Biosensors and Bioelectronics 92 (2017) 549–562

Contents lists available at ScienceDirect

Biosensors and Bioelectronics

journal homepage: www.elsevier.com/locate/bios

Mobile phone-based biosensing: An emerging "diagnostic and communication" technology

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ARTICLE INFO

Keywords:
Biosensor
Mobile phone
m-Health
Point-of-care
Diagnostic and communicate
3D-printing

ABSTRACT

In this review we discuss recent developments on the use of mobile phones and similar devices for biosensing applications in which diagnostics and communications are coupled. Owing to the capabilities of mobile phones (their cameras, connectivity, portability, etc.) and to advances in biosensing, the coupling of these two technologies is enabling portable and user-friendly analytical devices. Any user can now perform quick, robust and easy (bio)assays anywhere and at any time. Among the most widely reported of such devices are paper-based platforms. Herein we provide an overview of a broad range of biosensing possibilities, from optical to electrochemical measurements; explore the various reported designs for adapters; and consider future opportunities for this technology in fields such as health diagnostics, safety & security, and environment monitoring.

1. Introduction

1.1. Capabilities of mobile phones

On April 3rd, 1973, Martin Cooper, who is considered the father of mobile phone technology, made the first public call using a cordless phone, which weighed nearly 1 kg (Kennedy, 2013). Since then, mobile phones have evolved continuously, becoming ever smaller and more powerful. The first mobile phone did not have internal memory, and its functionality was limited to making calls. In contrast, modern mobile phones boast up to several Gb of memory and their range of applications is quite wide, spanning high definition (HD) photography and video; internet browsing; sending and receiving emails and multimedia messages; electronic payment; videogames; music; health monitoring; etc. Moreover, these phones can regularly be upgraded by simply installing new applications.

In fact, the power of current mobile phones, also called *smartphones*, is far beyond that of the computer that controlled Apollo 11, first rocket landing on the Moon (NASA). That computer had a processing unit of 1 MHz and an internal memory of roughly 4 kB. In comparison, the processing speed of an iPhone 6s is roughly 2 GHz and its storage capacity is 128 Gb. This means that today, anyone can carry in their pockets 32 million times more information, and access it 2000 times faster, than could the Apollo 11 crew.

Intriguingly, modern mobile phones may contain up to 70 different elements (Rohrig, 2015), including indium and rare-Earth metals. Indium, which, in its oxide form, is necessary for the fabrication of touch screens, is in fact a controversial element, due its abundance on Earth is not clear. Some scientists affirm that there is still more indium in the Earth's crust, whereas others believe that the indium mines will soon be fully depleted. A possible candidate to substitute indium on tactile screens is graphene, as it derives from carbon, which is cheap and abundant; its amenability to touch-sensitive devices has already been demonstrated (Baptista-Pires et al., 2016); and its physical properties enable flexible and more robust screens. Regarding mobile phone touch screens, there exist two main types: resistive and capacitive screens. Resistive screens are based on pressure: when the screen is pressed, the resistive layers enter into contact. In contrast, capacitive screens are based on electrical charge, which is modified when the screen is touched. Under the screen is located the display, also made of rare elements such as yttrium, lanthanum, europium or gadolinium. These elements are responsible for the color and brightness of the display. Other elements, such as tin, copper, silicon and iron, are also present in mobile phones: specifically, in the circuitry.

Abbreviations: AR, augmentedreality; AuNPs, gold nanoparticles; CV, cyclic voltammetry; DCT, "diagnostic and communicate" technology; ELISA, enzyme-linked immuno-sorbent assay; GPS, global positioning system; HD, high definition; LED, light-emitting diode; LF, lateral flow; LOD, limit of detection; NFC, near-field communication; RGB, red-green-blue; SERS, surface-enhanced Raman spectroscopy; PCR, polymerase chain reaction; POC, Point-of-care; QD, quantum dots; QR, code, quick response code; SPCE, screen printed carbon electrodes

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http://dx.doi.org/10.1016/j.bios.2016.10.062
Received 15 June 2016; Received in revised form 4 October 2016; Accepted 23 October 2016
Available online 27 October 2016
0956-5663/

Noble metals such as gold and silver can also be found in the circuitry, albeit in smaller amounts.

A crucial feature of mobile phones is their cameras. Modern mobile phones have at least two cameras: one on the front and one on the back, the latter normally of higher resolution. Some phones have two cameras on the back, to enable 3D imaging. However, a camera is much more than its lens: it includes ambient light sensors, stabilizers, optical zoom machinery, night-vision filters, and many other electronics for image enhancement. The quality of mobile phone camera images is on the order of megapixels, which means that each image is divided into millions of monochromatic portions. However, the number of megapixels are not the only parameter that defines the quality of a camera: a camera with fewer megapixels can obtain better quality photos and videos than a camera with a higher value, provided that the lens and sensors of the former are superior in terms of controlling ambient light, contrast, exposure time, etc.

As a last highlight, the several communication possibilities integrated into mobile phones, such as Bluetooth, WiWi-Fi, 3G/4G, near-field communication (NFC) and global positioning system (GPS), will help facilitate the future construction of Smart Cities. In the Smart City concept, sensors are located everywhere to report on urban parameters (e.g. traffic, weather and pollution) and are connected to mobile phones to form an expansive network. Thus, the combination of GPS and internet connections can yield accurate, real-time information on public transportation, parking spaces, air or water quality, etc. Lastly, but equally important, is NFC, a relatively young connection technology in which radio tags are used to label objects for close-range tracking and control. Such technology can be used in conjunction with mobile phones in a Smart House environment: for instance, as soon as someone enters their house, a central controller could detect their phone and automatically turn on the lights, turn off the alarm, adjust the heating/cooling, etc.

1.2. Mobile phone-based biosensing

Among the major concerns of mobile phone users is health, an area that can greatly benefit from biosensors (Nanhore and Bartere, 2013; Nasi et al., 2015). A mobile phone contains all the components required for a common analytical reader: the screen, which can act as display and controller; an input to capture a signal, which could work via the camera (Otten et al., 2013; Chen et al., 2014; Coskun et al., 2013a; Wei et al., 2014a; Oncescu et al., 2014); ambient light sensors (Fu et al., 2016) and headphone jacks (Wang et al., 2015); memory to store the data; and several wired and wireless (Wi-Fi, Bluetooth, NFC, etc.) connectivity modes. Therefore, considering the billions of mobile-phone users in the world, these phones are an invaluable resource for biosensing. This premise leads us to the emerging "diagnostic and communication" technology (DCT).

The data transmission capabilities of mobile phones are important for health applications: for example, through an internet connection, users can access data libraries (e.g. their medical records) or send biometric measurements to health specialists in real time. In addition, connectivity through GPS could enable studies on global health (e.g. tracking of pandemics) or even environmental monitoring. Along these lines, Wei et al. (2014a) used a Google Maps-based interface on a mobile phone to perform spatiotemporal mapping of mercury contamination in water.

Regarding the possibilities for signal measurement, most of the mobile phones currently on the market feature an HD camera that can detect visual stimuli at high resolution and sensitivity, either in solution (Otten et al., 2013; Chen et al., 2014; Coskun et al., 2013a; Wei et al., 2014a) or on a substrate such as paper (Shafiee et al., 2015; Guan et al., 2014; You et al., 2013). Paper is a cheap and abundant material on which several types of point-of-care biosensors, such as lateral flow (LF) strips, have been developed (Parolo and Merkoçi, 2013; Quesada-González and Merkoçi, 2015). Coupling of different gadgets has enabled optical measurement for colorimetric or fluorescent (Wei et al., 2013; Coskun et al., 2013b; Roda et al., 2014a), microscopic (Tseng et al., 2010; Navruz et al., 2013) or surface plasmon resonance (SPR) (Roche et al., 2011; Fu et al., 2016; Preechaburana et al., 2012) applications. Further possibilities to translate the signal include electrochemical measurements (Wang et al., 2015; Nemiroski et al., 2014; Sun et al., 2014), and even magnetoresistive (Choi et al., 2016) or NFC-based measurements (Azzarelli et al., 2014).

Sometimes adapters or other devices need to be connected to the mobile phone, in order to maintain the distance between the camera and the sample constant; to make a dark chamber for fluorescence; or simply to integrate the biosensing process without compromising the phone's portability. However, creating a universal design is challenging, as each mobile phone has a different design and size. One possible solution for this problem is 3D-printing at home. Three-dimensional printers and related materials are becoming more affordable and offering increasingly higher resolution and material strength, thereby enabling ready fabrication—at home or in the laboratory—of personalized adapters for any mobile phone.

An interesting tool to connect mobile phones to biosensors or other devices, within the reach of any user, is the open-source platform Arduino. This combination of user-friendly software and tunable hardware can be configured to execute several tasks, including remote switching; facial recognition; motion detection; weather sensing; artificial intelligence; and even control of microfluidic systems (Chen et al., 2014). Furthermore, Arduino is remarkably affordable (the cheapest version costs roughly $50) and easy to use (it can be assembled by hand), embodies an open-source philosophy (the hardware and the software are both expandable), and offers wide compatibility with different operating systems (Windows, Linux or Macintosh).

In the future, other DC-based devices could coexist with mobile phones. A past example of such a device was Google Glass, a pair of spectacles designed to integrate augmented reality (AR) into daily life. This device had an integrated camera, such that it theoretically could have been linked directly to a biosensor (Feng et al., 2014). Unfortunately, the project to bring Google Glass to market has tentatively been stopped. Currently, Google is working on Google Lens (Google Official Blog), a smart contact lens that can perform biometric measurements (e.g. measuring glucose levels in the user's tears) and then communicate the results directly to a mobile phone. Other notable devices that could be connected to mobile phones include electronic bandages (Kassal et al., 2015), drones (Priye et al., 2016) and videogame systems (Lee et al., 2011; Karim et al., 2012). Furthermore, new materials such as nanopaper (Morales-Narváez et al., 2015a) and graphene (Baptista-Pires et al., 2016) will soon be exploited for mobile phone-based biosensing.

Over the past few years, various reviews on wearable sensors (Patel et al., 2012) and on the use of mobile phones in biosensing (Vashist et al., 2014; Preechaburana et al., 2014; Xu et al., 2015; Zhang and Liu, 2016; Roda et al., 2016; Comina et al., 2016; Sun et al., 2016a) have been published. These focus mostly on different measurement methods. In contrast, in the present review, we provide a detailed discussion of the capabilities of mobile phones, the different adapters that can be designed for biosensing and how such measurements can be taken. Moreover, we discuss many of the companies currently working with this technology and consider how the marriage of biosensing to such smart devices will influence medicine in the future.

2. Optical-based biosensors

Optical-based biosensors are advantageous for their simplicity and low cost. Using these devices, a qualitative response (e.g. Yes/No) can often be gauged by the naked eye, although quantitative measurement requires an optical detector. In fact, the area of quantification is one in