Editorial

Flexible Analytical Devices for Point-of-Care Testing

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Over the last decade, flexible analytical devices have received considerable attention in both academia and industry. Compared with conventional analytical devices that are made from rigid materials, such as silicon, glass, and plastics, flexible devices offer several unique advantages, such as simplified fabrication, lower costs, enhanced disposability, and compliance to curved or deforming surfaces. For these reasons, flexible analytical devices are well suited for many diagnostic applications, including wearable and in vivo sensing, and point-of-care testing for disease detection and health monitoring. This special issue showcases a comprehensive review and exciting original research on topics including wearable sensors for human motion monitoring and disease diagnosis, flexible electrochemical sensor arrays for human cell culture monitoring, paper-based sensors and immunoassays for diagnostic testing, a paper-based biological solar cell for power generation and storage, and a 3D printing strategy for rapid prototyping of flexible microfluidic devices.

This special issue kicks off with a review article on wearable electronic sensors for human motion monitoring by Homayounfar and Andrew.[1] The ability to precisely measure medium to large movements and pressures associated with human motion has broad applications, ranging from the assessment and optimization of athlete performance, to the diagnosis of human diseases and disorders, such as Parkinson's disease and certain types of dementia. This review starts by introducing three commonly used types of wearable sensors for gait analysis (inertial sensors, optical fiber sensors, and angular sensors) and briefly discussing their advantages and limitations. To address the limitations associated with these three sensor types, researchers have been developing wearable electromechanical sensors that can offer improved portability, sensing performance, and integration with wearable garments. The second part of this review offers a comprehensive survey of various types of electromechanical sensors, including piezoresistive sensors, capacitive sensors, piezoelectric sensors, triboelectric sensors, and transistive sensors, and concludes with the authors' perspective on the challenges and future opportunities in the area of flexible sensors for human motion measurement and monitoring.

Next, an original research article by Ganguly et al.[2] presents a wearable electrochemical biosensor for biomarker detection in sweat. With the recent emergence of the Internet of Medical Things (IoMT) and at-home healthcare monitoring devices, patients are more empowered to monitor their own health and make medical decisions. This means, however, that such at-home monitoring devices need to be accurate, avoiding false-positive and false-negative diagnoses. One of the most commonly demonstrated applications of wearable chemical sensors is sweat analysis, due to the simplicity and noninvasive nature of sweat sampling. However, one of the main limitations associated with sweat analysis is the high variability of sweat constituents, which can influence the accuracy of measurements. To address this issue, this article proposes the combinatorial detection of both a disease biomarker of interest and a reference/indexing biomarker in order to improve the accuracy of monitoring a patient's disease state. Using sweat cortisol and sweat chloride ion as the disease biomarker and the reference/indexing biomarker, respectively, Ganguly et al. successfully demonstrated that their combinatorial sensing approach enables differentiation between acute and chronic disease conditions. This work is the first-time demonstration of the proposed combinatorial sensing approach for a sweat-based electrochemical biosensor. While this article highlights the importance of measuring multiple biomarkers for benchmarking a primary disease marker, sensing multiple biomarkers/analytes also has an apparent advantage of providing a set of data on multiple targets that can collectively determine the state of a disease, health condition, cell

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culture quality, or phenotype of a biological or chemical system more accurately. Toward this end, the research article by Nolan et al.[3] reports a novel direct writing method to fabricate biosensor arrays on a variety of substrates, including flexible laminate, for multianalyte measurements. Compared with conventional microfabrication techniques for creating flexible biosensors, the direct writing method presented in this article is cheaper, faster, and customizable. Using this approach, flexible sensors were successfully fabricated and used for simultaneous measurements of glucose, glutamate, and lactate in human astrocyte culture for up to 2 days. This direct writing technique offers several advantages for cutting-edge biomedical platforms, such as organ-on-a-chip devices, smart culture dishes, and flexible in vivo biosensors.

The next set of articles in this special issue present paper-based analytical devices that have soared in popularity over the last decade. The reasons behind their popularity include simple device fabrication, low cost, spontaneous fluid transport without an external pressure source, and simplified device operation without the need for dedicated laboratory equipment. The research article by Kudo et al.[4] reports a colorimetric microfluidic paper-based analytical device (μPAD) for the quantitative detection of lactoferrin, a glycoprotein having clinical significance in homeostasis and antibacterial activity, as well as being a candidate biomarker for Alzheimer's disease. A unique sensing scheme is employed by taking advantage of lactoferrin's strong affinity to ferric ions (Fe^{3+}), which is combined with 2-(5-bromo-2-pyridylazo)-5-diethylaminophenol (5-Br-PADAP) and encapsulated in poly(styrene-block-vinylpyrrolidone) nanoparticles. The color intensity of 5-Br-PADAP-Fe^{3+} nanoparticles on the paper chip changes as lactoferrin in the sample removes Fe^{3+} from the complex, resulting in a colorimetric readout. Because this device is antibody-free and uses a smartphone to read the colorimetric signal, it enables simplified lactoferrin detection in a point-of-care format. The report by Kalish et al.[5] presents distance-based detection of nucleic acids in paper-based microfluidic devices. The mechanism of this detection scheme is based on the aggregation of polystyrene microspheres conjugated with single-stranded DNA that is partially complementary to a target DNA strand. When a sample contains the target DNA strand, the microspheres aggregate due to DNA hybridization, resulting in large aggregates that cannot travel through pores in the paper substrate. Consequently, the distance wicked by the microspheres is inversely proportional to the target DNA concentration. This unique sensing scheme is employed for semiquantitative detection of DNA spiked in plant extracts, presenting the possibility of using this device for agricultural applications. In the article by Bradbury et al.,[6] a rapid diagnostic kit was developed for the detection of cerebrospinal fluid (CSF) leaks. The kit includes a semiquantitative, barcode-style lateral flow immunoassay for measurements of beta-trace protein (βTP), an indicator of CSF leaks, and other consumables, such as a collection swab, buffers, and disposable pipettes. The testing process can be completed in approximately 20 min and does not require any external equipment. This kit was successfully validated with a variety of clinical samples with or without CSF.

Many paper-based analytical devices, including the ones reported above, employ colorimetric sensing schemes, which is one of the simplest methods for generating a readout of the test results. However, colorimetric sensors are generally limited to qualitative or semiquantitative measurements, which may not be adequate for some biosensing applications. Therefore, researchers have been developing paper-based analytical devices incorporating electrical sensors that can provide quantitative measurements, but require electrical components for sensing, data processing, and/or reporting. These devices typically require a battery or power source, which hinders their flexibility and portability, and increases overall costs. To address these limitations, the article by Liu and Choi[7] introduces a paper-based biological solar cell for power generation and storage. This device is composed of five layered components: transparent sealing tape (for light transmission), a paper chamber where cyanobacteria are loaded, an anodic layer, a proton exchange membrane (PEM), and a cathodic layer with an embedded Ag_2O catalyst. All of the layers, except for the sealing tape and PEM, were fabricated on chromatography paper. This paper-based biological solar cell successfully achieved a maximum power and current density of 10.7 $\mu W/cm^2$ and 65.0 $\mu A/cm^2$, respectively, and, more importantly, could provide electrical power for up to 5 h. This study is an important advancement in paper-based energy generation and storage, providing a realistic and accessible power source for paper analytical devices. The last research article in this special issue, by Su et al.,[8] reports a new method for fabricating flexible microfluidic chips using 3D-printed polylactic acid (PLA) structures as a paper-based analytical master mold for polydimethylsiloxane (PDMS) microfluidic channels. Compared with conventional photolithography-based techniques for generating PDMS molds, this approach is less expensive and faster, making it suitable for rapid prototyping of both conventional PDMS-glass microfluidic devices and flexible PDMS-PDMS devices.

The eight articles featured in this special issue offer a snapshot into the recent technological advances, remaining challenges, and future directions of flexible analytical devices. We thank all of the authors who have contributed to this special issue, as well as the external referees who have provided objective and speedy reviews, helping us to maintain a high standard for all of the published articles. We

sincerely hope you enjoy the work of our colleagues in this special issue.

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