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Smartphones for Cell and Biomolecular Detection

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Abstract—Recent advances in biomedical science and technology have played a significant role in the development of new sensors and assays for cell and biomolecular detection. Generally, these efforts are aimed at reducing the complexity and costs associated with diagnostic testing so that it can be performed outside of a laboratory or hospital setting, requiring minimal equipment and user involvement. In particular, point-of-care (POC) testing offers immense potential for many important applications including medical diagnosis, environmental monitoring, food safety, and biosecurity. When coupled with smartphones, POC systems can offer portability, ease of use and enhanced functionality while maintaining performance. This review article focuses on recent advancements and developments in smartphone-based POC systems within the last 6 years with an emphasis on cell and biomolecular detection. These devices typically comprise multiple components, such as detectors, sample processors, disposable chips, batteries, and software, which are integrated with a commercial smartphone. One of the most important aspects of developing these systems is the integration of these components onto a compact and lightweight platform that requires minimal power. Researchers have demonstrated several promising approaches employing various detection schemes and device configurations, and it is expected that further developments in biosensors, battery technology and miniaturized electronics will enable smartphone-based POC technologies to become more mainstream tools in the scientific and biomedical communities.

Keywords—Point-of-care testing, Biosensors, Diagnostics, Smartphones, Mobile phones, Microfluidics.

INTRODUCTION

The detection and quantification of cells and biomarkers provides a wealth of information that is valuable in many disciplines including medicine, biotechnology, cell biology, and chemistry. Currently, most analytical measurements are performed using laboratory-based technologies, which are costly, time consuming and labor intensive. As a result, diagnostic testing is limited to resource-rich countries where it plays a significant role in rising health care costs.[1,3] Additionally, there is a growing interest to develop compact health monitoring systems that can be used outside of hospital and clinical settings.[15,16,20] To address these issues, researchers have been working on the development of point-of-care (POC) diagnostics, which offer several advantages over conventional laboratory-based analytical methods, including enhanced portability and automation, faster processing times, reduced sample volumes, and lower costs.[45] One of the ultimate goals of POC technology is to make diagnostic testing more widely accessible (e.g., outpatient centers, health clinics, doctor's offices) and cost effective, which can ultimately improve several areas of healthcare including early disease detection, health maintenance, and therapeutic monitoring.

While much work has focused on the diagnosis of human diseases, POC systems have also been applied to other important applications, including the identification of animal and plant pathogens,[41,59,70] biological warfare agent detection,[32,40] food quality assurance,[24,51] and environmental monitoring.[62] The broad applicability of POC systems is in part due to their versatility in identifying and analyzing a wide variety of biological targets (e.g., chemical compounds, nucleic acids, proteins, metabolites, biological cells) within clinical and environmental samples. For this reason, numerous companies have been working to commercialize POC platforms, mainly for healthcare applications. In 2012, POC testing constituted roughly $20 billion, one-third of the entire *in vitro* diagnostics market in the world.[65] With an increasing ageing population and a growing obesity epidemic, the

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demand for cost-effective diagnostics is expected to rise[43] and it is predicted that the POC testing market will reach approximately $25 billion by 2016.[38] Therefore, next generation POC systems need to be economical and simple to use, while still providing valuable clinical information. To achieve this goal, researchers have employed Micro-Electro-Mechanical System (MEMS) and nanotechnology to develop microfluidic platforms and miniature sensors for POC testing.[9,24] While this offers improvements in assay sensitivity and automation, most MEMS-based POC systems still require external components for operation such as detectors, computers or power supplies, which increases their bulkiness and overall costs. To address this challenge, researchers have recently sought to integrate smartphones with MEMS-based devices to reduce the overall footprint of these systems. Smartphones are equipped with numerous components that can be employed for biodetection, such as a fast multicore processor, visual display, digital camera, battery and an intuitive user interface. Smartphones also possess numerous modes of wireless data transfer (e.g., cellular data service, WI-FI, Bluetooth) allowing test results to be immediately accessed by the user and/or transmitted to digital medical record databases. Beyond these benefits is the ubiquitous availability of smartphones throughout the world enabling broad accessibility. In 2013, nearly 87% of the world's population (6.8 billion people) were mobile phone subscribers.[19] While these numbers include all mobile phones, the smartphone market is expected to grow by 50% by 2015, with annual shipments approaching 1 billion units.[69] In response, a number of consumer mobile health accessories that integrate with smartphones have already been developed (e.g., Nike + FuelBand and Jawbone UP24), and more than 40,000 health-related mobile phone applications (apps) are currently available in online app stores. This trend will only continue to grow as mobile electronics and smartphones become more integrated into our society and daily lives.

One of the simplest and earliest demonstrations of employing mobile phones for healthcare is telemedicine.[5,57,68] For many of these applications, the mobile phone is used as a portable, wireless computational platform to record, store and transit physiological measurements, such as heart rate,[2,21] blood pressure,[50] blood glucose concentration,[56] cardiac electrical activity[12,26] and body temperature,[58] from one site to another. Taking advantage of the fact that modern mobile phones are equipped with a digital camera, researchers have devised strategies to utilize a camera's phone to capture images of measurements from colorimetric assays, which are digitized and can be transmitted to an off-site laboratory for analysis by an expert or trained medical professional.[39] Researchers have also focused their efforts to develop mobile phone-based microscopes for cell imaging, which is a common technique for the diagnosis and pathology of many diseases. Recently, efforts have been focused on integrating microfluidic devices with smartphones for advanced functionalities, including sample processing, fluidic manipulation and biomolecular detection. In addition to these assays, smartphones have also been combined with portable diagnostic tools and instruments for the measurement of blood oxygen saturation[28,48] PH measurement in sweat and saliva,[46] ultrasonic imaging,[66] and nuclear magnetic resonance imaging.[23]

This review summarizes the latest developments in smartphone-based platforms for cell and biomolecular detection reported within the past 6 years. Research in this area has mainly focused on healthcare applications, and emphasis in this review is directed towards the detection of cells and biomarkers relevant to disease diagnosis. Since the configuration of smartphone-based POC devices can vary widely, this review is categorized based on the target that is being detected; i.e., cells, proteins and nucleic acids. Insights into the sensing mechanism and its integration with the smartphone will be discussed in the context of the target molecule that is being detected. We will conclude with a brief discussion on the current limitations and future direction of this technology and its potential to transform healthcare by improving the accessibly and delivery of POC testing.

DETECTION TARGETS

Cell and biomolecular detection is critically dependent on the availability of high quality reagents (e.g., recombinant proteins and nucleic acids, antibodies, aptamers) and highly specific and sensitive analytical tools, which is the basis for the prognosis and diagnosis of many types of diseases including cancer, diabetes, AIDS/HIV, tuberculosis, and other communicable diseases.[34,53] Therefore, research on the characterization of existing biomarkers and the discovery of new ones plays an important role in the development of POC tests. Generally, these tests are designed to detect the presence or measure the concentration of one or more disease-specific cell or biomarker, which can offer much more diagnostic information than physiological measurements alone. The insights gained from biomarker research provide tremendous opportunities not only for the diagnosis of diseases, but also for the development of novel molecular-targeted therapeutic strategies.[37] Therefore, the realization of these opportunities depends on the availability of sensitive, low-cost, easy to use analytical instruments, which is the

basis for smartphone-based POC technology. To date, these systems have been primarily directed towards the detection and quantification of cells and biomarkers, as summarized in Table 1.

Human Cells and Pathogens

The identification and counting of human cells and pathogens is one of the most common techniques in medicine for disease diagnosis and health monitoring. For example, the CD4 count is a widely used test to assess immune functionality and monitor HIV infection, and researchers have already demonstrated POC devices for counting CD4 + T-cells.[7,8,33] Additionally, the identification of pathogens and abnormal cells (e.g., tumor cells) is the gold standard for diagnosing many infectious diseases and cancers, which is generally performed using a microscope. Therefore, the ability to perform microscopy using a portable, low-cost device has immense potential to improve disease diagnosis, particularly in resource-limited countries. To date, several smartphone-enabled imaging systems have been demonstrated for cell counting, which integrate the phone's camera with a compact microscope attachment.[4,64,72] The use of a mobile phone for microscopic imaging also enables rapid transfer of the images to experts and trained medical personnel for analysis, thereby improving diagnostic accuracy and patient follow-up care.

Using standard microscope eyepieces and objectives, a smartphone-integrated microscope attachment was developed by Breslauer *et al.*[6] for brightfield and fluorescence imaging. Different requirements of magnification and resolution can be achieved by simply using different objectives. Ambient light and white LEDs are used for brightfield imaging, whereas a trans-illumination geometry incorporating a UV LED excitation source and UV filters are utilized for fluorescence microscopy. This device can produce high quality images of human blood cells and parasite, as well as measure their density. Thin and thick smears of *P. falciparum*-infected blood samples and sickle cell anemia blood samples were successfully imaged using this system. *M. tuberculosis*-infected sputum smear samples were also imaged, where individual tuberculosis (TB) bacteria could be easily identified as illustrated in Fig. 1c. Due to its ability to image, count and analyze cells in clinical samples, this platform reveals that smartphone-based microscopy can be a promising technique for disease diagnosis and water quality monitoring, particularly in remote and resource-limited settings.

Zhu *et al.*[73] demonstrated a compact imaging cytometry platform coupled with a cell phone for measuring the density of blood cells and hemoglobin in human blood samples. This system attaches directly to the cell phone's camera for simplified integration and utilizes the phone's LEDs for sample illumination. Add-on attachments were designed for three different types of measurement: leukocyte imaging/counting, erythrocyte imaging/counting and hemoglobin density quantification. Erythrocyte imaging is performed using

TABLE 1. Smartphone-based devices for cell and biomolecular detection.

Technologies	Target(s) being detected	Time to complete a single test	Limit of detection/resolution	Reference
Fluorescence and brightfield imaging	*P. falciparum*, blood cells	2 min	1.2 μm (0.85 NA 60$\times$ objective and 20$\times$ microscope eye piece)	6
Fluorescence and brightfield imaging	Blood cells, hemoglobin	–	–	73
Lens-free imaging	Blood cells, *Giardia lamblia*	–	2.2 μm per color pixel	61
Brightfield imaging	Blood cells	$<$1 min	1.6 μm	44
Fluorescence detection, quantum dots	*E. coli*	2 h	5–10 CFU/mL (buffer)	74
EIS, microfluidics	*E. coli*	–	10 cells/mL (buffer)	25
Mie scattering detection, paper-based microfluidics	*Salmonella*	1 min	10 CFU/mL (buffer)	47
Colorimetric detection	*E. coli*	–	–	27
Fluorescence detection	Human albumin	5 min	5–10 μg/mL (buffer and synthetic urine)	10
Mie scatter detection, optofluidics	*Pf*HRP2	10 min	1 pg/mL (10% diluted blood)	55
Reflection spectrum detection	Porcine IgG	20 min	4.24 nM (buffer)	14
RPI	HBsAg and p24Ag	30 min	10s of ng/mL (diluted bovine fetal serum)	17
Electrochemical detection, microfluidics	*Pf*HRP2	15 min	16 ng/mL (human serum)	35
Electrochemical detection, microfluidics	*E. coli* DNA	30 min	100 nM (buffer)	30
Fluorescence detection, microfluidics	*E. coli* and *S. aureus* DNA	9 min	–	54
Fluorescence detection, paper-based microfluidics	*Salmonella* DNA	5 min	10^3–10^4 CFU/mL (10% poultry packaging liquid)	13

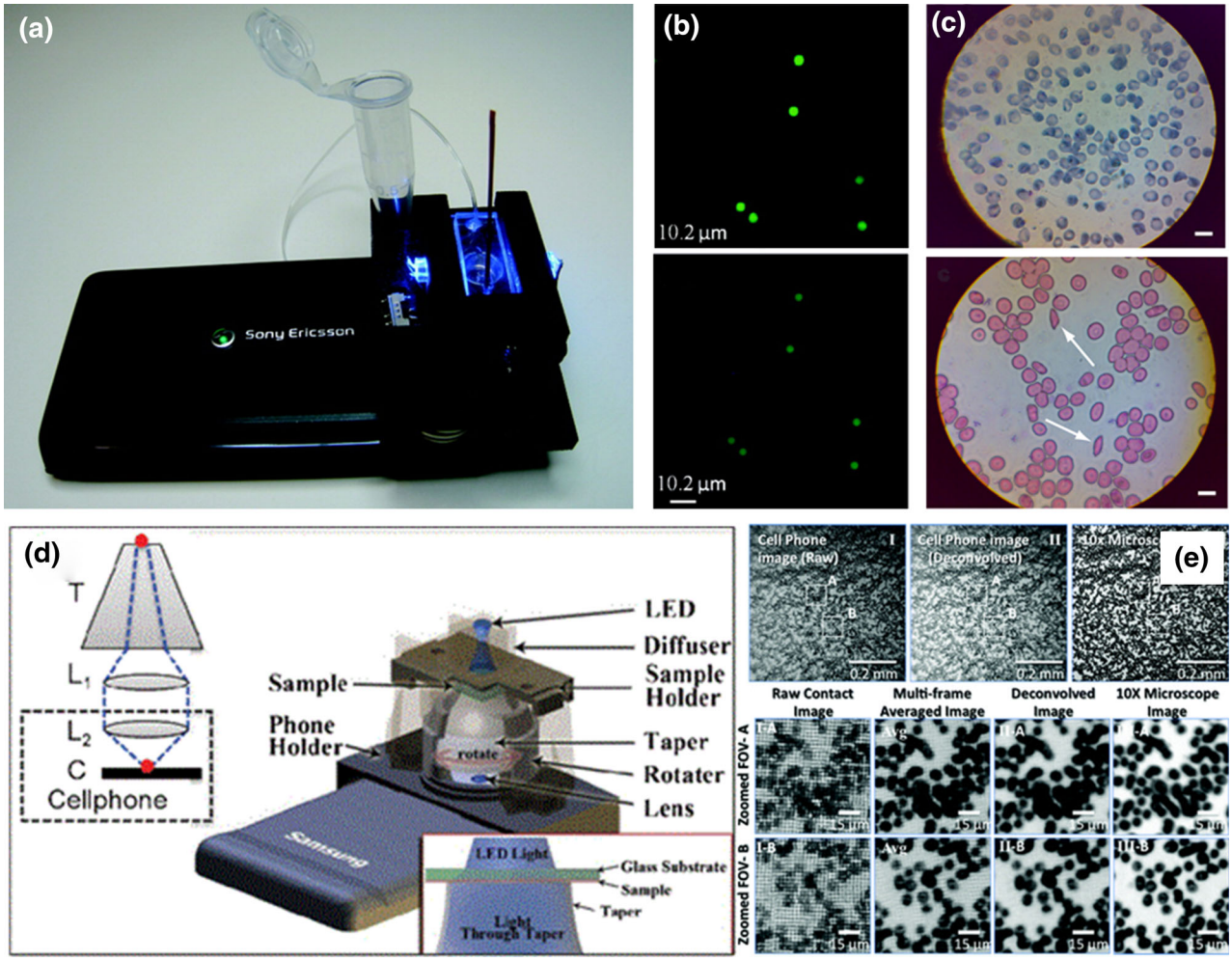

FIGURE 1. Smartphone-based microscopes for cell imaging and counting. (a) Photograph of an optofluidic fluorescence imaging cytometry developed by Zhu *et al.*,[71] and (b) comparison of fluorescence images of microbeads taken by the mobile phone device (top) and a conventional fluorescence microscope (bottom). (c) Images of diseased blood smears taken with a smartphone microscope developed by Breslauer *et al.*[6] Thin smear of Giemsa-stained malaria-infected blood (top) and sickle-cell anaemia blood (bottom). White arrows point to two sickled red blood cells. Scale bars are 10 mm. (d) Schematic illustration of the *Contact Scope*, and (e) brightfield images of a blood smear sample acquired using the *Contact Scope*.[44]

incandescent light while leukocyte imaging requires fluorescence illumination for enhanced image contrast. For hemoglobin density measurements, a water sample is used as a reference image from which the hemoglobin absorbance can be computed to calculate hemoglobin concentration. The performance of this device was compared to that of a conventional microscope, which showed that images produced using this cell phone microscope exhibited an absolute error within 7% for leukocyte counts, 5% for erythrocyte counts and 5% for hemoglobin density measurements respectively.

One of the main constraints in miniaturizing optical imaging systems is the optical components themselves. Therefore, Tseng *et al.*[61] developed a lens-free cell phone microscope, which does not utilize lenses, lasers or other bulky optical components. Instead, it uses white LEDs for sample illumination in conjunction with a large aperture to produce holograms of the objects of interest. Briefly, light from the LEDs passes through the aperture, interacts with objects in the sample and interferes with the unscattered light to create holograms. These raw holograms are captured by the phone's camera, transmitted to a computer through wireless communication and reconstructed by digital processing. The spatial resolution of this platform is ~2.2 μm for each color pixel. Using this device, blood cells, platelets and *Giardia lamblia* (a waterborne parasite) were successfully imaged, exhibiting comparable quality with images obtained using a conventional lens-based microscope.

Since older mobile phone cameras have lower resolutions compared to modern smartphones, a portable microscope attachment, named *Contact Scope*

(Fig. 1d),[44] was developed by Navruz *et al.* which is capable of imaging highly dense samples using a lower resolution camera. This device employs a unique tapered fiber-optic array, where the top facet consists of fiber optic cables having a density 9-fold higher compared to the bottom facet. Samples are placed on the top facet of the array and are illuminated by LEDs. The resulting light pattern of the sample is transmitted onto the bottom facet of the array, and projected through two lenses to the phone's camera. By manually rotating the fiber array with discrete angular increments (e.g., 1–2°), contact images are captured at each position and digitally fused together based on a shift-and-add algorithm through a custom-developed Android app, and displayed on the phone's screen. The *Contact Scope* can achieve a spatial resolution of 1.5–2.5 μm over a field of view of 1.5–15 mm.[2] Wide-field images of blood smears were obtained using the *Contact Scope*, which showed good agreement with images taken using a brightfield microscope. While this platform exhibits comparable imaging performance as conventional microscopy at lower magnifications, the resolution limits of this system can be further improved for imaging at higher magnifications.

Towards a mobile phone-based platform for targeted cell detection, Zhu *et al.*[74] developed a system based on a quantum dot sandwich assay. In this device, glass capillaries functionalized with primary antibodies directed against *E. coli* O157:H7 are used to capture the target bacteria in water samples, which are loaded into the capillaries. Secondary antibodies, conjugated with quantum dots, are subsequently dispensed into the capillaries and serve as the fluorescence signal reporter. Due to the exceptional brightness and photostability of quantum dots, this device can offer improved detection sensitivity over assays that use fluorescence probes. The excitation signal for the quantum dots is provided by UV LEDs and the light emission is captured by the phone's camera through a microscope attachment. Images are analyzed on a computer using ImageJ software to correlate the fluorescence intensity with *E. coli* concentration. The entire test can be completed within 2 h, including sample preparation, sample loading and incubation. The authors report a detection limit of 5–10 CFU/mL in buffer solution, which is comparable to previously reported microfluidic-based devices.[22]

Another smartphone-based platform for *E. coli* quantification was reported by Jiang *et al.*[25] which is based on electrochemical impedance spectroscopy (EIS). This device is comprised of an HTC ONE X smartphone, a custom detection circuit and a microfluidic chip, which contains an impedance sensor and series of porous structures to filter and preconcentrate the target bacteria from the sample. The sensor is comprised of interdigitated gold electrodes fabricated on a silicon substrate having an array of microholes. EIS measurements are carried out by the detection circuit, which includes an impedance converter network analyzer, a microcontroller and a Bluetooth shield. An Android app enables recording and visualization of the test results, which are transmitted to the smartphone *via* Bluetooth. Experiments were performed to calibrate the sensor by measuring water samples containing serial concentrations of *E. coli*, revealing a lower limit of detection of 10 cells/mL with a dynamic range from 10 to 1000 cells/mL. Additional experiments were performed to estimate *E. coli* concentration based on this calibration data, which demonstrated an error of 36.4% with respect to the actual concentration. While these preliminary results show that this device offers a unique strategy to quickly detect *E. coli* in water samples, future work is needed for improved detection accuracy and specific cell targeting in environmental samples.

A smartphone-based assay utilizing Mie scatter detection and a paper-based microfluidic chip for the detection of *Salmonella typhimurium* was demonstrated by Park *et al.*[47] Since Mie scatter measurements are less vulnerable to signal and wavelength fluctuations compared with fluorescence or chemiluminescence measurements, this detection method offers good sensitivity without requiring expensive light sources or optical components. Microchannels are fabricated on cellulose paper by pattering SU-8 photoresist *via* photolithography. The chips are preloaded with anti-*S. typhimurium* antibody-conjugated latex nanobeads and sample loading is achieved by simply dipping the edge of chip into an aqueous sample. The presence of target pathogens in the sample causes the beads to agglutinate, and the resulting scattered light is captured by the phone's camera. The images are analyzed by a custom app and displayed on the screen of the phone for immediate access. The authors note that one of the disadvantages in using paper chips is inconsistency in the detection signals due to the inhomogeneity of paper. To resolve this issue, the authors employed signal processing to filter out the background signal from the light scatter intensities. It was also noted that residues from dried PBS (14%) and Tween 80 (from washing) resulted in signal variations. Therefore, during the final step of preparing antibody-conjugated particles, deionized water was used for washing. Based on preliminary experiments, the lower detection limit of this assay for detecting *S. typhimurium* in buffer is 10^2 CFU/mL with a linear range up to 10^5 CFU/mL.

In addition to the detection of pathogens, antimicrobial susceptibility testing (AST) is another diagnostic application that has been explored using

smartphone-based POC technology. A smartphone-based microphotometric system for AST was recently demonstrated by Kadlec *et al.*[27] This system consists of an iPhone and optical attachment, termed *iPhotometer*, and a polymer chip containing a microwell array for sample containment. A colorimeter cell viability assay is employed for optical measurements, and the results are captured by the *iPhotometer*. Briefly, bacterial samples and water-soluble tetrazolium salts-8 (WST-8, used as a colorimetric indicator) are loaded into the microwell chip (precoated with antibiotics), and inserted into the device. Light from a white LED light passes through a narrow slit and diffuser before contacting the chip. The transmitted light is collimated by a condenser lens, captured by the phone's camera, and transmitted to a computer for data analysis using ImageJ software. Absorbance measurements are taken at ~450 nm, which was determined by the authors to produce the highest intensity values. Antimicrobial resistance profiling for four *E. coli* isolates (EC132, EC136, EC137, and EC462) were performed in Mueller–Hinton broth and human urine. Bacteria in microwells containing *E. coli*-specific antibiotics resulted in absorbance values at least 10-fold lower than those of microwells containing no (control) or non-specific antibiotics. Based on this approach, the antimicrobial resistance of bacteria can be determined with comparable results obtained from conventional microbiological techniques. Additionally, this system can accommodate samples with bacterial concentration from 10 to 10^6 CFU/mL by simply adjusting the incubation time.

Proteins

Proteins are the most commonly employed biomarkers for POC testing due to their abundant presence in clinical specimens (e.g., blood, saliva, urine) and ability to be detected with minimal sample preparation. Enzyme-linked immune sorbent assay (ELISA) currently serves as the gold standard for protein quantification, however, this technique is not amenable for POC testing since it requires considerable labor and technical expertise, expensive equipment, and lengthy processing times.[63] Therefore, protein-based POC systems commonly employ detection strategies similar to ELISA, but modified for portability, lower costs and improved automation. Briefly, these assays employ capture probes (e.g., primary antibodies or aptamers), immobilized onto a sensor, which are directed against the target protein. This protein binds to the sensor surface (*via* the capture probes) and either modifies an optical or electrical signal, or generates one *via* reaction with an enzyme-conjugated secondary antibody. Due to its sensitivity and robustness, this type of sandwich assay is widely employed in microfluidic and smartphone-based POC platforms.

A smartphone-based fluorescence assay for quantifying albumin in urine was demonstrated by Coskun *et al.*[10] This platform, termed the *Albumin Tester*, integrates a compact attachment that is mechanically affixed to the phone's camera. This attachment consists of a battery-powered LED for UV illumination, two test tube holders (one for the sample and one for a control solution) and plastic lenses. To perform the test, a urine sample is loaded into the sample tube, which is partially prefilled with a fluorescence reagent solution, and inserted into the attachment. The control tube, which is fully prefilled with the same fluorescence reagent solution, is subsequently inserted into the attachment. UV light successively passes through the sample and control tubes and the fluorescence emissions are collected perpendicular to the excitation beam through a plastic filter and captured by the phone's camera. The acquired images are digitally processed on the phone through a custom Android app that correlates the fluorescence signals with the albumin concentration. Based on proof-of-concept experiments, the *Albumin Tester* exhibits a lower limit of detection of 10 μg/mL in synthetic urine with a linear relationship (correlation coefficient $R = 0.99$) between the albumin concentration and corresponding fluorescence signals from 0 to 200 μg/mL.

Alternatively, Stemple *et al.*[55] demonstrated a smartphone-based POC device for protein detection which utilizes a microbead immunoagglutination assay combined with Mie scatter detection (Fig. 2e). In this approach, the protein concentration is calculated by analyzing the light scattering intensity due to particle agglutination. Briefly, samples are incubated with 920 nm polystyrene beads that are conjugated with antibodies directed against the target proteins. Following a washing step, the samples are dispensed into a Y-shaped microfluidic chip which contains two oil-filled optofluidic channels (fixed at 45°) that are employed as optical waveguides. The chip is inserted into an external attachment that is affixed to the back of the phone. Light flashes from white LEDs are applied to the sample *via* the waveguides. The presence of target proteins in the sample results in microbead immunoagglutination, causing the light to scatter. The scattered light is reflected through a series of mirrors and lenses within the attachment, and captured by the phone's camera (Fig. 2f). For proof-of-concept, this device was used to detect *Plasmodium falciparum* histidine-rich protein 2 (*Pf*HRP2), a biomarker for malaria detection. A lower limit of detection of 1 pg/mL was achieved in 10% diluted blood with a linear detection range from 1 pg/mL to 10 ng/mL. While these results are comparable to the sensitivity of previously demonstrated POC protein assays, further work is needed to make this system compatible with raw specimens, such as whole blood.

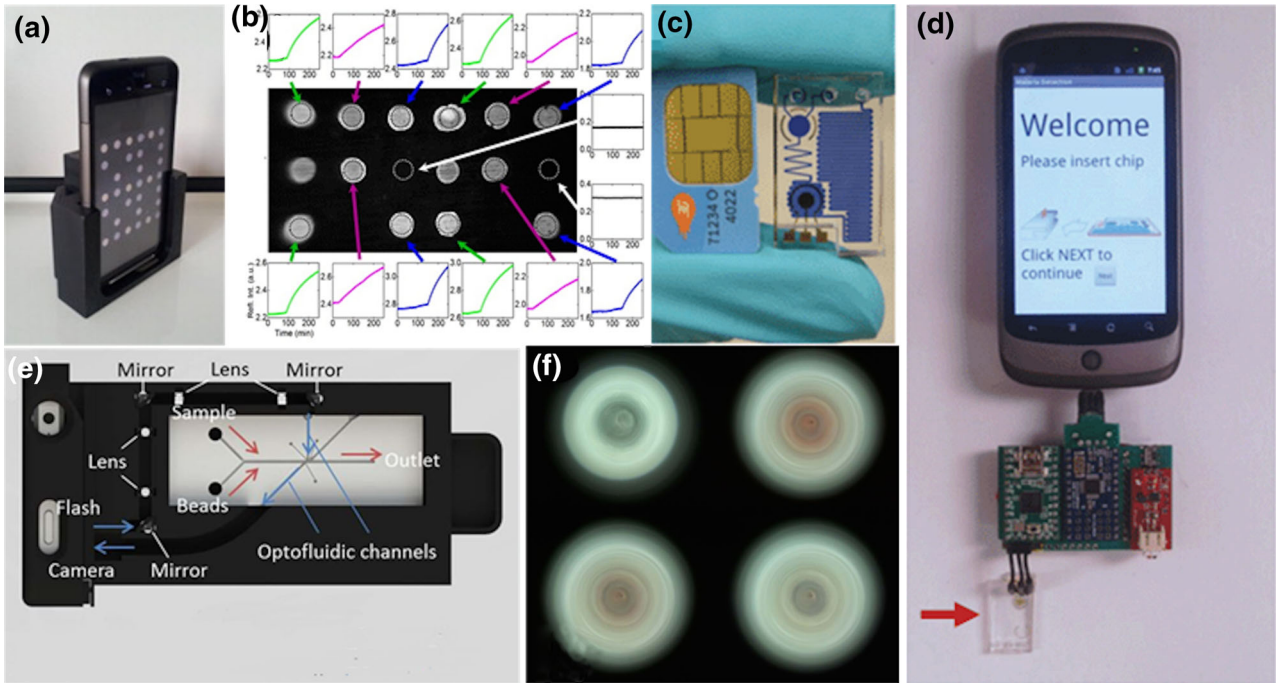

FIGURE 2. Smartphone-based systems for protein detection. (a) Photograph of the smartphone immunoassay developed by Giavazzi *et al.*[17] The device incorporates a custom cradle which houses a magnetic stirrer, optical components and a disposable cartridge. (b) Reflected light signals of polyclonal IgG antibodies from mouse, guinea pig and rat in buffer with corresponding plots of the intensity as a function of time averaged on the surface regions indicated by the arrows and the dashed circles. (c) Photographs of the microfluidic chip next to a mobile phone SIM card and (d) smartphone platform for electrochemical detection developed by Lillehoj *et al.*[35] (e) Schematic of the smartphone-based optofluidic device by Stemple *et al.*,[55] (f) raw images from a control (top left), sample containing 10% blood without target (top right), sample containing 1 pg/mL *Pf*HRP2 in 10% diluted blood (bottom left) and sample containing 1 pg/mL *Pf*HRP2 in 10% diluted blood (bottom right).

A smartphone-based label-free photonic crystal (PC) biosensor was developed by Gallegos *et al.*,[14] which utilizes the smartphone as a spectrometer to detect shifts in the resonant wavelength of the sensor. The PC is comprised of a one-dimensional grating surface structure (with a grating period of 360 nm and grating depth of 60 nm) on a flexible plastic substrate, which is coated with thins films of SiO_2 and TiO_2. The PC was designed to behave as a highly efficient narrowband reflectance filter with a center wavelength of $\lambda = 565$ nm and a resonance bandwidth of $\lambda = 5$ nm (when the surface is dry). Adsorption of analytes or biomolecules onto the PC effectively shifts the wavelength of the resonant reflection, with a magnitude that is proportional to the optical density of the bound material. The PC biosensor is housed inside a cradle, containing a light source and additional optical components, which is secured to the back of the phone. During a measurement, unpolarized light (from an incandescent bulb or LED) sequentially passes through a pinhole, a collimating lens and polarizing filter before reaching the PC. After passing through the PC, the light passes through a cylindrical lens and diffraction grating (1200 lines mm^{-1}) and is captured by the phone's camera. Intensity spectrum profiles are obtained from each spectra image by a custom app where PC transmission spectra are analyzed to determine shifts in the Peak Wavelength Value (PWV) that result from analyte binding. For protein detection, capture probes are immobilized on the PC, followed by a blocking step to prevent nonspecific binding. A reference measurement is taken prior to the addition of the sample and used as a baseline reading. The sample is dispensed onto the sensor, incubated, and washed in deionized water or buffer. After drying in N_2, a second measurement is taken. Experiments were performed to validate the operation of this system by measuring the adsorption of poly-phe-lysine (PPL), which resulted in a PWV shift of 1.66 nm. A second experiment was performed to measure porcine immunoglobulin G (IgG) in buffer, which could be detected at concentration down to 4.25 nM. This sensitivity is commendable for label-free detection and the authors suggest that the limit of detection can be further reduced by employing secondary antibodies or nanoparticles to amplify the wavelength shift.

Another optical, label-free biosensing platform was recently demonstrated by Giavazzi *et al.*[17] consisting of a smartphone integrated with a custom cradle, as shown in Fig. 2a. The cradle houses a magnetic stirrer,

optical components and a disposable cartridge. The detection principle is based on the Reflective Phantom Interface (RPI), where the intensity of reflected light is measured at the interface between a liquid sample and an amorphous fluoropolymer substrate having a refractive index very close to that of the sample. Antibodies directed against the target proteins are immobilized onto the substrate in a spotted array. Light from the phone's LED is used as the illumination source, and the reflected light signals are subsequently captured by the phone's camera. The binding of target proteins to the interface increases the intensity of the reflected light, which can be correlated to the concentration of bound molecules. The reflected light signals (Fig. 2b) are processed and analyzed on a computer using MATLAB. Experiments were performed to characterize the sensor by measuring IgG antibodies of mouse, guinea pig and rat in buffer, which revealed that the assay exhibits $<5\%$ variations in identical measurements and $<10\%$ cross-binding with irrelevant antibodies. Further studies were performed to detect hepatitis B surface antigen (HBsAg) and p24 capsid protein (p24Ag) in diluted bovine fetal serum. Based on these preliminary results, the lower limit of detection and effective dynamic linear range of this platform is estimated at tens of ng/mL and spans up 10 μg/mL respectively. While further work is needed to characterize this device for measurements of raw specimens, it offers the advantages of portability, ease of use, enhanced automation and fast measurements times (~30 min).

While these previous systems employ optical detection techniques, Lillehoj *et al.*[35] developed a smartphone biosensing platform based on electrochemical detection for rapid protein quantification (Fig. 2d). In contrast to optical measurements, which are prone to fluctuations due to variations in imaging sensors and lighting, electrochemical measurements provide quantifiable electrical signals which are less susceptible to these variations. This device consists of a disposable microfluidic chip for fluidic handling and biosensing (Fig. 2c), a detection circuit for signal processing and data analysis, and a Nexus One smartphone. The detection circuit provides an electrical and physical interface between the microfluidic chip and the smartphone *via* the microUSB port. This assay is based on a sandwich ELISA where primary antibodies are immobilized onto electrochemical sensors. The presence of target antigens in the sample enables binding of horseradish peroxidase-conjugated secondary antibodies, which generates an electrochemical current in the presence of a TMB/H_2O_2 substrate and a small bias voltage. The detection signals are digitized by the circuit and transmitted to the phone, where they are analyzed by a custom Android app and displayed on the screen of the phone. Proof-of-concept experiments were performed to measure *Pf*HRP2, which could be detected at concentrations down to 16 ng/mL in human serum. Furthermore, the entire detection process can be completed within 15 min. Due to its portability, simplicity and capability to perform analytical measurements in raw clinical samples, this device offers great potential for POC testing, particularly for the diagnosis of infectious disease in resource limited settings.

Nucleic Acids

Nucleic acid-based diagnostics detect for various nucleic acids biomarkers (e.g., DNA/RNA fragments, pathogen-specific virulence genes, or disease-specific mutation) associated with an invading pathogen or a genetic (non-infectious) condition.[42,52,67] The detection of nucleic acids is generally more complex than protein detection due to the additional processing steps that are required, including nucleic acid extraction, purification, and signal amplification. As such, nucleic acid-based POC tests are designed to simplify the detection process by combining multiple steps and automating the sample preparation process. Several microfluidic devices have been developed which automate individual steps or the entire sample preparation process.[31,49] For example, to prevent interference from ribonuclease enzymes in cells and tissues samples, purification of nucleic acids is commonly performed using solid phase extraction (SPE) following cell lysis. To simplify this step for POC testing, the nucleic acid sample is prepared through SPE on silica-coated magnetic beads with lysis/binding buffers containing chaotropic salts and ethanol to inhibit degradation. The advancement of nucleic acid-based assays is largely attributed to the invention of polymerase chain reaction (PCR), which is currently the established method for nucleic acid amplification. Towards a POC device for nucleic acid detection, several groups have demonstrated microfluidic platforms for rapid PCR-based analysis.[18,29,36] However, PCR assays require thermal cycling and sensitive optics for real-time detection, both of which are not well suited for a compact and inexpensive battery-operated device. To address this issue, researchers have developed isothermal techniques which do not require thermal cycling for nucleic acid amplification, representing a more promising option for POC testing. Among these, loop-mediated isothermal amplification (LAMP)[11,60] has become a preferred technique for POC testing to diagnose infectious diseases due to its rapidity, low equipment cost and ruggedness.

Nucleic acid-based assays are commonly employed for environmental and water quality monitoring due to

their ability to detect extremely low concentrations of molecules. Kim *et al.*[30] demonstrated a mobile phone-interfaced microfluidic electrochemical DNA-based biosensor capable of continuous, real-time detection of waterborne pathogens. AC voltammetric measurements are performed using a commercial electrochemical analyzer, which is interfaced with a mobile phone (*via* USB), analyzed by a custom app and displayed on the phone's screen, as shown in Fig. 3c. The electrochemical sensor (Fig. 3a) comprises a working electrode immobilized with DNA probes directed against bacterial RNA. In the presence of target RNA, the DNA probes hybridize with the target sequences and undergo a conformational change, resulting in a decrease of the reduction peak current (Fig. 3b). Based on preliminary experiments, *E. coli* RNA could be detected in water at concentrations as low as 100 nM. One of the unique features of this platform is its capability to sync the test results with Goggle Maps, enabling the user to post the location of contaminated water sources. By doing so, this information can be made readily available to the general public and/or governmental agencies (i.e., the U.S. Environmental Protection, EPA) minimizing potential hazards resulting from toxin contamination.

Towards a more portable and economical system for genetic testing, Stedtfeld *et al.*[54] developed Gene-Z, a compact and lightweight smartphone-interfaced device capable of multiplexed genetic measurements, as shown in Fig. 3d. In addition to smartphones, this stand-alone device can be integrated with other mobile devices (e.g., iPod touch, iPhone, Android-based tablet) *via* Wi-Fi, and incorporates an internal rechargeable battery for use outside of laboratory settings. Green LEDs are used for sample excitation and polymer optical fibers are employed to enhance the collection of emitted fluorescence signals, which are detected by a single photodiode with a build-in photovoltaic amplifier. Polymer microfluidic chips are employed for sample loading and processing, which incorporate reaction wells that contain dehydrated LAMP primers directed against the target nucleic acids. To perform a test, samples are loaded into the microfluidic chip (*via* pipetting), which is inserted into the device. Figure 3e shows test results demonstrating simultaneous detection of two genes of two pathogens (mecA and vicK for *S. aureus* and the stx2 and eaeA for *E. coli*), two pathogens per sample, and three samples per chip. The average time to run one chip is 8.6 min, which is comparable to that of a benchtop real-time PCR instrument (9 min). While this device is still under development, the authors estimate that this device can be manufactured for $<$\$1000 with chips costing \$2–\$10, depending on the application and production volume.

Toward a method for directly detecting nucleic acids without amplification, Fronczed *et al.*[13] developed a smartphone platform for rapid detection of *S. typhimurium* using paper microfluidic chips. This system consists of an iPhone 4 and a custom fluorescence microscope attachment, which incorporates two 10× objective lenses, two band-pass filters (492 and 520 nm), and one 500 nm dichroic shortpass filter. A blue LED is used to illuminate the sample and the fluorescence signals are captured by the phone's camera and processed on a computer using ImageJ. Measurements are performed by loading a sample onto the paper chip, adding Tris–EDTA (TE) buffer for cell lysis, and adding Qubit dye (which fluoresces when bound to double stranded DNA). Experiments were performed to measure samples of 10% poultry packaging liquid containing three different concentrations of *Salmonella*, which could be detected at concentrations down to 10^3–10^4 CFU/mL. Additional experiments were performed to detect *Salmonella* at 10^5 CFU/mL in three different solutions (10% poultry packaging liquid, 10% fecal solutions and 10% whole blood), which resulted in comparable fluorescence signals for all three samples. From these proof-of-concept studies, this platform offers a portable, easy to use method for measuring *Salmonella* DNA without amplification. Additional work is needed to enable species-specific targeting and high sensitivity measurements in raw specimens.

CONCLUSIONS AND PERSPECTIVES

Much progress has been made within the past decade in the field of POC testing. In particular, advancements in biomedical science and engineering have led to new diagnostics which are more portable, economical, and easier to use than conventional lab-based assays. Furthermore, the universal presence of mobile phones in our society makes it possible to leverage these devices for POC testing. In this review, we presented recent developments in smartphone-based diagnostic platforms within the past 6 years with an emphasis on those for cell and biomolecular detection. Currently, two main approaches are employed: (1) an optical attachment is added to a phone's camera for cell imaging or acquisition of optical measurements; (2) an electrical detector is integrated with the phone for electrical measurements. In both of these approaches, the phone provides a simplified user interface, visual display, data processing, storage and wireless transmission. While there are advantages to both strategies, they also face several limitations. For systems employing optical-based detection strategies, the results heavily rely on the

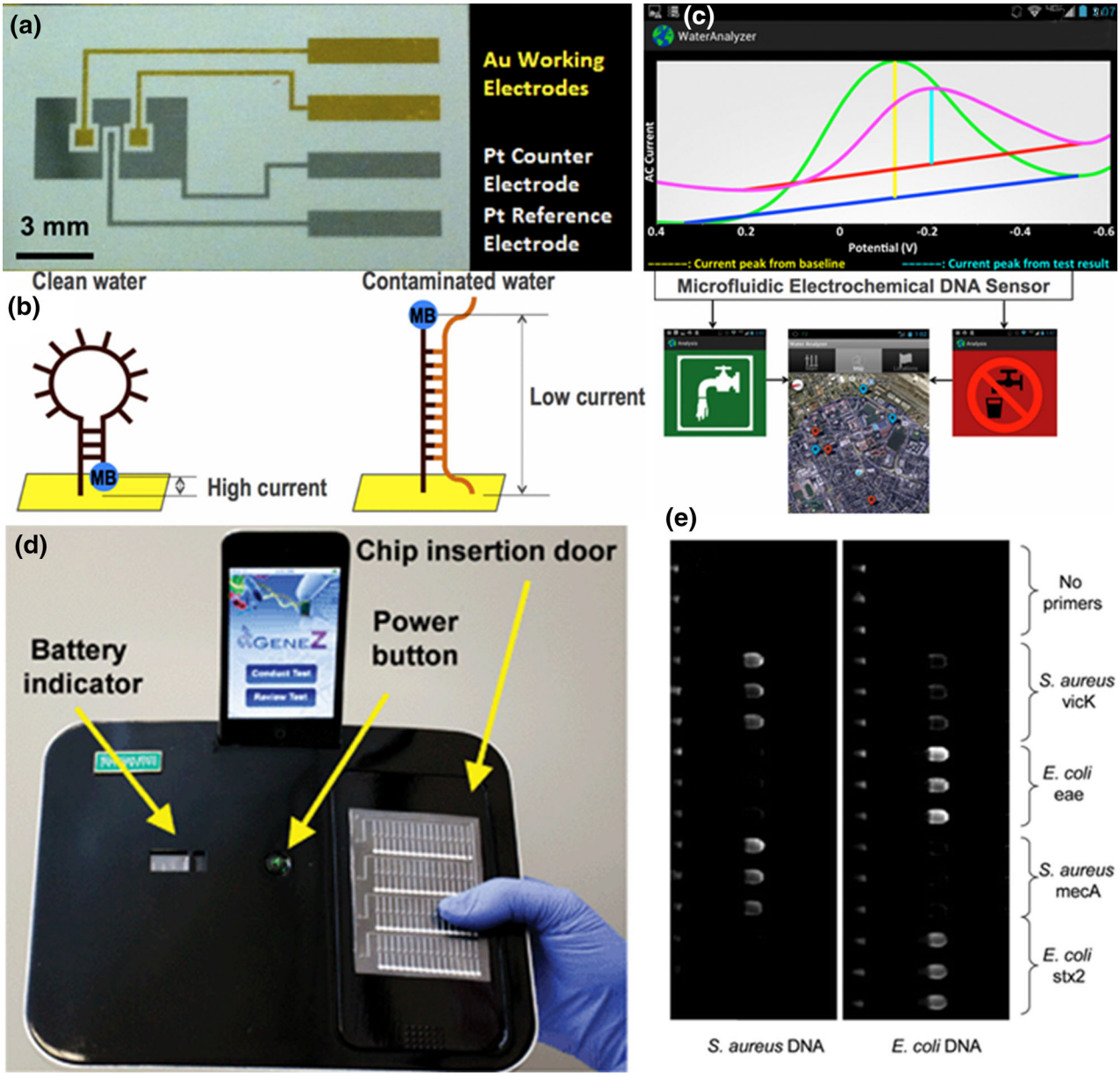

FIGURE 3. Smartphone-based systems for genetic testing. (a) Photograph of a DNA electrochemical sensor developed by Kim *et al.*,[30] (b) schematic illustration of the electrochemical DNA detection scheme, and (c) snapshots of the mobile app displaying AC voltammetric measurements (top), and regions of safe and unsafe water sources on Google Maps (bottom). (d) Gene-Z prototype with an iPod, and (e) parallel assays results for multiplexed detection of *E. coli* and *S. aureus* DNA.[54]

performance of the phone's camera. Therefore, with further advancements in smartphone hardware, phone cameras will likely have improved features including higher pixel density, faster focusing, and better image stabilization. All of these improvements will result in higher quality images which will likely enable enhanced cell imaging and lower detection limits. Systems based on fluorescence imaging/detection must address photostability issues of the fluorescent dyes, especially if testing is to be performed outside of a laboratory setting. Alternative tags with improved photostability, such as quantum dots, can be used or the device can be designed to minimize light exposure from the ambient. For electrical-based systems, digital noise is an important factor that needs to be addressed to obtain accurate measurements. In response, analog and digital filters can be implemented to improve the overall detection sensitivity as well as employing data post-processing. In general, many POC tests are designed to be used outside of laboratory settings with minimal user involvement. However, many smartphone-based platforms require temperature sensitive

reagents or dilution of the sample, which is not practical for use in field settings. To addresses these issues, temperature stable chemicals can be used and sensitivity enhancement strategies (e.g., incorporation of conductive nanoparticles) can be employed for improved sensitivity using raw specimens.

Although the concept of employing smartphones for POC testing is relatively new, researchers have already demonstrated several promising prototype devices which are capable of detecting cells and biomarkers at clinically relevant concentrations. Continued progress in this field will require close collaboration among researchers, clinicians, and industrial partners to improve device performance while maintaining portability and cost effectiveness. Next generation devices should be capable of multiplex biomarker detection which can offer improved detection specificity (i.e., multiple markers for a single disease), and enhanced functionality (i.e., multiple markers for multiple diseases). Syncing test results with Google Maps is a promising approach for applications where rapid, public awareness is crucial, such as water and environmental contamination. Additionally, this feature can be employed to minimize the spread of contagious diseases by mapping disease outbreaks in real-time. Wireless data transfer also offers the potential to improve patient follow-up, particularly in rural settings, by providing faster diagnosis and treatment. While smartphone-based POC technology offers much promise for improving global healthcare, further developments are needed to realize fully functional systems that are simple, cost effective and amenable for use outside of laboratory and hospital settings.

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