explored, may offer a way for paper-based devices to mitigate these issues in the future. Overall, even though most new techniques focus on lowering the detection limit, signal transduction methods that are simple, universally applicable, and robust remain elusive.

4.2.2. Multi-Purpose Electrode Usage

Beyond electrochemical sensing, electrodes have broader applications in diagnostic testing, for example in, electrophoretic separations,[215] electroactuated flow valves,[216] and Joule heating,[217] all of which have been demonstrated on cellulose paper. The modularity of these multifunctional electrodes allows for the assembly of customizable toolkits, whose configurations can be tailored for specific assays or applications. Moreover, although not yet explored, electrodes can be patterned on both sides of a paper substrate, allowing for interesting arrangements, such as placing a heater directly underneath an electrochemical sensor. Also, electrodes could serve multiple purposes depending on how they are driven, an aspect that appeals to the ability of microcontrollers to reconfigure electrode functions through programming. For example, the counter electrode of a printed sensor could act as a resistive heater during incubation.

Looking ahead, we envision self-contained devices that incorporate all the necessary electronics to perform the assay, including paper-embedded batteries[218] and near-field commu-

nication antennas,[72,81,219] although complex circuitry on cellulose is a long way off.[85,220] In addition, real-time monitoring capabilities for dynamic control of assay conditions are still underdeveloped but would turn electrodes into feedback components that can dynamically optimize assay conditions. Combining these functionalities with electrochemical detection offers the prospect of a single device that leverages paper-embedded electrodes for sample preparation, timing, and incubation. This is particularly promising for integrated nucleic acid testing, which currently requires separate "off-chip" devices for tasks such as sample extraction or elevated temperature incubation.[221]

4.2.3. The Need for Benchmarking

A fundamental aspect of sensor development is comparison with established methods.[222] For colorimetric and fluorescence assays, well-established methods such as enzyme-linked immunosorbent assay (ELISA) or PCR, validated over decades, serve as benchmarks.[223] Although not perfect, they provide a gold standard for new research. For example, the efficacy of novel fluorescent nanoparticle labels in lateral flow assays is typically evaluated against gold nanoparticles.[49] Similarly, the biotin-avidin system provides a metric for assessing analyte-agnostic performance. In contrast, electrochemical affinity-based biosensors lack a standard reference, rendering comparisons between systems or labeling strategies meaningless,[187,210,224] notwithstanding the fact that electrochemistry adds a layer of complexity with electrode material and functionalization affecting detection. In this regard, commercial screen-printed electrodes frequently serve as a reference electrode material.[225] With the proliferation of paper-based systems, the development of a standard and accessible electrode fabrication method for benchmarking would greatly facilitate development efforts.

New studies often combine advances in electrode materials, assay, and signal generation. Evaluating the contribution of each of these elements is challenging. Ideally, innovative methods should be evaluated in a stepwise fashion against prior established systems (incremental innovation). This workflow not only improves our understanding of these sensors but also facilitates the widespread adoption of new electrode materials or signaling pathways into other systems. Similarly, electrochemical tests that can leverage existing LFIA platforms, either as an add-on to existing tests or by using some of their components, are well positioned for rapid translation and production.[208,226]

4.3. Toward Agile Platforms for Smart Integrated Tests

If we consider the assembly of electrofluidic components into a diagnostic device, significant challenges remain. These are primarily related to complete assay integration and the robustness of these devices in point-of-need applications. In this context, the development of platform technologies that harness digital tools for their fabrication and operation offers opportunities to accelerate progress through widespread dissemination and to improve test reliability via dynamic assay monitoring.

4.3.1. Sample-to-Result Testing

Assay integration is a critical yet often under-addressed aspect of diagnostic testing. While most research focuses on improving detection and quantification, end-to-end integration of the entire diagnostic workflow, from sample collection to result interpretation, is often overlooked. This consideration is particularly relevant in nucleic acid testing, where steps such as sample lysis and nucleic acid extraction currently require separate instrumentation.[221] As the field progresses toward point-of-care molecular testing, addressing the complexities of assay integration becomes increasingly urgent.

Toward this goal, paper-based microfluidic devices present a unique set of challenges and opportunities.[227] Because these devices operate passively by capillary action, the integration of multiple complex steps into a single device requires innovative designs to perform all steps in a predefined sequence.[228] While many steps in the sample-to-result diagnostic process have been successfully demonstrated in isolation on paper-based platforms,[65] their combination into a cohesive and easy-to-use system remains to be seen. Achieving this feat requires a thorough understanding of capillary flow dynamics and its interaction with electrodes.

Despite these challenges, there are promising avenues for innovation, with electrodes emerging as a compelling tool for streamlining testing operations. For example, cell lysis by electrochemically induced local pH changes shows promise for performing pretreatment, whilst requiring minimal footprint in a DNA analysis device.[229] The shift toward multi-step operations should aim to maintain the simplicity and robustness of lateral flow immunoassays. Indeed, the translation of paper-based tests to a clinical environment and in-the-field testing has proven to be a formidable challenge and one that grows exponentially with device complexity.[230]

4.3.2. Toward Smart Diagnostics Tests

Advances in low-cost digital technologies provide an untapped opportunity to improve point-of-care diagnostic tests which have traditionally relied solely on naked-eye endpoint readouts. Leveraging increasingly powerful microcontrollers and portable devices, including smartphones, we now have the ability to collect a rich array of data throughout the testing process. This data-driven approach, which should aim to maximize the quality and volume of information collected, could be incorporated to improve aspects such as device authentication, quality control, test reliability, and the ability to detect device malfunction or user error.[231–233]

In the field of paper-based microfluidics, we anticipate that dynamic data acquisition and monitoring will become increasingly prominent. Indeed, device reliability is often an obstacle to the clinical translation of low-cost diagnostic technologies.[230] Integrating decision algorithms into dynamic data acquisition could guide users through the test procedure, providing immediate feedback on test validity or malfunction.[234] This level of guidance could significantly improve test reliability, especially for complex bioassays that require proactive user operations.

Electrochemical, or more generally, electrode-based, sensors offer a prime avenue in this direction, given their direct interface with external readers and microcontrollers. Their small footprint allows for the implementation of multiple sensors throughout the device for comprehensive monitoring of variables such as capillary flow, temperature, and chemical environment. Going further, we could envision feedback mechanisms that can adjust test conditions in real-time, increasing test adaptability and precise assay control in challenging or unpredictable environments.

Looking ahead, we anticipate a future in which intelligent diagnostic tests operate dynamically, increasing reliability and enabling users to navigate the testing process with greater confidence. Such a dynamic testing approach also streamlines the integration of cloud-based resources, making tests more connected, actionable, and accurate.[235] This would extend the utility of diagnostic testing beyond simply providing a result and provide a transition to care pathways.

4.3.3. Digital Fabrication

Digital fabrication refers to the direct process of transforming computer-aided designs into physical objects.[236,237] These transformative fabrication tools, such as 3D printers and laser engravers, are becoming ubiquitous and revolutionizing the way we approach manufacturing. Digital fabrication labs are now accessible to the general public in over 100 countries, including low-resource areas.[160,238] The ability to share fabrication files digitally enables highly decentralized manufacturing that can be rapidly deployed globally, especially in contexts such as pandemics.[239] These tools, along with low-cost programmable microcontrollers, streamline the fabrication, assembly, and operation of low-cost functional devices. The main advantage of using these tools is the ability to customize designs on demand with fast turnaround times. In a research and development context, this greatly accelerates prototyping and device optimization. In addition, digital fabrication files and designs can be easily shared across the scientific community, fostering collaboration and accelerating progress.

For paper-based electrochemical devices, the most common fabrication techniques still require prefabricated stencils and specialized machinery. However, advances in laser engraving and inkjet printing for electrode fabrication offer real opportunities to create diagnostic test technologies that do not require specialized equipment or even laboratories for fabrication.[132,154] It is possible to envision a future where disease-specific reagents would be shipped and paper-based diagnostic tests produced at the community level, or even at home. Using parametric design files, these tests could be designed with the flexibility and versatility to adapt to different test formats and targets based on the needs of the community in any given location.

5. Conclusion

In conclusion, our analysis of the landscape of electrochemical paper-based microfluidics reveals a delicate balance between simplicity and sophistication. The benefits of electrochemical readouts in μPADs are undeniable and mark a significant step forward for a new generation of diagnostic tests that are quantitative and digitally connected. However, most development efforts have deviated from the hallmark attributes that made lateral flow immunoassays and the field of paper-based microfluidics successful diagnostic tools: their simplicity, cost-effectiveness, and ease of use. This trend is particularly evident from current state-of-the-art electrochemical μPAD technologies, which in comparison to their optical counterparts, lag in terms of design ingenuity, construction simplicity, and ease of operation. In this context, we have identified the integration of the electrode material with capillary flow as a critical obstacle, as it may impede the flow and add constraint and complexity to the device. To address this, recent innovations in paper-based electrofluidics have made significant progress by embedding porous electrode material directly into the porous paper network. This emerging approach, although still in its infancy, has set a compelling precedent. By integrating permeable electrodes seamlessly with paper, these platform technologies not only streamline device construction but also unlock novel functionalities through the synergy of capillary flow and electrode interaction. Such progressive developments suggest a vast, untapped potential in electrochemical μPADs for point-of-need diagnostic testing, offering advanced features like precise quantification, real-time monitoring, and enhanced connectivity, all while maintaining the foundational principles of simplicity and accessibility in device fabrication.

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Conflict of Interest

The authors declare no conflict of interest.

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electroanalytical devices, electrochemical sensors, laser-induced graphene, paper microfluidics, point-of-care diagnostics, printed electronics

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