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Origami-paper microfluidics device for rapid diagnostics in low-resource settings

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Abstract

For microfluidic platforms used for medical diagnostics, paper-based substrates offer a low cost, ease of access, and environmentally friendly solution. The combination of origami-paper microfluidics with sensing techniques such as colorimetry, fluorescence, electrochemistry, and surface plasmon resonance (SPR) has expanded their applications in point-of-care testing, rapid diagnostics, public health, and water quality and environment surveillance.

Main text:

Introduction

Microfluidics enables handling of micro-to-picoliter scale fluids in micrometer-sized channel networks,[1] with applications in chemical analysis, disease diagnostics, and single-cell studies. Due to their low cost, portability, availability, and eco-friendliness, microfluidic paper-based analytical devices (μPADs) offer advantages for resource-limited settings, defined here as environments where access to centralized laboratories, stable electricity, specialized equipment, and trained personnel is restricted. These systems exist in two configurations: two-dimensional (2D) devices employ thin and flat hydrophilic paper with hydrophobic-patterned fluidic paths; and three-dimensional (3D) systems, such as origami-paper microfluidics, incorporate vertically stacked paper layers for complex fluidic networks. This hierarchical architecture facilitates advanced fluid control and programmable routing for multi-step biological or chemical processes.

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In microfluidics, the processing and manipulation of fluid volumes through microscale channel networks have been integrated with other functionalities including automation, multiplexed analysis, and high-throughput screening. The requirement for minimal sample consumption are impactful for biomedical research, environmental surveillance, and chemical analysis. For instance, the integration of microanalytical methods with laser technology enables sensitive and high-resolution analyses with minimal sample input. The development of a silicon-based miniature gas chromatograph, scaled to one-third of conventional systems, marked the origin of lab-on-a-chip technology.[2] Microfabricated devices have been developed for high-throughput DNA sequencing, which integrated clone isolation, template amplification, and electrophoretic analysis into a single microfluidic circuit. As microfluidics applications continue to expand, there are increasingly specific demands depending on application requirements and manufacturing considerations, which extends to their material selection and design. Paper-based microfluidics can leverage capillary-driven flow to enable pump-free and power-free operation.[3] Advanced fabrication approaches including photolithography, wax printing, and screen-printing facilitate rapid prototyping and customizable design of paper-based microfluidics.

As a subset of paper-based microfluidics, origami-paper microfluidics are useful for point-of-need (PON) applications in resource-limited settings. Critical to their function is the alignment of ports and hydrophilic channels to form leak-free 3D fluidic pathways and reaction compartments upon folding. Among contemporary folding techniques, accordion method enables sequential layer alignment for integrating complex components, while T-folding involving substrate-centered layer folding is optimal for assays requiring sequential sample addition or stepwise analytical unfolding.[4] Folding introduces an additional spatial dimension, permitting the creation of more sophisticated channel architectures and advanced fluid control. Origami-paper microfluidics can operate multi-step protocols with enhanced fluid dynamic regulation, broadening the utility of paper microfluidic platforms in resource-limited settings.

Origami-paper microfluidics for point-of-care testing

Origami-paper microfluidics enable sensing applications through their geometrically multilayered architectures. These systems incorporate colorimetric assays, leveraging analyte-specific chromogenic reactions for visual readouts. Pre-deposited reagents within folded paper channels facilitate analyte detection, as demonstrated in a device for urine adulteration screening that integrated picric acid, 3,5-dinitrobenzoic acid, and Nessler's reagent for semi-quantitative analysis. In another example, colorimetric enzyme-linked immunosorbent assay (ELISA) is combined with origami-paper device to enable human immunodeficiency virus

(HIV) diagnosis, incorporating a viscosity-regulated, fluidically controlled timer to automate washing and development steps.[5]

Electrochemical origami-paper microfluidics demonstrate enhanced sensitivity compared to colorimetric approaches. The initial microfluidic paper-based electrochemical device, developed for glucose, lactate, and uric acid detection, established critical device designs and operating principles despite its 2D architecture. Examples include an origami-based electrochemical aptasensor for label-free detection of epidermal growth factor receptor (EGFR) with 5 pg/mL sensitivity, achieved through amino-functionalized graphene, thionine, and gold nanoparticle modification.[6] This platform leverages aptamer advantages including minimal sample requirements and microfluidic integration. Another group incorporated inkjet-printed chemiresistive biosensor arrays with silver leads and carbon nanotubes for multiplexed biomarker detection.[7] Such origami cyto-devices enable translation of cytological/histological analyses into adaptable, cost-effective and rapid-test platforms.

Origami-paper microfluidics have been integrated with fluorescence detection to develop portable systems. One group employed quantum dot (QD)-functionalized molecularly imprinted polymers (MIPs) on paper substrates for phycocyanin detection, where target binding induced fluorescence quenching through energy transfer.[8] Another group used smartphone cameras as tool-free fluorometric detectors. This approach enabled origami-paper devices for alkaline phosphatase quantification using smartphone-captured fluorescent images and RGB analysis,[9] as well as cortisol detection via MoS_2 nanosheet-mediated Förster Resonance Energy Transfer (FRET) coupled with smartphone imaging. The latter system achieved sweat collection, transport, and detection within 25 min using a wearable microfluidic patch, demonstrating real-time physiological monitoring.

While origami-paper microfluidics can function as a standalone analytical platform, its integration with lateral flow assays (LFAs) facilitates *in situ* detection in resource-limited settings. This combination is valuable for molecular diagnostics, where rapid pathogen identification informs therapeutic interventions. One research group achieved cost-effective and multiplexed DNA-based malaria detection through origami-paper microfluidics, where loop-mediated isothermal amplification (LAMP) products were transferred via manual whole blood pumping to lateral flow strips functionalized with species-specific capture ligands. [10] The platform demonstrated 98% accuracy in a double-blind clinical evaluation within 50 min.

Wastewater-based epidemiology (WBE) serves as a powerful surveillance tool for monitoring infectious disease transmission dynamics.[11] Recent advances in this application area include an

integrated paper-origami device for SARS-CoV-2 detection in wastewater, incorporating a glass fibre disc for RNA adsorption, a channel for elution buffer distribution, and multiple paper discs for loading samples. This system coupled LAMP amplification with CRISPR/Cas12a-mediated target recognition, followed by paper-based lateral flow detection, which was a more complex but illumination-independent alternative to fluorescence readouts. Our group yielded a field-deployable multiplexed WBE platform capable of pathogen detection from raw wastewater within two hours,[12] demonstrating high-resolution monitoring in resource-limited settings. Such paper microfluidic designs enable scalable wastewater analysis from community-level to building-specific surveillance, offering potential as pandemic early-warning systems.

Looking ahead

Origami-paper microfluidics has emerged as a promising platform for rapid diagnostics in low-resource settings. Its cost effectiveness and minimal infrastructure requirements make it attractive for PON diagnostics. However, several challenges remain before they can achieve widespread application. Future advances should focus on improving their sensitivity, specificity, robustness, and digitalization. One direction for improvement is the incorporation of functional nanomaterials. Catalytically active nanomaterials (e.g., palladium- and iron-based nanozymes), can catalyze chromogenic reactions on paper substrates, thereby amplifying colorimetric signals and lowering detection limits. Nanocarrier-based signal amplification systems capable of loading numerous reporter molecules can further enhance sensitivity.

Advances in synthetic biology offer opportunities to improve molecular recognition components. Although antibodies are widely used in current diagnostics, they are limited by high costs, limited stability, and complex manufacturing. Engineered recognition elements (e.g., aptamers, nanobodies) provide attractive alternatives. These molecules are optimized through directed evolution to achieve high affinity and specificity while maintaining stability under challenging environmental conditions. They can be produced through cell-free synthesis to enable scalable and economical manufacturing. Their integration into origami-paper microfluidics may enhance diagnostic reliability in low-resource settings.

It is essential to develop standardized signal readout systems for target quantification. Equipped with high-resolution cameras, optical sensors, and wireless connectivity, smartphones can function as portable analytical readers that capture and analyze colorimetric signals generated by origami-paper microfluidics. When combined with customized mobile applications, these systems can automate image acquisition, signal processing, and result interpretation, enabling

user analytics with minimal training. Standardized image-analysis algorithms will ensure reproducibility and accuracy across different operating conditions.

Embedding traceable identifiers (e.g., barcodes, QR codes) within origami-paper microfluidics enables user-friendly data management and quality control. When connected to cloud-based databases and wireless communication networks, results are transmitted, stored, and analyzed in real time. Such connectivity may transform origami-paper microfluidics from isolated diagnostic tools into components of health monitoring systems. The incorporation of machine learning and artificial intelligence may enhance analytical capabilities. Computational methods can improve signal interpretation by reducing noise, identifying subtle patterns, and integrating multidimensional datasets. Data-driven models trained on large datasets may support predictive analytics, enabling early risk assessment and responsive public health interventions

Another application of origami-paper microfluidics is its integration with WBE for environmental surveillance. Wastewater contains aggregated biological signals (e.g., pathogens, metabolic biomarkers) from entire communities. Monitoring these signals provides a non-invasive means of assessing population health and identifying early signs of disease outbreaks. Unlike traditional wastewater analyses that rely on centralized laboratories and bulky instrumentation, origami-paper microfluidics perform filtration, analyte detection, and signal generation within portable devices. When coupled with smartphone-based and cloud-connected data analysis, such systems could support near real-time environmental surveillance.

The integration of origami-paper microfluidics, nanotechnology, synthetic biology, machine learning, and artificial intelligence will promote the application of PON diagnostics. Advances in manufacturing (e.g., industrial printing, automated assembly) may further reduce production costs and accelerate global adoption. With these advancements, origami-paper microfluidics may evolve from simple rapid tests into diagnostic networks capable of providing real-time information on individual health and population disease dynamics.

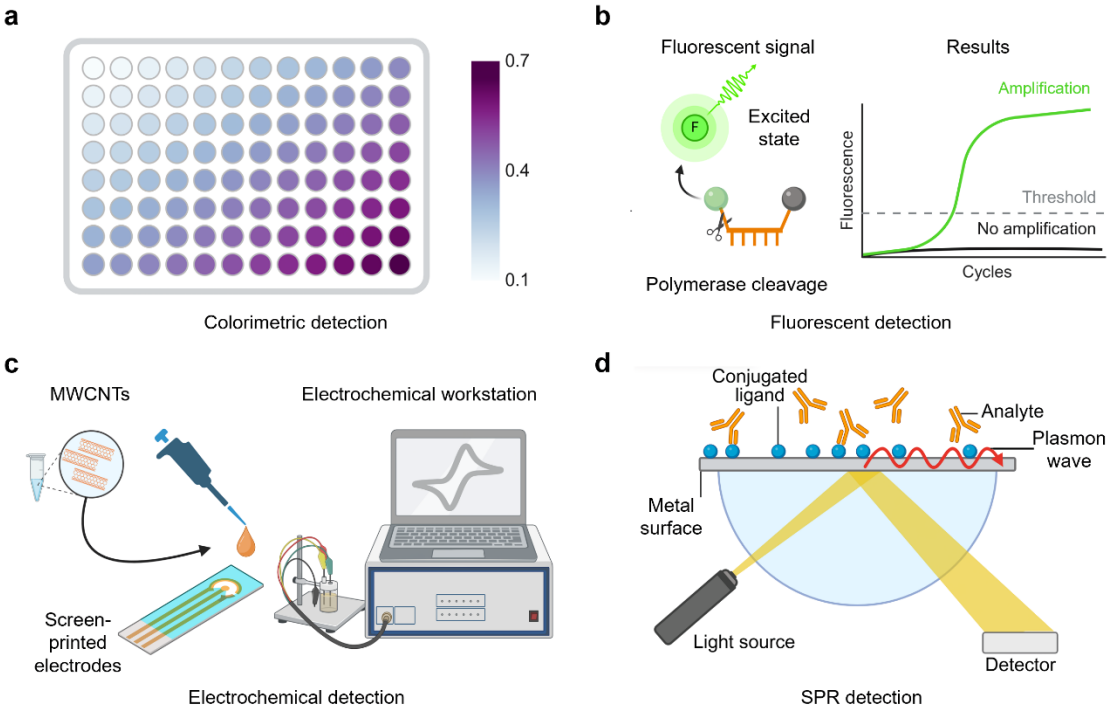


Figure 1. Detection methods employed in origami-paper microfluidics. (a) Colorimetric detection. (b) Fluorescent detection. (c) Electrochemical detection. (d) SPR detection.

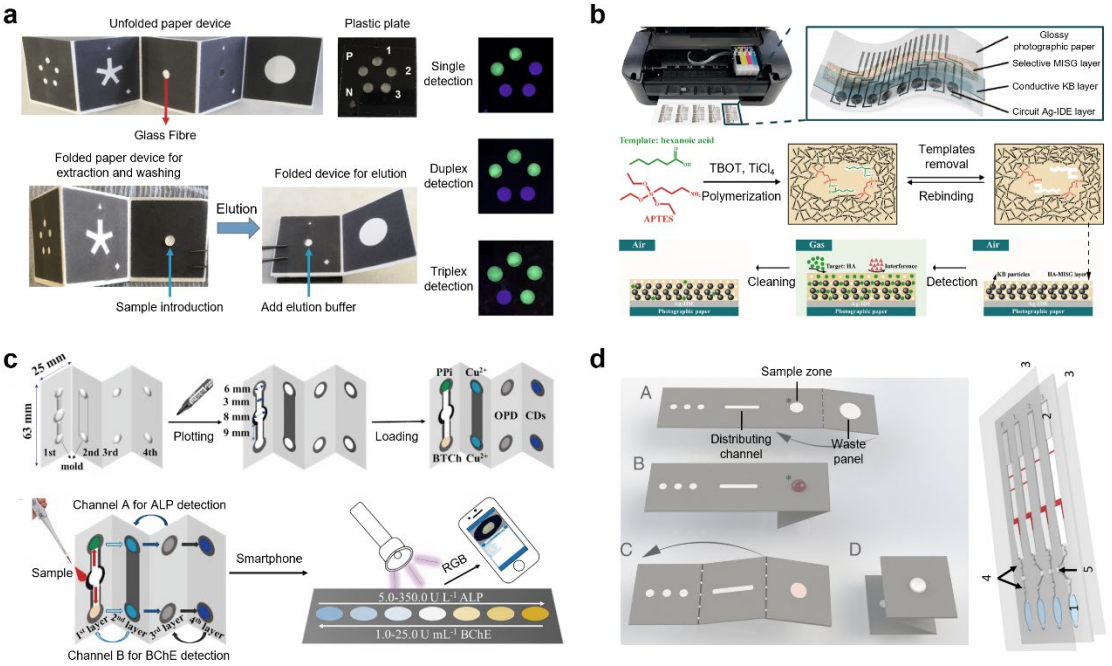


Figure 2. Representative applications of origami-paper microfluidics. (a) Semen-based veterinary diagnosis of bovine infectious diseases using DNA microfluidics.[4] (b) Inkjet-printed chemiresistive sensor array employing molecularly imprinted sol-gel materials.[7] (c) 3D origami paper device for ratiometric fluorescent detection of alkaline phosphatase and butyrylcholinesterase.[9] (d) Low-cost paper microfluidics for malaria DNA diagnostics.[10]

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Author contributions

P. Y. and Z.Y. conceived and wrote the manuscript. All authors reviewed and commented on the manuscript.

Declaration of interests

The authors declare no competing interests.

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