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Smartphone-based biosensors: A critical review and perspectives

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ABSTRACT

The ubiquitous distribution and international connectivity of smartphones is changing the concept of mobile health and promising to reshape the biosensor market. Smartphone-based biosensors have been explored using different approaches, either using the smartphone as detector or as instrumental interface. Smartphone-based biosensors have great potential as point-of-care and point-of-need platforms for healthcare, food safety, environmental monitoring, and biosecurity, especially in remote and rural areas. Here, we critically review the most recent papers on the use of smartphones as analytical devices and biosensors. We focus on analytical performance and on prospects for commercialization.

Contents

1. Introduction

Smartphones are now similar to miniature computers with operating systems, internal memory, and high-quality camera lenses. They are, however, potentially more accessible and cheaper than portable analytical laboratory devices [1]. These portable, low-cost devices could be used to run routine tests, which are currently performed by trained personnel using laboratory instrumentation such as microscopes and spectrophotometers. This would offer tremendous potential for improving the diagnosis and treatment of pathologies, particularly in low-resource countries [2–5]. There is increasing interest in using smartphones to detect analytes of clinical interest [6]. This includes the detection of human pathogen cells to diagnose cancer and tuberculosis [7]. The recent development of point-of-care (POC) instruments has allowed many tests to be performed at the point of need, outside the laboratory. But thanks

Abbreviations: POC, point-of-care; CMOS, complementary metal-oxide semiconductor; LED, light emitting diode; CL, chemical luminescence; LFIA, lateral flow immunoassay; SPR, surface plasmon resonance; BL, bioluminescence; CL, chemiluminescence; ELISA, enzyme-linked immunosorbent assay.

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to the exponentially increasing performance of complementary metal-oxide semiconductor (CMOS)-based photocameras, it may be more appropriate to use smartphones as portable biosensors and analytical devices [8]. In most cases, smartphones do not function alone as laboratory instruments. Rather, they are augmented by other accessories. Such augmented devices have great potential as point-of-care platforms for healthcare [9,10], food safety [11,12], environmental monitoring [13,14] and biosecurity [15], especially in remote and rural areas.

There have been many recent publications on the use of smartphones as bioanalytical devices. This has created unexpected opportunities for expanding the diagnostic and prognostic approach to a large number of pathologies and for evaluating pharmaceutical therapies.

The continuous improvement of smartphone electronics and the development of new apps have stimulated research into the use of smartphones as biosensors. By using the smartphone photocamera as a 'smart detector', almost all the optical-based methods have been integrated, including absorbance, reflectance, fluorescence, surface plasmon resonance (SPR), bio-chemiluminescence, and electrochemiluminescence.

However, following the initial emotional approaches related to the novelty and charm of the smartphone, there must be a more critical evaluation of the real analytical performance and usefulness of these devices in performing point-of-care and point-of-need tests and analyses in resource-limited settings. Here, we critically review the most recent papers on the use of smartphones as analytical devices and biosensors. We focus on analytical performance and on prospects for commercialization.

The main concerns are that the technology and wide use of smartphones is overestimated and that they do not add any scientific or diagnostic value when compared to miniaturized conventional devices, such as portable photometers or luminometers. Moreover, to have a complete overview of the real advantages and prospects of smartphone-based clinical diagnostic devices, it is important to point out the problems with the sampling of biological fluids.

Most diagnostic methods require blood or plasma whose collection, even if performed with a simple lancet device, is invasive and not fully appropriate. This limits the scope of diffusion of these biosensor formats. Some analytes such as cortisol [16] and lactate [17] have been measured in saliva and sweat, since sampling these biological fluids is simpler and less stressful for the patient. But there are drawbacks in using these fluids. The main limitation is that several analytes show lower concentrations in saliva than in blood (at least a factor 10–100) [18]. They thus require highly sensitive analytical methods. Moreover, the salivary concentration of many analytes does not reflect plasma levels. This makes it difficult to correlate the analytical data to relevant diagnostic information.

Smartphone-based biosensors have been explored using different approaches. The ideal biosensor format fully integrates the biorecognition process with the detector (smartphone), providing a standalone biosensor. This is probably the optimal solution; however, it has been explored less for obvious technical reasons. As an alternative, smartphones can simply be exploited as portable detectors or as instrumental interfaces.

2. Smartphone-based devices

Smartphone-based devices can be divided into two categories: the smartphone as detector and the smartphone as instrumental interface.

2.1. The smartphone as detector

In this case, a smartphone is coupled with an apparatus that contains the components of an instrument in a simplified format. The smartphone camera is used to detect the output signal. An elegant example was reported by Breslauer et al., who developed a microscope attached to a smartphone for both bright-field and fluorescence imaging [19]. The system comprises different elements integrated into a compact apparatus. In particular, for fluorescence imaging, the system includes a standard microscope eyepiece, an emission filter, an objective, a condenser lens, an excitation filter, a collector lens, and a Light Emitting Diode (LED) as excitation source (Fig. 1). Removing the filters and LED, the apparatus becomes a bright-field microscope. The authors demonstrated the applicability of this device for clinical diagnostics by capturing bright-field high-resolution images of *P. falciparum* malaria-infected blood samples and fluorescent images of Auramine-O-stained *M.-tuberculosis*-positive sputum smears. These tests are currently performed with standard microscopes. However, the authors demonstrated that microscope imaging is also possible with conventional smartphone camera technology. This is because the camera's high resolution is adequate for imaging blood cell and microorganism morphology. The concept could be used to overcome the issue of limited access to clinical microscopy in developing and rural areas, where clinical laboratories are scarce but cellphone infrastructure is extensive.

Tseng et al. reported a smartphone-based lens-free digital microscope that does not use lenses, laser, or other optical components, greatly simplifying the system architecture [20]. The authors used an LED to vertically illuminate the sample area. When it interacts with the sample, the LED light is scattered and refracted. The light waves that pass through the sampled objects (e.g. cells) interfere with the unscattered light, creating a hologram of each object, which is detected using the smartphone camera (Fig. 1). The authors demonstrated the system's performance by imaging various sized microparticles, red and white blood cells, platelets, and a parasite. This lens-free smartphone microscope has several important features, including compactness, lightness (38 g), and cost-effectiveness, which make it very suitable for decentralized point-of-need use, particularly in developing areas.

On the other hand, the spatial resolution of images is limited by the pixel size at the sensor, making the system less accurate than a standard microscope. In addition, obtaining real images requires a holographic reconstruction algorithm, which cannot reasonably be installed on the smartphone because it would drastically reduce its speed. This implies that the holographic reconstruction process must be performed remotely, e.g. in a central hospital.

Using a tablet with a larger screen could also be very useful, particularly when the image of the target is relevant for diagnosis. For standard use, a simple cellphone could be used even if it has a small screen. The same research group also described different approaches to developing smartphone-based fluorescent microscopes [21,22], smart-phone based microscopes using fiber-optic array [23,24], a smartphone-based rapid-diagnostic-test (RDT) reader platform for LFIA [25], and different devices for fluorescence or photometric detection using cost-effective and compact attachments.

Erickson et al. have reported a portable smartphone device based on reflectance photometry. It consists of a smartphone accessory, a cartridge, and a strip on which the color-based assay takes place [26]. The built-in smartphone flash is used as a light source to illuminate the reaction area, and a diffuser allows homogenization of the light. Thanks to a dedicated app, the device correlates the variations of color and brightness to analyte concentrations.

Of particular interest is the smartphone-based angle-resolved surface plasmon resonance (SPR) detection system proposed for the first time by Preechaburana et al. [27]. The attachment was designed to adhere to the smartphone screen surface, where it is illuminated from a red rectangle on the screen and directs the SPR image to the frontal phone camera. It comprises an optical element made of PDMS rubber and epoxy, covered with a gold-coated glass