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Introduction to 'Paper-Based Point-of-Care Diagnostics'

Daniel Citterio, [a] Thiago R. L. C. Paixão [b] and William Reis de Araujo [c]

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Paper-based point-of-care (POC) diagnostics are increasingly becoming vital tools in expanding global access to healthcare. Their affordability, portability, and simplicity make them ideal for use in low-resource settings, remote areas, and decentralized testing environments. This themed issue of *Sensors & Diagnostics* explores recent advancements in this growing field, emphasizing innovative strategies that enhance sensitivity, specificity, and user-friendliness.

Among the contributions, Hasan *et al.* (**https://doi.org/10.1039/D4SD00262H**) present a comprehensive review of biosensing technologies for the early detection of dengue virus (DENV). Dengue continues to pose a significant public health threat in tropical and subtropical regions, with symptoms ranging from mild to severe and life-threatening complications, such as dengue haemorrhagic fever. Given the limitations of conventional diagnostic methods—such as cross-reactivity, cost, and complexity—this review highlights how paper-based biosensors can offer rapid, sensitive, and cost-effective alternatives for antigen and antibody testing. The authors critically examine current approaches and provide insights into emerging technologies with potential for field-deployable, scalable diagnostics that could mitigate disease spread through timely intervention.

Another paper by Khachornsakkul *et al.* (**https://doi.org/10.1039/D4SD00361F**) introduce a headspace paper-based analytical device (hPAD) for ammonia detection in human biological samples. This cleverly designed platform leverages a gas-phase reaction between ammonia and copper sulfate to yield a vivid color change, eliminating many challenges associated with direct liquid-phase measurements—such as interference from sample pH or color. The assay, which requires no heating and produces results within minutes, demonstrates excellent linearity, precision, and selectivity. It showcases how minimal instrumentation combined with smartphone-based readout can provide a robust and low-cost alternative for clinical or environmental applications.

Pushing the boundaries of paper-based diagnostics into the digital domain, Özarslan *et al.* (**https://doi.org/10.1039/D4SD00348A**) report a pioneering integration of colorimetric paper assays with synthetic imagery and YOLOv8—an advanced object detection algorithm. Targeting the often-overlooked issue of male infertility, the authors develop a fertility test that leverages reaction zones on paper to assess sperm count and pH, with images captured and interpreted *via* smartphone. Despite limited training data, their synthetic imagery-enabled model achieved a notable accuracy of 0.86. This approach exemplifies the potential of merging artificial intelligence (AI) with paper-based devices, creating robust, low-cost diagnostic tools that operate reliably across diverse lighting and imaging conditions.

In a similar vein, Mata Calidonio and Hamad-Schifferli (**https://doi.org/10.1039/D3SD00327B**) showcase how machine learning can be harnessed to optimize paper-based immunoassays for the detection of SARS-CoV-2 IgG and IgM antibodies. The authors developed a multiplexed nitrocellulose-based strip assay with a multicolor readout, utilizing red and blue gold nanoparticles to differentiate between antibody types and targets—specifically, spike *versus* nucleocapsid proteins. Instead of relying on traditional trial-and-error optimization, the assay's performance was fine-tuned through iterative machine learning and linear discriminant analysis (LDA), eventually achieving 100% classification accuracy across nine antibody profiles. This work not only demonstrates the power of supervised learning in improving diagnostic accuracy and development speed but also proposes a paradigm shift: treating immunoassays as

[a] *Department of Applied Chemistry, Faculty of Science and Technology, Keio University, 3-14-1 Hiyoshi, Kohoku-ku, Yokohama 223-8522, Japan*
[b] *Departmento de Química Fundamental, Instituto de Química, Universidade de São Paulo, São Paulo, SP, 05508-000, Brazil*
[c] *Laboratório de Sensores Químicos Portáteis, Departamento de Química Analítica, Instituto de Química, Universidade Estadual de Campinas – UNICAMP, Campinas, SP, 13083-970, Brazil*

selective arrays capable of generating nuanced disease information beyond binary test results.

Chu *et al.* (**https://doi.org/10.1039/D2SD00108J**) contribute a novel fabrication strategy that enhances paper's biochemical sensing capacity using monolith-modified cellulose. By grafting a poly(GMA-*co*-EDMA) monolith onto cellulose paper, the authors developed a surface-engineered paper-based analytical device with covalent immobilization of biomolecules, improving assay performance. Their system enables the rapid detection of tuberculosis through a colorimetric immunoassay targeting tuberculin purified protein derivative, achieving detection in under 30 minutes with a sub-nanogram-per-milliliter detection limit. This work not only advances tuberculosis diagnostics for resource-limited regions but also demonstrates how tailored surface chemistry can significantly improve paper-device functionality.

Abbasiasl *et al.* (**https://doi.org/10.1039/D2SD00032F**) expand the scope of paper-based diagnostics into wearable healthcare with a skin-mounted paper-integrated microfluidic device for sequential sweat analysis. Addressing the limitations of conventional absorbent pads—particularly sweat evaporation and leakage—the device uses filter paper's capillary action to channel sweat into sealed reservoirs without air exits. This enables chrono-analysis of biomarkers such as glucose and pH during exercise at flow rates up to 5 μL min^{-1}, with no loss of sample integrity. The platform demonstrates real-time, on-body chemical sensing capabilities while maintaining simplicity in fabrication, showing strong promise for non-invasive monitoring of physiological states.

Biswas and Maitra (**https://doi.org/10.1039/D4SD00124A**) present an application of paper-based diagnostics using a simple, non-peptide probe that enhances lanthanide luminescence upon enzymatic cleavage. The authors developed a paper-based sensor with time-gated, turn-on readout capabilities. This system enables not only rapid detection from commercial tablets but also screening of α-chymotrypsin inhibitors, offering a compact and sensitive luminescent platform for potential clinical translation. The elegant coupling of time-resolved luminescence with paper substrates could be a way for accessible oncology diagnostics with minimal background interference, specifically for the detection of the pancreatic cancer biomarker α-chymotrypsin.

Bhardwaj *et al.* (**https://doi.org/10.1039/D3SD00340J**) provide a comprehensive review offering a broad perspective on the future of paper-based diagnostics in cancer care. The authors critically examine recent innovations aimed at enhancing sensitivity in paper-based devices by improving paper chemistry, detection formats, and signal amplification strategies. Special emphasis is placed on the use of advanced nanomaterials—both organic and inorganic—for more robust biosensing performance. The review also highlights validated devices using clinical samples and discusses challenges such as sample variability and detection limits. By mapping key advances and unmet needs, this work underscores the transformative potential of paper-based biosensors in affordable, routine cancer screening.

Ali and Trouillon (**https://doi.org/10.1039/D4SD00154K**) introduce an innovative electrochemical paper-based platform for detecting the release of nitric oxide (NO) from endothelial cells. Given NO's short lifetime and key biological role, its accurate quantification in *in vitro* systems remains a challenge. The authors develop Nafion-coated and eugenol-functionalized paper sensors capable of selective NO detection while minimizing interference from nitrite. Impressively, they demonstrate real-time NO release monitoring directly from 100 000 endothelial cells cultured on the paper matrix in response to vascular endothelial growth factor. This work highlights the growing utility of paper-based devices in dynamic cell-based assays and tissue-level sensing.

Collectively, these papers illustrate the diversity and adaptability of paper-based POC diagnostics. The strategies highlighted here reflect the field's technological ingenuity and global health relevance, spanning infectious disease detection, metabolic analysis, reproductive health, oncology, and live-cell monitoring. By combining chemistry, engineering, and digital tools, these platforms aim to democratize diagnostic access and lay the groundwork for future advancements in personalized and decentralized healthcare.

Moving forward, the future of paper diagnostics is bright—and increasingly multidimensional. Merging stretchy electronics, advanced machine learning, and environmentally friendly materials will unlock the potential of these devices to beyond conventional limits. Furthermore, as digital ecosystems of health continue to develop, paper-based instruments will continue to lead the way for real-time data collection, remote monitoring, and telemedicine. Their sustainable nature and low production footprint also make them strong candidates for cleaner diagnostics. Ongoing cross-disciplinary and cross-industry collaboration will be required to harvest these advances and bring them as scalable, regulatory-sanctioned products to the market with the power to revolutionize global health systems.

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