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Smartphone-based mobile biosensors for the point-of-care testing of human metabolites

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ABSTRACT

Rapid, accurate, portable and quantitative profiling of metabolic biomarkers is of great importance for disease diagnosis and prognosis. The recent development in the optical and electric biosensors based on the smartphone is promising for profiling of metabolites with advantages of rapid, reliability, accuracy, low-cost and multi-analytes analysis capability. In this review, we introduced the optical biosensing platforms including colorimetric, fluorescent and chemiluminescent sensing, and electrochemical biosensing platforms including wired and wireless communication. Challenges and future perspectives desired for reliable, accurate, cost-effective, and multi-functions smartphone-based biosensing systems were also discussed. We envision that such smartphone-based biosensing platforms will allow daily and comprehensive metabolites monitoring in the future, thus unlocking the potential to transform clinical diagnostics into non-clinical self-testing. We also believed that this progress report will encourage future research to develop advanced, integrated and multi-functional smartphone-based Point-of-Care testing (POCT) biosensors for the monitoring and diagnosis as well as personalized treatments of a spectrum of metabolic-disorder related diseases.

1. Introduction

Detection and quantification of the concentration of metabolites provide useful insights for the health of individuals for disease prevention and management [1–6]. Any change of these metabolic biomarkers, either due to acute fluctuations or chronic disease, can help to determine the health status of an individual in clinical diagnostics. Though the medical treatments have made great progress, it still cannot meet the increasing demand of medical services. Especially in medical resources limited areas, delayed diagnosis and treatment usually resulted in aggravation or even death. It is important to provide insight for dynamic biochemical processes in bio-fluids via continuous, real-time monitoring of biomarkers.

Over the past decades, detecting metabolite biomarkers have been achieved by mainly using laboratory-based technologies including chromatography [7–10], spectrophotometry [11–13], electrochemical analysis [14,15], titrimetric [16], chemiluminescence [17,18], resonance light scattering assays [19]. However, such laboratory-based methods are expensive since they usually require large instruments and professionally trained operators. Furthermore, patients need to wait for a long time because of the time-consuming preparation of reagents and clinical samples, which fails to diagnose the patient's physical change in real time. Therefore, it is necessary to develop a quick and sensitive method for health monitoring and clinical diagnosis in resource-limited condition or non-clinical settings.

Compared to laboratory-based analytical technologies, point of care testing (POCT) is simple, cost-effective, convenient, rapid, portable, and less sample-required [20–25]. It is an ideal and effective alternative to laboratory-based testing that offers tremendous potential for improving the diagnosis and treatment of pathologies especially in resource-limited areas. Owing to the high selectivity and specificity, biosensors are always integrated with POCT [26–30]. The traditional biosensors contain two basic functional units: a bioreceptor (for example, enzyme, antibody or DNA, *etc.*) which is responsible for specific recognition of the target, and a physical/chemical transducer (for example, electrochemical, optical or mechanical) that converts biologically signals into a physical or chemical signal. With its key merits such as user-friendly, high-resolution image acquisition, data-processing capabilities, large internal memory, wireless connectivity, excellent data transfer capability, and friendly operation interface, smartphone has been considered as an inexpensive, quick, easy

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Table 1
A comparison among different smartphone-based sensing methods.

Methods	Description	Advantage	Disadvantage
Fluorescent sensing	emission of light by a excited substance	Good sensitivity, high specificity, rapid response	Background interference; expensive fluorometers
Colorimetric sensing	Change in absorbance or reflectance	Simple process, rapid response, naked-eye reading	Poor accuracy; requirement of clear samples
Chemiluminescent sensing	A light radiation in chemical reactions	High signal-to-noise ratio, high accuracy	Low luminescence, high cost, time-consuming
Electrochemical sensing	Electrons transferred in electrochemical reactions	Rapid response, good sensitivity, high specificity	Environment sensitive; requirement of power supply

to use, and portable device for POCT and mobile diagnostics outside the laboratories [31,32]. Further integration with cloud computing, artificial intelligence, machine learning, and other promising technology (*e.g.* paper-based sensors [33,34], microfluidic chips [35,36], *etc.*), smartphone-based mobile POCT applications will play an essential role in realizing mobile and wearable POCT-based self-tests.

Different techniques have been recently explored to combine smartphones with biosensors and achieved the measurement of blood oxygen saturation [37], pH in sweat and saliva [38], ultrasonic imaging [39], nuclear magnetic resonance imaging [40], and human metabolites such as glucose [41,42], cholesterol [43,44], lactate [45], *etc*. This review will provide a summary of the recent progress on emerging smartphone-based mobile platforms for human metabolites detection within the past several years [46–49]. Insights into the optical and electrical sensing mechanism and its integration with smartphone-based accessories will be discussed in detail, and the comparation of different sensing methods are provided in Table 1. Current challenges and potential emerging research directions desired for reliable, accurate, cost-effective, and multi-functions smartphone-based biosensing systems will be also discussed.

2. Overview of metabolite biomarkers in clinics

Biomarkers are regarded as indicators that can judge the occurrence of metabolic diseases, monitor the development and severity of diseases, evaluate clinical effects and predict the risk of individual or population morbidity. For example, Diabetics perform higher blood glucose levels than normal people owing to insufficient insulin secretion or defective insulin action [50,51]. Uncontrolled diabetes are associated with serious complications, including nephropathy, retinopathy, limb ulcers, and cardiovascular disease. Another well-known metabolite is uric acid (UA) which is the metabolite of purines produced in the liver. The normal range of UA levels in whole blood was reported to be 3.5–7.5 mg/dL and 2.5–6.5 mg/dL for males and females, respectively [52]. However, the people with an excessive UA level suffers from hyperuricemia and even serious complications such as gout, uric acid stones, chronic kidney disease, and even fatal cardiovascular diseases [53–56]. In addition, cholesterol is divided into high-density cholesterol and low-density cholesterol. High-density cholesterol has a protective effect on the cardiovascular system while a high level of low-density cholesterol may increase the risk of coronary heart disease [57]. Moreover, in the early stage of ketoacidosis (DK)/diabetic ketosis acid (DKA), the patients always have a higher serum level of ketone, because the acetoacetate was converted into beta β-hydroxybutyric acid which is highly linearly correlated with the blood ketone level [58,59]. Specially, long-term abnormal levels of such metabolite biomarkers can cause others diseases or symptom. Therefore, monitoring such metabolites biomarker can provide useful information on wellness and health, and facilitate the management of chronic diseases. The metabolites biomarkers in different diseases are summarized in Table 2.

Table 2
The detail of metabolic biomarkers related to diseases.

Metabolic biomarkers	Related-diseases	Ref.
Glucose	Diabetic, Hypoglycemia, Hyperglycemic hyperosmolar syndrome, Diabetic ketoacidosis	[75, 106–108]
Uric acid	Gout, Acute/chronicnephritis, Cardiovascular cerebrovascular diseases, Hyperuricaemia	[33, 109–111]
Lactate	Fatigue, Septic shock, Respiratory insufficiency, Heart failure, Systemic disorder, Toxin intake, Hereditary disorders	[66,90,92]
Cholesterol	Fatty, Coronary heart disease, Atherosclerosis, Dyslipidemia, Cardiovascular diseases	[43,112,113]
Acetylcholine	Alzheimer's disease, Parkinson's disease, Schizophrenia, Motor dysfunction	[114,115]
Galactose	Galactosemia, Hypoglycemia, Growth retardation, Intelligent development	[93,116]
Blood β Ketone	Diabetic ketoacidosis	[58,98]

3. Smartphone-based optical sensing of metabolic biomarkers

Smartphone-based optical sensing is typically divided into three categories, including fluorescent, colorimetric, and chemiluminescence-based detection. Taking advantage of smartphone in both advanced hardware and software, the optical signals are firstly captured by smartphone camera and output as optical images and then using self-designed Android application (App) to convert optical images into color space mode. Color space values show a great relation to analyte concentration, typically divided into RGB (red, green, blue), HSV (hue, saturation, value), HSL (hue, saturation, lightness), CMYK (cyan, magenta, yellow, black) and CIE (international commission on illumination). However, imaging is not always easy, particularly when lighting conditions are hard to be controlled. Hence, some external components have being developed such as light diffuser, dark box, white box, disposable analytical cartridge.

3.1. Smartphone-based fluorescent biosensing

With the characteristics of strong specificity, high sensitivity, and simple operation, fluorescent analysis is commonly used to detect antibodies, nucleic acids, and metabolites biomarkers in clinical diagnosis [60–64]. Since the generation of fluorescence requires radiative excitation, smartphone-based fluorescent detection typically requires external accessories, such as an emission filter, an excitation filter, an excitation source or a black box. The details regarding smartphone-based fluorescence detection listed in this section are shown in Table 3.

Due to the simple process, low cost, and high fluorescence yield, nano-materials have gained much attention. Recently, boronic acid-modified carbon nanoparticles (BCNPs) were proposed as a new fluorescent probe for glucose assay applications [65]. Taking advantage of the strong covalent bond between glucose and boronic acid, BCNPs selectively bind to glucose resulting in fluorescent intensity increase, which is ascribed to aggregation-induced emission (AIE) (Fig. 1A). Further using smartphone to capture fluorescence images and image analyzing software to analyze images, a linear relation between fluorescence intensity and glucose concentrations was found in a range of 3.2 $\times 10^{-5}$-2 $\times 10^{-3}$ M.

Table 3
Smartphone-based fluorescent sensing of metabolic biomarkers.

Target	Accessories	LOD (M)	Linear range (M)	Probes	Ref.
Uric acid	Sample cell, UV flash-lamp, optical filter	2.03×10^{-5}	1×10^{-4}-9×10^{-4}	Alg@QDs-UOx MSs	[68]
Glucose	Battery, led, 3D-printed holder, cuvette	8×10^{-6}	3.2×10^{-5}-2×10^{-3}	BCNPs	[65]
Glucose	Color-scanning app, UV lamp	3.8×10^{-6}	0–1×10^{-4}	GelRed/$[G_3T]_5/Tb^{3+}$ hybrid	[73]
Glucose	Wearable skin pad, UV LED	–	0–1.5×10^{-2}	BiM-CQDs@PSi	[74]
Glucose	Black box, UV lamp,	–	2×10^{-5}-1×10^{-4}	C-dots/Rhodamine B/ thiamine	[75]
Glucose/ Lactate	3D printer, UV-LED lamps, optical filter, wearable sweat patch	7×10^{-6}/4×10^{-4}	1×10^{-5}-2.50×10^{-4}/1×10^{-3}-1.25×10^{-2}	Fluorescein, Ferric ion	[66]

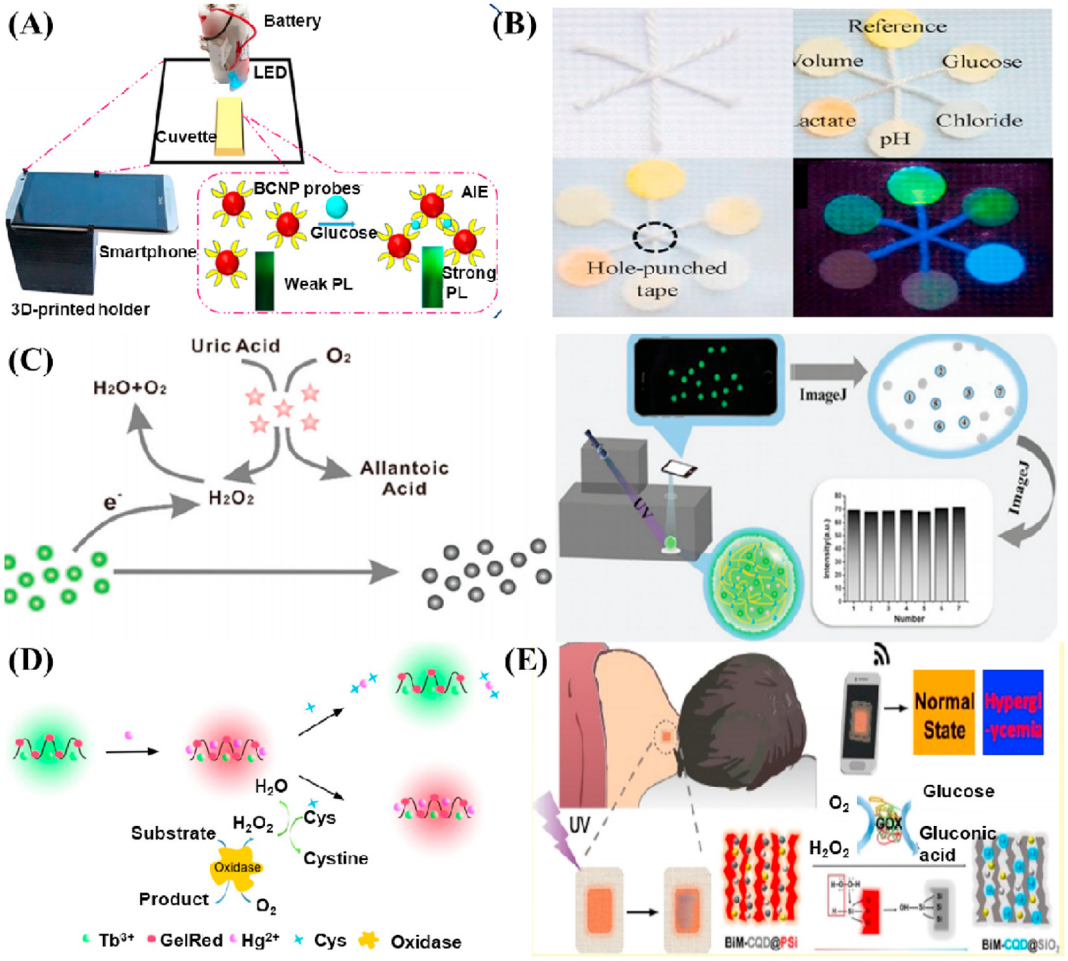

Fig. 1. (A) Schematic illustration of the working mechanism of the smartphone-based fluorescent sensing system for glucose detection, using boronic acid modified carbon nanoparticles. Reprinted by permission from Springer Nature, Microchimica Acta [65], Copyright 2020. (B) Images of step by step fabrication of the sweet, using medical tape, cotton thread and fluorescein embedded in paper substrates [66]. Reprinted from Biosensors & Bioelectronics, Copyright 2020, with permission from Elsevier. (C) Schematic illustration of the principle of uric acid detection based on CdZnTeS QDs [68]. Republished with permission of Royal Society of Chemistry, Copyright 2020. (D) Schematic illustration of the mechanism of ratiometric fluorescent sensing system and its application for H_2O_2, glucose detection [73]. Reprinted from Biosensors & Bioelectronics, Copyright 2018 with permission from Elsevier. (E) Schematic illustration of the smartphone-based wearable sensor for the glucose monitoring using ratiometric fluorescence of BiM-CQDs@PSi upon the stimulation of H_2O_2 generated in GOX-catalyzed oxidation of glucose. Reprinted with permission from Ref. [74]. Copyright 2020 American Chemical Society.

Ardalan et al. fabricated a microfluidic wearable patch and equipped smartphone with UV-LED lamps and an optical filter for the multi-sensing of sweat biomarkers including glucose, lactate, *etc.* [66]. As illustrated in Fig. 1B, the patch consists of five filter papers coated with fluorescein, cotton threads to harvest sweet. Each analyte could be selectively monitored and quantified since each filter paper contains specific fluorescent probes. In this work, glucose was firstly oxidized by glucose oxidase (GOX) to produce H_2O_2, which further was decomposed with horseradish peroxidase (HRP)-catalysis to form ·OH and induced the fluorescence quenching of fluorescein. Lactate detection is based on the recovery of quenched fluorescence of fluorescein caused by the release of FL quencher (Fe^{3+}). Also, a smartphone app has been designed to quantify the concentration of analytes, using a detection algorithm to measure fluorescence intensity. As a result, the sweat glucose and lactate could be detected with a linear range of 1×10^{-5}-2.50×10^{-4} M and 1×10^{-3}-1.25×10^{-2} M, respectively. Furthermore, Zhou et al. designed a luminescent wearable sweat tape (LWST) consist of multi-component nanoprobes for detection of uric acid, glucose and alcohol in sweat [67]. The nanoprobes consist of responsive luminophores, enzyme-loaded gold nanocluster (AuNCs) nano-networks and covered

with MnO_2 nanosheets. The three biomarkers were recognized by their specific enzymes together with the generation of H_2O_2, which further degraded MnO2 nanosheets and turned on the luminescence of three kinds of AuNCs. With the help of a smartphone, the wearable patch and tape allow multiple bio-markers detections at one time. However, such system could not avoid using enzymes and its application would be limited if considering the disadvantages of enzymes such as the high cost and instability of enzymes in harsh environmental factors (*e.g.* temperature, pH, *etc.*). Much efforts have been made to stabilize enzymes, some protective materials are developed. For example, alginate hydrogel microspheres which consists of CdZnTeS QDs and urate oxidase (Alg@QDs-UOx MSs) was developed to improve the stability of urate oxidase and CdZnTeS QDs [68]. Due to the dense multi-layer network structure on microsphere surface, the Alg@QDs-UOx microspheres can not only improve the stability of urate oxidase, but also effectively prevent proteins from attaching to QDs, resulted in a high detection sensitivity. As illustrated in Fig. 1C, the fluorescence of CdZnTeS QDs was quenched by H_2O_2 which was the oxidation product of uric acid in the presence of urate oxidase. Finally, uric acid was detected in a range of 1 $\times 10^{-4}$-9 $\times 10^{-4}$ M with a limit of detection (LOD) of 2.03 $\times 10^{-5}$ M.

Although fluorescent-based sensing can achieve high sensitivity, the fluorescence emission is easily interfered by the background excitation, which can suppress the accuracy of fluorescent-based sensing. Ratiometric fluorescence is a promising strategy for high-sensitivity fluorescent biosensing where the intensities at two or more wavelengths of an emission spectrum or excitation are measured [69–72]. Chen et al. synthesized a fluorescent probe, GelRed/$[G_3T]_5/Tb^{3+}$ hybrid, for ratiometric fluorescence analysis [73], and proposed a smartphone-based fluorescence assay for monitoring the oxidase-related reactions. As illustrated in Fig. 1D, GelRed/$[G_3T]_5$ emitted red fluorescence while $[G_3T]_5$ (i.e. $[G_3T]_5/Tb^{3+}$) shown green fluorescence. The sensing mechanism is based on a specific reaction between H_2O_2 and cysteine, which generates the disulfide and reverses the cysteine-mediated fluorescence changes of $[G3T]_5/Tb^{3+}$. The sensing system presented a linear detection from 0 to 1 $\times 10^{-4}$ M with a LOD of 3.8 $\times 10^{-6}$ M for the glucose detection and a range of 1 $\times 10^{-6}$-3 $\times 10^{-5}$ M for acetylcholine detection.

Noninvasive and visual monitoring of metabolites is highly desirable for patients' diagnostics and long-term home-based health management. Cui et al. firstly proposed a wearable skin pad based on the ratiometric fluorescent nanohybrid, which can achieve a sensitivity of 3.46% mM^{-1} for sweat glucose monitoring [74]. The GOX was co-immobilization with BiM-CQDs@PSi which consisted of red luminescent porous silicon (Psi) particles and carbon quantum dots with blue emission. In the presence of H_2O_2 generated by GOX-catalyzed oxidation of glucose, the red fluorescence of Psi was quenched while the blue fluorescence of CQDs was recovered, resulting in a fluorescence change from red to blue (Fig. 1E). Wearable biosensors are convenient, lightweight and easy to realize automatic biosensing. However, the optical images can not directly be captured and transmitted to smartphone. Hence, integrating wearable devices with mini digital imaging systems should be more desirable in future clinical applications.

Up to date, most of these fluorescence-based sensors exhibit good selectivity, high sensitivity and rapid response [65,66,68,73–76]. However, these smartphone-based assays are not standalone devices and performed with different accessories such as filters and external light sources. Multiple accessories can be affected by variations in environmental temperature, light, humidity and even the sample conditions. Hence, future research should figure out the interference caused by the background microenvironment [77].

3.2. Smartphone-based colorimetric biosensing

Colorimetric measurements have attracted increasing attention due to their great convenience and low cost [78]. Traditional colorimetric measurements evaluate the color intensity with naked-eye or colorimeter. However, naked-eye detection easily suffers from poor sensitivity and accuracy, and is not suitable for those people who exhibit poor color vision. Colorimeter measures the amount of light transmitted through a sample at a specific wavelength in order to determine the concentration of a solution for quantification analysis. However, such colorimeters are of high cost and not portable for daily applications. Handheld devices for colorimetric assays due to their portability and uncomplicated operation are somewhat more promising than bench-top apparatus. Owing to the high-resolution camera and high-performance processer for smartphones, the color quantifications can be completed in a single smartphone with no need of other extra equipment, which contributes to the miniaturization and simplicity of colorimetric measurements. Corresponding information of smartphone-based colorimetric detections are shown in Table 4.

Dipstick or diagnostic reagent strips are commonly used in colorimetric analysis for blood or urine samples [79,80]. However, several concerns such as time-dependent variation and uncontrolled reaction volume caused by the dipping of a strip into biofluid, impair their detection accuracy. Due to the low fabrication cost and easy to batch manufacturing, microfluidic paper-based analytical devices (μPADs) have been applied for low-cost diagnostics, with the advantage of less sample consumption, fast detection speed, simple operation, multi-functional integration, small size and easy portability. Wang et al. reported a novel timer-based μPADs with smartphone for precise cholesterol monitoring [81]. As illustrated in Fig. 2A, the μPADs were embedded with color and enzyme reagents which allowed for colorimetric detection to monitor the fluid residence time on different areas. Smartphones were employed to evaluate the color intensity and record both starting timing and the detection time. Coupling with the oxidase-mediated enzymatic oxidation, cholesterol was precisely monitored with a linear range of 3 $\times 10^{-3}$-6 $\times 10^{-3}$ M. Interestingly, this assay not only analyzed the color images but also read the Quick Response (QR) code information for the highly sensitive metabolite detection. Another method of smartphone-based urine analysis was proposed by integrating a strip in paper-plastic hybrid microfluidic lab-on-a-chip (LOC) [36]. As illustrated in Fig. 2B. The chip was designed as a single microfluidic channel structure with a single inlet for drawing sample solution and embedded with a PDMS micropump to control the sample volume and sampling time. The artificial urine first flowed through the microchannel after pressing and releasing the PDMS micropump, then the urine samples interacted with the test strip inside the microchannel. Finally, the images were automatically processed to measure the hue value for glucose quantification using a customized Android app. However, paper-based colorimetric assays easily suffer from poor color uniformity and intensity which is due to the uncontrolled flow of the reagents.

Several works have been reported to solve this problem, including the modification of paper, the covalent immobilization of enzymes. For example, Wang et al. designed a chitosan-modified multilayer test paper and immobilized detection reagents on the test paper layer by layer (Fig. 2C) [33]. The metabolites detection was achieved by the H_2O_2/HRP/3,3′,5,5′-tetramethylbenzidine (TMB) colorimetric system. A LED lamp was used to provide constant illumination and a smartphone performed as a detector to capture images. The gray value of images was quantified by ImageJ and increased linearly with the concentrations of uric acid and glucose, within the range from 1 $\times 10^{-5}$-1 $\times 10^{-3}$ M and 2 $\times 10^{-5}$-4 $\times 10^{-3}$ M, respectively.

Another challenge for colorimetric measurements is the interference of ambient light. One recent study reported a new smartphone-based platform to quantify glucose concentrations under various light conditions without any restriction [82]. As shown in Fig. 2D, paper-based microfluidic devices were modified with enzyme mixture (GOX and HRP) and divided into three detection zones which immobilized three different detection reagents containing: (i) KI, (ii) KI+Chi, and (iii) TMB. With the presence of glucose, both GOX and HRP work and drive the color change of KI or TMB. Four smartphones with different properties

Table 4
Smartphone-based colorimetric sensing of metabolic biomarkers.

Target	Accessories	LOD (M)	Linear range (M)	Probes	Ref.
Glucose/Uric acid	Multilayer-modified paper, a LED lamp	$1.4 \times 10^{-5}/3 \times 10^{-5}$	1×10^{-5}-$10^{-3}/2 \times 10^{-5}$-4×10^{-3}	TMB	[33]
Glucose	MPAD, closed box, halogen, fluorescent, sunlight light	4.7×10^{-5}	–	TMB/KI	[82]
Glucose	Lab-on-a-chip, imaging box, light diffuser, LED arrays, external lenses	–	0–1.94×10^{-2}	–	[36]
Glucose/Cholesterol/ Acetylcholine/Uric acid	3D closed system device, LED strips	$5 \times 10^{-9}/1 \times 10^{-8}/7.5 \times 10^{-9}/1.3 \times 10^{-8}$	2.5×10^{-8}-$1 \times 10^{-6}/2.5 \times 10^{-8}$-$7 \times 10^{-7}/2.5 \times 10^{-8}$-$9 \times 10^{-7}/5 \times 10^{-8}$-$7.5 \times 10^{-7}$	TMB	[85]
Uric acid	Lateral flow pad, imaging box, a white LED	–	8.9×10^{-5}-5×10^{-4}	TMB	[117]
Lactate	Multilayer paper, light diffuser, a mini dark box, an analytical cartridge	1×10^{-4}	6×10^{-4}-1×10^{-2}	TMB	[45]
Cholesterol	Tpads	1×10^{-4}	3×10^{-3}-6×10^{-3}	Phenol, 4-aminoantipyrine	[81]
Acetylcholine	Portable kit	2.5×10^{-4}	1×10^{-4}-2×10^{-3}	TMB	[114]
L-cysteine	3D-printed black box	6×10^{-8}	1×10^{-6}-5×10^{-4}	AuNPs	[118]

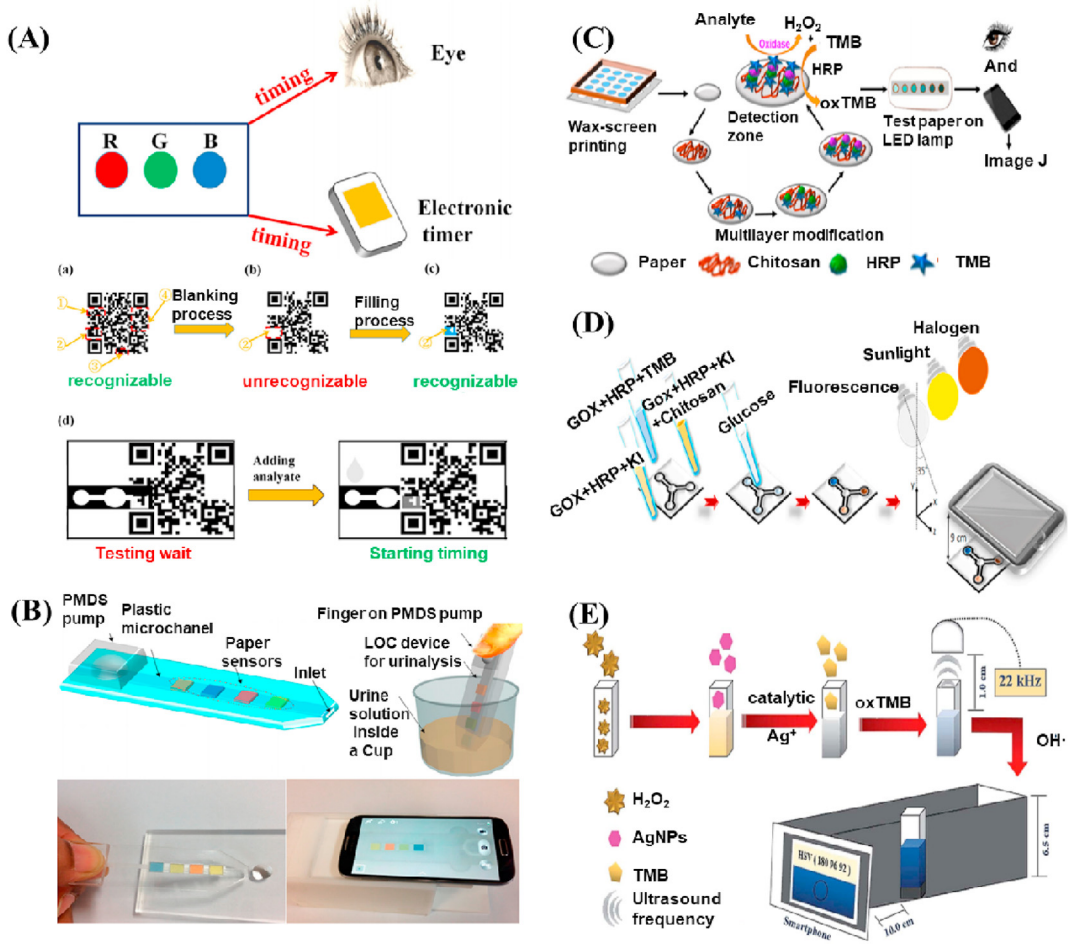

Fig. 2. (A) Schematic illustration of using the timing μPAD for colorimetric detection of cholesterol, based on the color evaluation and monitoring the fluid residence time. Reprinted by permission from Springer Nature, Biomedical Microdevices [81], Copyright 2018. (B) Images of the structure of paper–plastic hybrid microfluidic chip, and incorporation with smartphone for uric acid detection. Reprinted with permission from Ref [36]. Copyright 2017 American Chemical Society. (C) Schematic illustration of colorimetric detection of uric acid and glucose based on a multilayer-modified paper with smartphone as signal readout. Reprinted by permission from Springer Nature, Analytical and Bioanalytical Chemistry [33], Copyright 2018. (D) Schematic illustration of using smartphone coupled μPAD for glucose determination under seven different illumination conditions created by three light sources [82]. Reprinted from Sensors and Actuators: B. Chemical, Copyright 2021 with permission from Elsevier. (E) Schematic illustration of ultrasound-enhanced smartphone colorimetric assay for the H_2O_2 detection [85]. Republished with permission of Royal Society of Chemistry, Copyright 2020. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

were used to acquire colorimetric images under seven light conditions created by three light sources. Those images were used for machine learning after feature extraction, resulting in a more robust and adaptive platform against illumination variation. Combined with a cloud system to

run the machine learning classifiers, this platform achieved the highest classification accuracy with TMB (98.24%) and the LOD of glucose detection was calculated as 4.7×10^{-5} M based on the RGB image model.

Another method to eliminate the interference of ambient light was using scanners for quantitative detection. For example, Hou et al. proposed a WiFi scanner in conjunction with multiplex paper assay for detection of uric acid, glucose, and triglyceride in blood plasma [83,84]. This scanner was controlled by smartphone through WiFi, and allows for rapid images collection. In contrast to imaging using smartphone, scanner can greatly avoid the changes of light conditions, which help increase the accuracy of detection. What's more, integration WiFi scanner with smartphone will greatly simplifies the hardware requirement and facilitates the data transfer and processing. Combining with ultrasound technology, a smartphone-based colorimetric method was presented to achieve an ultrasensitive hydrogen peroxide detection for multiple metabolites detections [85]. As shown in Fig. 2E, silver nanoparticles (AgNPs) can oxidize H_2O_2 into hydroxyl free radicals (·OH), resulting in the oxidization of TMB with a blue color change. With the assistance of ultrasound generated from a smartphone, more and more ·OH could be generated due to the acceleration of the decomposition of H_2O_2, which eventually contributed to the increase of color intensity. As a result, it achieves the detection of glucose, uric acid, acetylcholine, and total cholesterol with a LOD of 5×10^{-9}, 1.25×10^{-8}, 7.50×10^{-9}, and 10^{-8} M, respectively.

Inspired by the development of wearable biosensors, microfluidics technical and paper-based analytical devices, some smartphone-based assays for multiplex detection of metabolites biomarker have been proposed [84,86–88]. For example, Pomili et al. also proposed a paper-based multiplexed device [86]. This μPADs contain three detection zones for the detections of glucose, lactate, and cholesterol based on morphology-dependent Localized Surface Plasmon Resonance (LSPR) resulting from the etching of gold nanoparticles. The three biomarkers were oxidized by their specific enzymes, generating H_2O_2 and further etching gold nanoparticles. Baek et al. reported a multiplex detection platform that integrated μPADs with a smartphone for simultaneous detection of eight biomarkers [84]. A snowflake-liked μPADs were designed and consisted of one sample reservoir connected to 24 detection zones through eight microchannels. The 24 detection zones were divided into 8 groups and each one contained three detection zones that enabled multiplex detection. Every detection zone contains corresponding detection reagents, such as GOX/HRP/4-aminoantipyrine for detection of glucose. The results were displayed by calculating the grays intensities of their colorimetric images through a smartphone.

Compared to fluorescent-based mobile biosensing (Table 1), colorimetric-based assays allow for naked-eye readout, which is more convenient and friendly to users. However, fluorescent-based assays easily achieve increased sensitivity and accuracy, although they require expensive and precise fluorometers for biomarker quantification, which may increase the platform cost and complexity. Thus, colorimetric-based assays should be improved for both sensitivity and accuracy.

3.3. Smartphone-based chemiluminescence biosensing

Chemiluminescence (CL) is a light emission produced from chemical reactions, which consists of two categories: biochemiluminescence and electrochemiluminescence. CL-based biosensors are ideal for portable biosensor development due to their inherent merits of high signal-to-noise ratio and high sensitivity. However, CL is of very low intensity of light emission, and requires highly sensitive detectors for signal quantification. Backside-illuminated complementary metal-oxide-semiconductor (BSI-CMOS), thermoelectrically cooled charge-coupled device (CCD) and complementary metal-oxide semiconductor (CMOS) cameras are normally required to improve the image resolution for smartphone-based CL detection, where the smartphone cameras are used as the detector for image acquisition, and a processor for imaging analysis. The smartphone based biosensors discussed in this section are summarized in Table 5.

A biochemiluminescence-based portable biosensor integrated with a smartphone was reported by Aldo's research group using 3D-printing smartphone accessories for controlling bio-specific reactions to detect cholesterol in biological fluids [89]. As shown in Fig. 3A, the 3D-printing accessories consisted of a smartphone adapter using a dark box, lens holder, a mini-cartridge for blood holder, an enzyme (cholesterol oxidase, cholesterol esterase, HRP) chamber and a CL reagent (luminol) reservoir. Once the blood sample was injected and exposed to the specific enzyme, cholesterol was hydrolyzed by cholesterol esterase, and further oxidized by cholesterol oxidase. The produced H_2O_2 could be hydrolyzed by HRP to form –OH, which driven the luminol oxidation for CL. A smartphone with a BSI-CMOS and 8-megapixel (8 MP) camera was used to capture the CL images, while quantitative analysis of the CL signal was performed using ImageJ software. This assay achieved a linear detection range of cholesterol from 5.17×10^{-4} to 9.98×10^{-3} M (140–386 mg/dL) with a calculated LOD as low as 5.17×10^{-4} M (20 mg/dL). The same group further proposed a 3D printed analytical device that consisted of a disposable analytical cartridge with two reaction chambers, two reagents' reservoirs, a sample chamber, a mini dark box and a smartphone adapter [90]. In this research, smartphone-based BCL sensors were developed to detect lactate based on the lactate oxidase (LOX)-induced enzymatic oxidation and the CL system of luminol/-H_2O_2/HRP. Using a BSI-CMOS sensor and Image J, lactate can be rapidly quantified with a LOD of 5×10^{-4} M and 1×10^{-4} M in oral fluid and sweat, respectively.

Different from the biochemiluminescence assay, electrochemiluminescence is driven by electrocatalysis. Electrochemiluminescence detection exhibits highly localized and time-dependent characteristics because ECL signals are only generated on the electrodes with an applied potential. Chen et al. proposed a smartphone-based hand-hold paper-based bipolar electrode-ECL system for glucose detection in phosphate buffer solution (PBS) and artificial urine (AU) samples with a LOD of 1.7×10^{-5} M and 3×10^{-5} M, respectively [91]. As illustrated in Fig. 3B, the handheld system consisted of a rechargeable lithium battery, a smartphone, a paper-based device, a bipolar electrode (BPE) and an instrument container. Glucose was oxidized by the GOD immobilized on the BPE anode to generate H_2O_2, which oxidized luminol to 3-aminoph-thalate under appropriate voltage, which triggered luminescence. A smartphone camera performed as a luminescence detector to acquire the luminescent images. The obtained images were wirelessly transferred to a computer and quantified by Image J. Such paper-based bipolar or three-electrode biosensors are easy to fabricate and functionalize, however, the poor “wet-strength”, low

Table 5
Smartphone-based chemiluminescence sensing of metabolic biomarkers.

Target	Accessories	LOD (M)	Linear range (M)	Probes	Ref.
Glucose	Instrument container, charging cable, battery, paper device, potentiometer, cmos	3×10^{-5} (AU) 1.7×10^{-5}(PBS)	0–5×10^{-3}	Luminol	[91]
Lactate	3d printed analytical device, minicartridge, mini dark box, adapter, bi-cmos	5×10^{-4} (oral fluid) 1×10^{-4} (sweat)	–	Luminol	[90]
Lactate	Instrument container, cables, potentiostat, cloth-based device, CMOS	3.5×10^{-5}	5×10^{-5}-2.5×10^{-3}	Luminol	[92]
Cholesterol	Minicartridge, mini dark box, adapter, bi-cmos	5.2×10^{-4}	5.2×10^{-4}-9.9×10^{-3}	Luminol	[119]
Galactose	Three-electrode system, fto glass, a black shading box	1.6×10^{-7}	5×10^{-7}-1.5×10^{-5}	N-dots	[93]

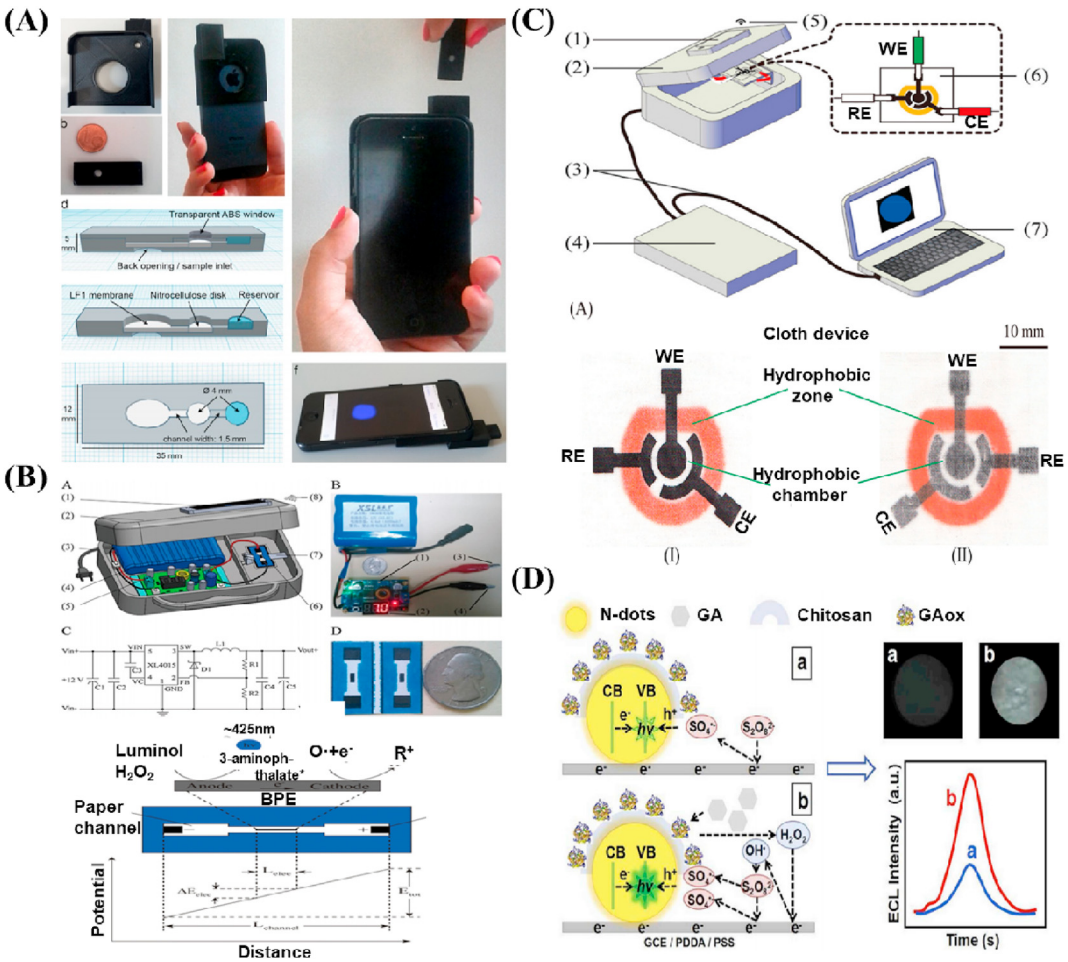

Fig. 3. (A) Images of the 3D-printing accessories embedded in smartphone, including a phone adapter, dark box, lens holder, a mini-cartridge. Reprinted with permission from Ref [89]. Copyright 2014 American Chemical Society. (B) Images of smartphone-based handheld paper-based bipolar electrode-ECL system, including the handheld devices coupled smartphone, the battery and electronic circuit model, the electronic circuit, paper device and schematic illustration the working mechanism [91]. Reprinted from Sensors and Actuators: B. Chemical, Copyright 2016 with permission from Elsevier. (C) Images of cloth-based analytical device containing an instrument container, a potentiostat, a cloth-based device, three electrodes and a computer [92]. Republished with permission of Royal Society of Chemistry, Copyright 2017. (D) Schematic illustration of galactose detection, based on the N-dots/GAox sensor [93]. Reprinted from Biosensors & Bioelectronics, Copyright 2019 with permission from Elsevier.

mechanical strength, weak durability, less flexibility and narrow choices for paper substrates restrict their clinical applications.

To develop a robust electrochemiluminescence system, a microfluidic-based analytical device was designed and coupled with the luminol/H_2O_2/lactate/LOX CL system, which achieved the detection of salivary lactate with a linear range of 5×10^{-5}-2.5×10^{-3} M [92]. The system contained a smartphone, an instrument container, a potentiostat, a cloth-based device, three electrodes and a computer (Fig. 3C). The CL images were firstly collected by a smartphone with an integrated COMS sensor and transferred to a computer by the WiFi network, followed by image processing using Matlab software in a computer. Compared to the paper-based device [91], this cloth-based device partially addressed the limitations such as bad "wet-strength", low mechanical strength, poor durability and flexibility. However, the low CL efficiency should be further improved to achieve a highly sensitive and accurate detection.

One promising approach is using nitrogen quantum dots (N-dots) due to their excellent performance for enhancing CL signals. Nie et al. modified N-dots rich in nitrogen functional groups and proposed an effective co-reactant modifier-based electrochemiluminescence sensing mode for the detection of galactose (GA) with a LOD of 1.6×10^{-7} M [93]. The system consisted of a smartphone, three electrodes and a black shading box. The electrochemiluminescence mechanism was shown in Fig. 3D. Taking advantages of sufficiently negative potential generated by the reduction of $S_2O_8^{2-}$, the electrons transferred from N-dots to the reduced $S_2O_8^{2-}$ ($SO_4^{\bullet-}$), which generated the excited-state of luminophore and light emission. With the presence of H_2O_2, much stronger oxidant ($SO_4^{\bullet-}$) generated and contributed to much stronger electroluminescence. Coupling with enzymatic oxidation, the electrochemiluminescence reaction was triggered and the CL images were collected by the smartphone camera. The results indicated a recovery rate of GA in human serum from 98% to 104% and the RSD was less than 4.23%. In contrast to other assays for GA detection, this method was simple, effective and sensitive.

Overall, chemiluminescent-based assays is more simple and designed to measure light output with high sensitivity in comparison with fluorescent and colorimetric-based sensing. But chemiluminescent-based assays always require sensitive CMOS sensors to improve the signal-to-noise ratio, which require high-cost accessories and complicated operation.

4. Smartphone-based electrochemical biosensing

Electrochemical biosensors have emerged as an alternative for metabolites detection as they have the advantages of high sensitivity, fast responses, low cost and little sample consumption [94]. The detection of electrochemical signals are usually achieved using amperometric and potentiometric measurements [76,95]. The basic principle is to apply an

excitation voltage or current waveform across different electrodes, and simultaneously measure the current or voltage waveform generated at the same electrodes. The accumulation of charge molecules on the electrode surface or a redox reaction will cause a change in the measurable electrical signal. To achieve specificity of detection, electrochemical biosensors require a substance with specific recognition of the target molecule *(e.g.* antibodies, proteins, peptides *etc.*). The electrochemical analysis techniques can be used to generate excitation signals and conduct signal quantification using various functional units of a smartphone including power supply, wired data transmission such as universal serial bus (USB) connectors and audio ports-based connectors [96], and wireless peripherals such as Bluetooth [97] and near-field communication (NFC). The following sections will focus on the smartphone-based electrochemical sensing and their peripherals. The smartphone-based electrochemical detection discussed in this section are summarized in Table 6.

4.1. Wired peripherals

Electrochemical analysis equipment can be integrated with smartphones via wired peripherals such as audio ports connectors and USB connectors. For example, Nemiroski et al. proposed a handheld smartphone device for the detection of glucose in blood using the chronoamperometry (CA) [96]. As shown in Fig. 4A, the integrated system comprised a universal mobile electrochemical detector (uMED) to perform CA and a smartphone to receive the testing results. With the help of an audio ports connector, the uMED can connect to smartphones that allow digital data to be transferred between uMED and smartphones. Interestingly, a customized application in MATLAB was developed for data transmission between smartphone and a remote personal computer, which enabled the remote diagnostic. However, an audio cable was required and typically required specific types of connecting ports.

Compared to audio port-based connectors, universal USB connectors have been used for smartphone-based electrochemical analysis. Guo et al. reported a smartphone-powered medical dongle for evaluation of blood ketone using a disposable enzymatic β-hydroxybutyrate test strip [98]. As illustrated in Fig. 4B, the medical dongle was powered by a smartphone via a USB connector and coupled with test strips via an OTG (On-The-Go: a kind of device communication standard). β-hydroxybutyrate was catalyzed by β-hydroxybutyrate dehydrogenase for acetylacetic acid, and nicotinamide adenine dinucleotide (NADH) was oxidized into NAD^+ with the reduction of Fe (III) to Fe (II). Since β-hydroxybutyrate, oxidation product in the enzyme-catalyzed process of blood ketone, showed a great linear correlation with the blood ketone levels, blood ketone level was evaluated by direct detection of blood β-hydroxybutyrate levels. Driven by a 200 mV direct current supplied from a smartphone, the electrochemical current was generated. Electrochemical data was transferred to a smartphone via a USB connector, then the concentrations of blood ketone were displayed in the smartphone screen and the data was uploaded and stored in the patient's personalized health center. Compared to the bulky biochemical analyzer, smartphone-powered medical dongles perform as a miniaturized electrochemical analyzer with a LOD of 1×10^{-6} M for on-site blood ketone detection. Inspired by the medical dongle, Guo et al. further developed a new test strip with dual enzymatic reaction channel that allows for simultaneously measuring glucose and blood ketone [99]. In this work, GOX was immobilized on the working electrode deposited in the channel 1, while the beta-hydroxybutyrate dehydrogenase (beta-HD) was immobilized on channel 2. Interestingly, only dropping one fingertip whole blood, glucose and blood ketone could be detected. Without the presence of medical dongles, smartphone-based amperometric analyzer has been developed for the total cholesterol (TC) measurements [43]. The test trips could be directly connected with a smartphone via USB with no need the help of medical dongle. The medical smartphone acts as both a power supply and an analyzer which quantifies the electrochemical current induced by the cholesterol esterase/cholesterol oxidase-mediated enzymatic oxidation.

To summary, either audio ports or USB ports can be used as interfaces between smartphone and peripheral devices, which allow for both power supply and data transfer to miniaturize the peripheral devices. However, the compatibility between different smartphones and the flexibility of biosensors should be improved due to the presence of physical cables between smartphones and samples.

4.2. Wireless peripherals

Wireless peripherals require no cables for connecting biosensors and smartphones, which are promising for wearable biosensors developments. Bluetooth is compatible with almost all types of smartphones regardless of the model or brand, more and more research work have used Bluetooth as wireless peripherals. Kang et al. developed a smartphone-based wearable glucose sensing system, using GOX functionalized single-wall carbon nanotubes coated electrodes. As shown in Fig. 4C, this system contained a glucose sensor to input signals, a main microcontroller unit (MCU) to convert input signals, and a Bluetooth-based signal processor unit to transfer data [100]. When electrodes were exposed to glucose, current was generated and then quantified by a semiconductor parameter analyzer. In conjunction with the GOX-mediated enzymatic oxidation, this sensor was capable of detecting glucose with a LOD of 5×10^{-5} M within 5 s. Bluetooth components provide great convenience for wearable biosensors, but batteries are required for power supply. Moreover, the communication between smartphones and sensors are limited by the distance when using Bluetooth.

WiFi is another emerging wireless peripheral with a larger coverage area, higher bandwidth and excellent prevalence in buildings and cities. WiFi allows handheld devices to connect with any internet connected devices for inter-communication. Mercer et al. proposed a WiFi-based glucose biosensing system that consisted of an integrated microfluidic electrochemical detector (iMED) with a three-electrode potentiostat for cyclic voltammetry and amperometry [101] (Fig. 4D). The electrode was coated using glucose-oxidizing films with lower redox potentials. In

Table 6
Smartphone-based electrochemical sensing of metabolic biomarkers.

Target	Accessories	LOD (M)	Linear range (M)	Ref.
Blood β Ketone	Test strip, medical dongle, OTG wire	1×10^{-6}	1×10^{-6}-6.1×10^{-3}	[98]
Uric acid	Screen-printed electrodes	5.4×10^{-6}	2.5×10^{-5}-2×10^{-4}	[120]
Glucose	Otg, three-electrode, detector Umed, cable, glucose test	–	2.78×10^{-3}-2.78×10^{-2}	[96]
Glucose	Strip, otg wire SWCNT thin films, microcontroller, wireless signal processor, glucose sensor	5×10^{-5}	5×10^{-5}-1×10^{-3} 5×10^{-2}-1	[100]
Glucose	Imed three-electrode multi-potentiostat, wifi-based microcontroller	–	1×10^{-3}-1×10^{-2}	[101]
Glucose	Printed circuit boards, ambient light shielding	2.4×10^{-2}	6.5×10^{-2}-7.5×10^{-1}	[103]
Glucose	Three-electrode system, Bluetooth, chipset, lithium, Battery	1.5×10^{-5}	3×10^{-5}-1.1×10^{-3}	[121]
Glucose/Lactate	MPotentiostat, four electrodes silicon chips	1.8×10^{-4}/1.2×10^{-4}	0–1.2×10^{-2}/0–5×10^{-3}	[122]

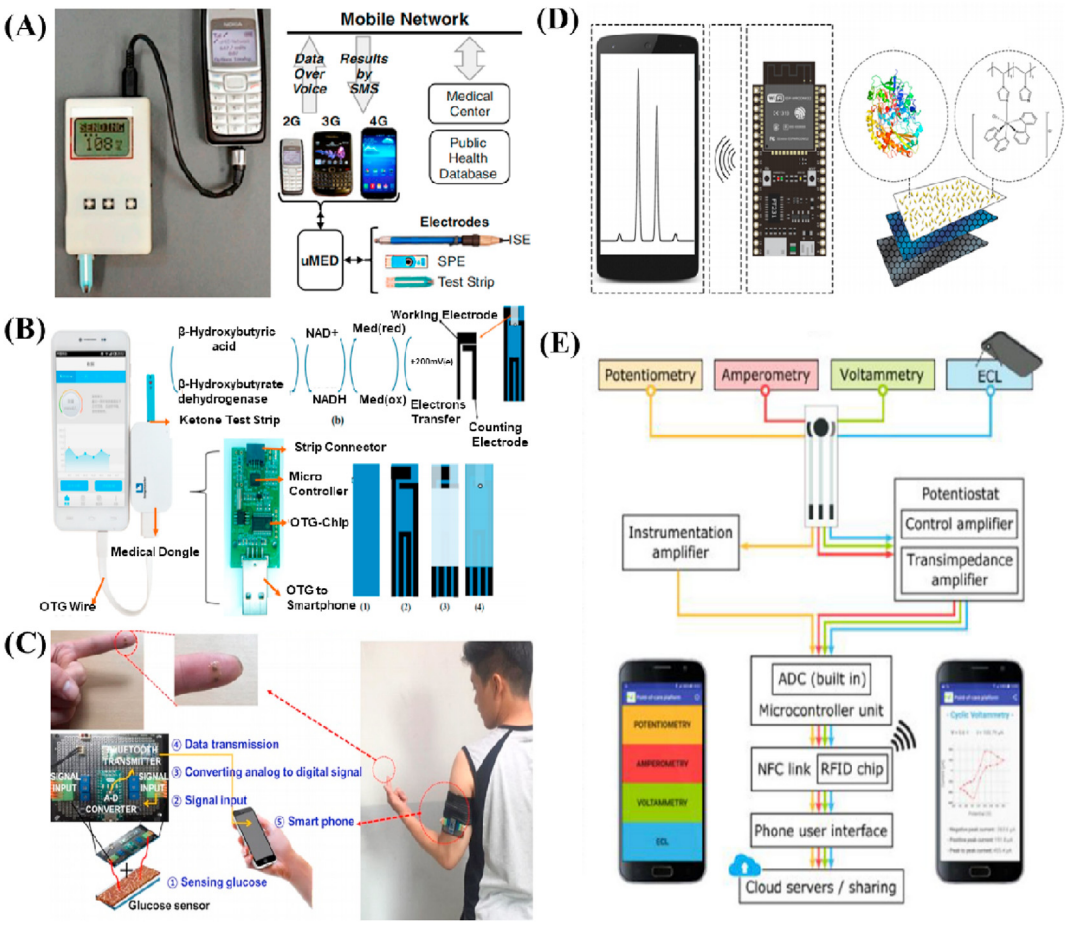

Fig. 4. (A) Image of μMED connected to a glucose test strip and smartphone through audio cable, and illustration of the working process when using smartphone-based μMED. Reprinted with permission Ref. [96]. Copyright 2014 National Academy of Sciences. (B) Image of the medical dongle interfaced to smartphone through OTG connector and to the blood ketone test strip, and schematic illustration of the mechanism of the blood ketone test strip. Reprinted with permission from Ref. [98]. Copyright 2017 American Chemical Society. (C) Images of the smartphone-based wearable glucose sensing system which comprises glucose sensor, a microcontroller unit, a bluetooth transmitter and a smartphone [100]. Reprinted from Applied Surface Science, Copyright 2019 with permission from Elsevier. (D) Images of automated microfluidic wireless potentiostat system containing functionalized carbon electrode, WiFi-enabled potentiostat and smartphone [101]. Reprinted from Sensors and Actuators: B. Chemical, Copyright 2019 with permission from Elsevier. (E) System-level block diagram of NFC-enabled passive system showing the signal measurements, processing and transmission paths [103]. Reprinted from Biosensors & Bioelectronics, Copyright 2019 with permission from Elsevier.

conjunction with flavin dependent glucose dehydrogenase (FADGDH)--mediated enzymatic glucose oxidation, glucose detection was achieved in a linear range of 1×10^{-3}-1×10^{-2} M. However, this system requires batteries for power supply. In addition, Su et al. designed a diaper coupling with a smartphone for in-situ urine analysis [102]. The diaper was embedded with a self-locking biosensor composed of electrodes, enzymes, a microcontroller and WiFi-based communication unit. Glucose and uric acid was detected based on this wearable sensing system, which provided a promising approach for in-situ monitoring multiplex biomarkers in urine.

As an alternative, NFC allows wireless power supply and data exchange between an NFC-enabled device and an NFC passive tag. Escobedo's group developed a passive wireless system (Fig. 4E) comprised of a NFC-enabled smartphone and a circuit board (PCB) which consisted of potentiostat chip (POT), a microcontroller unit, an instrumentation amplifier, an NFC chip and a custom-designed RFID antenna [103]. Specifically, cyclic voltammetry measurement was performed to quantify the current signal generated in the enzymatic oxidation of glucose and reduction of ferricyanide. The electrochemical signal was further amplified and transferred to a smartphone via NFC connection. A custom Android application was designed for both communication and power supply. Interestingly, power supply was achieved by harvesting energy from the electromagnetic field induced by an external RFID reader, which greatly reduced the device size.

To improve the sensitivity and selectivity for metabolites detection, conductive polymers, carbon nanomaterials and metal nanomaterials have been adopted to improve the conductivity and electrocatalytic properties of electrodes in electrochemical sensing [63]. For example, gold nanoparticles and single-wall carbon nanotubes modified screen-printed electrodes were developed for levodopa detection with a LOD of 5×10^{-7} M [104], while using traditional screen-printed electrodes can only achieve a LOD of 6.8×10^{-5} M [105]. This kind of design may accelerate the development of high-sensitivity mobile electrochemical biosensors.

Unlike optical-based mobile sensors, electrochemical-based biosensors require no clear samples and complex, expensive optical instrumentation to eliminate the color interferences. However, electrochemical-based biosensors can be unstable due to the sensitive response to environmental temperature and humidity, in addition to the initially complicated fabrication and testing procedures.

5. Challenges and future perspectives

Recent advances in mobile biosensing techniques based on smartphone and wearable electronics, have been envisaged to foster a paradigm shift in medical self-testing at home and remote diagnostics. New smartphone-based analytical assays with significant improvements in functionality, simplicity, automation, sensitivity, and economy have emerged to meet the growing need for mobile and timely metabolic preclinical analysis. However, the biosensors contain two basic functional units: a bio-receptor for specific target-recognition, and a signal transducer for converting bio-signals into measurable optical or electrochemical signals. Current smartphone-based biosensors were mainly used to transfer and digitalize the optical or electrical signals. Hence, we believe there are still several key challenges in terms of biosensors technique and smartphone application for the smartphone-based mobile biosensors.

Due to high sensitivity and specificity, the enzymes-catalytic reactions were applied in most currently reported platforms. However, the activity of the expensive enzymes is easily affected by a range of factors such as temperature, pH, and ionic strength, which seriously hinder their commercialization for medical self-testing at home. Nowadays, there is a great number of metallic nanomaterials have been proposed to perform enzyme protection or even enzyme-like characteristics. Compared to natural enzymes, they are low cost and simple for storage. However, their low substrate specificity and unclear clinical toxicity, pharmacokinetics, immunogenicity compared to natural enzymes present a significant barrier. We believe that a better understanding of the structure-activity relationship of the nanomaterials using novel concepts and technologies will continuously improve the sensitivity and specificity of smartphone-based mobile detection platforms, endorsing its wider application in POCT technology development for mobile self-testing.

Another challenge for future smartphone-based mobile detection platforms is for multiple analytes detection by non-invasive approach because single biomarker is always lacking of high sensitivity and specificity. Combination of a panel of biomarkers has been proposed in the precise diagnosis of plenty of diseases including cancers. Although there are great efforts have been made to improve the throughput of the mobile biosensors, simultaneously quantifying more metabolite biomarkers (> tens of metabolites) with a simple, economic and accurate manner would be promising for daily self-testing. Advanced microfluidic systems integrating functional nanomaterials would be an promising method because they consume minimal quantities of expensive reagents and samples, and allow multiple analytes to be processed at one time. Moreover, much effort should be put into the development of non-invasive mobile biosensors. Compared to handheld biosensors, non-invasive wearable biosensors have garnered more interest than handheld biosensors due to their potential to achieve continuous, real-time physiological monitoring via dynamic, noninvasive measurements of biomarkers in biofluids (*eg.* sweat, tears, saliva and interstitial fluid etc.) without disrupting the outermost protecting layers of the body's skin and without contacting blood. Such upgrades of the smartphone-based mobile detection platforms will be critical for end-users acceptance and their commercialization.

From the perspectives of smartphone application, smartphones mainly play key roles in optical imaging, data transferring and data post-processing in current smartphone-based biosensing platforms. First, optical image quality are important for the optical smartphone-based detection. Many efforts have been made to control the imaging environment using external accessories to eliminate the outsides lighting interference. Further development should pay attention to developing easy to use, lightweight and cost-effective and even standardized or universal accessories. Taking advantage of the advanced computational capacities of smartphones, developing advanced image processing algorithms such as machine learning and artificial intelligence in optical smartphone-based detection can further improve the accuracy and resolution of quantitative images and sensitivity of biosensing.

For the electrochemical biosensors, bidirectional data transfer between the smartphone and electrochemical analyzer can be achieved by electrochemical methods via either wired or wireless methods, which normally requires complex circuit design. In contrast to wired peripherals, wireless components are promising due to their portability and simplicity. Wireless components such as NFC allow both data and power bidirectional transfer from the phone to the sensor, which greatly reduced the size of the device and maintenance time due to the battery-free design. However, the available power is minuscule (<1 mW), so innovative designs and manufacturing techniques that either use passive sensing techniques or low energy integrated circuit design should be put more efforts in the future work.

6. Conclusions

The smartphone-based mobile biosensing system is an exciting emerging field. This concept holds a great promise for achieving reliable, accurate, cost-effective diagnostics of multiple analytes in resource-limited and non-clinical settings. In this review, we summarized recent trends in the development of smartphone-based portable and mobile POCT for personal healthcare at home and highlighted challenges in achieving reliable, accurate, cost-effective and multiple analytes diagnostics in non-clinical settings. We envision that such smartphone-based mobile biosensing tools will allow daily and comprehensive metabolites monitoring in the future, thus unlocking the potential to transform clinical diagnostics into non-clinical settings for optimal and personalized treatments of metabolic diseases.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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