Mobile phone–based biosensing: an emerging "diagnostic and communication" technology

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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 2,000 times faster, than could the Apollo 11 crew.

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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. 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, Wi-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 which mobile phones are poised to play a decisive role.

2.1. Colorimetric detection

Mobile phone cameras can recognize small differences in color tone, as can be confirmed even in simple home experiments. This capability is based on the Beer-Lambert law, which relates the concentration of an analyte to the intensity of its color in solution (Kehoe and Penn, 2013; Otten et al., 2013; Knuston et al., 2015; Montangero, 2015; Koesdjojo et al., 2015; Kuntzleman and Jacobson, 2016). A mobile phone app that can assign quantifiable values to these tonality differences could be used to maximize the potential of mobile phones coupled to optical-based biosensors as DCTs.

The simplest apps for performing colorimetric detection are based on the detection of the primary colors: red, green and blue (RGB). The standard RGB scale assigns a whole-number value from 0 to 255 for each of these three colors in a given tone, such that [0, 0, 0] corresponds to absolute black and [255, 255, 255], to true white. A good HD camera should be able to distinguish until 16777216 colors. Yetisen et al., 2014 developed a smartphone application algorithm for commercial

colorimetric tests based on RGB detection. However, accurate use of colorimetric measurements requires careful control over parameters such as ambient light, temperature, and the distance between the camera and the sample.

Otten et al., 2013 used a digital camera to capture images from an enzyme-linked immuno-sorbent assay (ELISA) in which they used gold nanoparticles (AuNPs) used as resolving agents, such that the intensity of the red in each cell corresponded to the quantity of protein immobilized onto it. The authors were able to count the number of pixels. They reported coupling of a mobile phone to this system to obtain a low-cost method for detection of different proteins. However, their system was neither portable nor user-friendly. An attempt to make ELISA tests more portable was made by Chen et al., 2014. They miniaturized the assay into a lab-on-a-chip microfluidic system controlled by an Arduino device that was able to automate the pumps and thus, drive the sample across the channels. The Arduino controller was connected to a mobile phone that served two purposes: it was an energy supply, and captured images from the incubation chamber for subsequent RGB analysis.

Berg et al., 2015 reported another interesting portable ELISA system, in which they 3D-printed a housing for the ELISA plates (Fig. 1). As shown in Fig. 1a, the device comprises a group of light-emitting diodes (LEDs) of blue wavelength that illuminate the 96 wells of an ELISA plate. The transmitted light is redirected via optical fibers to the camera of the mobile phone, for signal reading. Fig. 1b-d illustrates the device from different perspectives. Fig. 1e shows the camera reading the signal from the optical fibers, whereby each point corresponds to a single well on the ELISA plate (Fig. 1f). The device appears to be relatively portable and permits both qualitative and quantitative measurements with an acceptable error range and user-friendly interface. However, it has a few drawbacks: for example, it requires external batteries for the LEDs and it lacks an automation process, as the sampling and loading steps are not integrated into the device.

Coskun et al., 2013a and Wei et al., 2014a each reported obtaining a user-friendlier DCT device by integrating housings onto mobile phones (Fig. 2). The former group created a food-allergen detection platform with a very easy-to-use interface. The software gives step-by-step instructions to the user on the mobile phone screen: first the allergen is chosen on the app; then, the app explains to the user how to treat the sample (including which reagents they must add) and prepare the control solution; finally, the camera performs the analysis and displays the results. The system has two components: an LED, which serves as a light source that permeates both the sample and the control solutions; and the mobile phone camera, which works as a relative absorbance reader (Fig. 2a). Wei et al., 2014a developed a similar device except that it had two separate light sources: green and red. These two sources simultaneously provided four data points: red-control, red-sample, green-control and green-sample (Fig. 2b). Combining these four values, the authors obtained a normalized response to quantify the amount of mercury in water. They achieved a limit of detection (LOD) of 3.5 ppb, a value close to the maximum mercury concentration allowed in consumer water in the USA. As we mentioned in the introduction, integration of GPS into mobile phones has also enabled spatial mapping of mercury-contaminated water areas through a Google Maps-based interface for environmental monitoring (Fig. 2c).

Comina et al., 2015 developed an adapter for glucose detection that was even smaller than the adapters mentioned above. Specifically, they miniaturized a microfluidic circuit that contained unidirectional valves and manual pumps, and then placed the circuit over the phone camera. By 3D-printing the lens, they were able to obtain enhanced images.

Performing a field test can be tedious, even with a portable device, because the user must still bring along numerous reagents, sampling materials, etc. Moreover, field assays often require pre-treatment of the sample and careful control of the incubation times. However, many of these problems can be circumvented by developing an assay that runs on a substrate, rather than in solution, as the former type occupies less space and normally does not require sample pre-treatment: the sample is simply added and allowed to flow through the substrate.

The most commonly used substrate is paper, which has been used in several types of biosensors (Parolo and Merkoçi, 2013) due to its simplicity, natural abundance (cellulose is the most abundant polymer on Earth), low-cost production and recyclability. Moreover, in paper-based biosensors microfluidics can be easily generated by simply printing out the desired features using a standard printer or ink-jet printer and hydrophobic materials such as wax (Wang et al., 2014; Chun et al. 2014), polystyrene (Zhang et al., 2015; Shafiee et al., 2015) or ink (Lopez-Ruiz et al., 2014). This approach can be used to fabricate channels, cells, wells and other types of chambers, which can subsequently be photographed using a mobile phone camera.

Guan et al., 2014 performed pioneering work by developing a paper-based assay for blood-typing, whereby they printed hydrophobic bar-channels, made of alkyl ketene dimer, onto Kleenex® paper. In their assay, drops of a blood sample are added to three different channels: one channel to determine the presence of antigen A; another one, for antigen B; and a third channel, to ascertain the Rh factor. Then, buffer is added to help the blood flow through the channels. Finally, the results are transferred to a mobile phone, which informs the user of the blood type (Fig. 3).

Lateral flow (LF) biosensors (Quesada-González and Merkoçi, 2015) and similarly-structured paper strips are easy to integrate into mobile phones, owing to their simple architecture and to the fact that they can usually just be dipped into the sample and subsequently read by a mobile phone camera. Examples of this approach have been reported by Mudanyali et al., 2012, Lee et al., 2013a, You et al., 2013, Oncescu et al., 2013, 2014 and Lee et al., 2014. Fig. 4 (taken from You et al., 2013) illustrates how LF strips are introduced onto an adapter (previously fabricated by stereolithographic 3D-printing) for reading via light-scattering. Mainly, these adapters exploit the mobile phone flash, as a light source and the camera, with collimating lenses, as the detector (You et al., 2013; Oncescu et al., 2013, 2014). Alternatively, in other designs (Mudanyali et al., 2012; Lee et al., 2013a and Lee et al., 2014) an LED is used as the light source. Using LEDs facilitates monitoring of the incipient light (e.g. wavelength, exposure time, light angle and intensity), but requires the use of an external battery. An example of test-strip reading and signal extraction is provided in Fig. 5 (from Mudanyali et al., 2012). The test-strip image is adapted to gray-scale, and then the signaling areas are compared against the background, so that the software can decide whether the signal corresponds to a negative or a positive sample. Importantly, the data recorded by their app can be used to create a spatiotemporal map for tracking the possible spread of a

disease. As in the previously mentioned work of Wei et al., 2014a, this was based on a Google Maps interface.

In addition to analysis of contaminants and pathogens, colorimetric detection on mobile phones can also be used to measure pH. For example, Lopez-Ruiz et al., 2014 developed a microfluidics-on-paper platform to simultaneously measure pH and nitrite levels in different cells (Fig. 6a). Their assay is based on colorimetric reactions and the results are read by the phone camera. In this case, the ambient light is controlled with the flash, such that no adapter is needed. Alternatively, Oncescu et al., 2013, used an adapter to read pH strips (Fig. 6b) as an indirect measurement of sodium ion levels in sweat or saliva samples. Sodium concentration is correlated with the probability of suffering muscle cramps while playing sports; with the risk of enamel decalcification in saliva; and with the risk of calcium removal from teeth, due to low pH. The strips can be stored in a compartment included in the adapter (Fig. 6b 1), thus making the system highly portable. The user can check the pH of their sweat by simply rubbing the strip onto their skin, or the pH of their saliva by spitting on the strip (Fig. 6b 2). Once the sample is added, the strip is placed onto the adapter (Fig. 6b 3), and then flash of the mobile phone is used as light source and the camera, as reader, as in the previously mentioned examples. Finally, the mobile phone screen displays the results (Fig. 6b 4), comprising the pH value (measured directly) and the sodium-ion concentration (as calculated based on the former, using special software).

Surprisingly, a mobile phone camera alone can be sufficient to detect harmful elements in a sample, without the need for paper, antibodies, colorimetric reagents or labeling particles. For instance, Liang et al., 2014 used a phone to detect the bacterium Escherichia coli on spoiled meat. Due to the refractive index of bacteria, which is generally quite high, their presence can be detected with the help of a light source, which could be a lamp or an LED. Liang et al., 2014 were able to detect E. coli on beef samples without any pre-treatment, by measuring the scattered light from a LED with the mobile phone camera. However, detection of bacteria by this method is only possible at high concentrations. They tested several angles between the colliding light and the detector, obtaining their best LOD, 10 colony-forming units per mL, at an angle of 45º.

Another application that can be performed with a mobile phone camera alone is measurement of heart rate (Jonathan and Leahy, 2010; Pal et al., 2014; Huang and Dung, 2016). In this case, the user simply places their finger on the camera and, with the help of a flash or LED light, the camera subsequently records small variations in the pixels. It then uses the values to calculate the user’s heart rate.

2.2. Luminescence and fluorescence detection

An advantage of luminescent DCT–based biosensors is that they typically exhibit higher sensitivity than devices based exclusively on colorimetric reading. Moreover, they do not require a source of light, excluding those devices based on fluorescent methods. This means that luminescent DCT–based biosensors can be created using only a mobile phone camera and an adapter, the latter of which often serves as a dark chamber.

Regarding fluorescence detectors, common choices for the source of the excitation light include lasers (Wei et al., 2013; Coskun et al., 2013b; Yu et al., 2014) and LEDs (Zhu et al., 2011, 2013;

Awqatty et al., 2014). Lasers have the advantage that their light is monodirectional and powerful, and can penetrate the sample without losing too much signal on the way. However, the laser must remain motionless during the assay and the beam has to be placed perpendicular to the detector (the camera) to avoid reading errors or damaging the sensor. This in turn requires a wider and more complex adapter, one which is often equipped with mirrors to redirect the beam. A representative example of the resolution that lasers can provide for fluorescent techniques can be found in the work of Wei et al., 2013, who used a mobile phone camera to take images of isolated fluorescent nanoparticles 100 nm in diameter. Alternatively, LEDs, which are less powerful than lasers, can be used without the risk of damaging the camera or the user's eyes. Moreover, LED adapters are simpler, amenable to miniaturization and portable. This is another case in which the Arduino controller can be integrated into the system, as exemplified by Awqatty et al., 2014. They controlled the LED light emission using the mobile phone itself as energy source; as such, no external batteries were required.

Concerning adapters, they must completely isolate the system from ambient light to provide a dark chamber in which light emission can be measured without any background noise. Development of such chambers, which are important for both fluorescence (Coskun et al., 2013b; Lee et al., 2013b) and chemiluminescence (Roda et al., 2014a) work, should be easy through 3D-printing. Chemiluminescent assays exploit the fact that the sample can be excited without any light source: instead, it is excited using enzyme-coupled reactions, whereby the time elapsed between the addition of reagents and the integration of the samples in the device is not negligible. Roda et al., 2014a 3D-printed a mobile phone dark chamber for a chemiluminescence assay to detect lactate in sweat or saliva. They achieved an LOD lower than that of commercially available colorimetric assays. Thus luminescence-based assays, which give a relatively strong response, should enable sample dilution to reduce matrix noise during analysis of complex samples.

Barbosa et al., 2015 integrated a magnifying lens into a mobile phone (Fig. 7a) to register the intensity of the fluorescence occurring on a microfluidic system (Fig. 7b) with good sensitivity and low error. The critical factor in the assay was the choice of the circuit material: fluorinated ethylene propylene co-polymer (FEP-Teflon), which provides a high index of transparency to avoid signal loss. Interestingly, the microfluidics portion is flexible, making the device relatively portable; however, the method is slower than other methods, such as test strips.

Over the past few years, quantum dots (QD) have risen to great importance for fluorescence biosensing (Noor and Krull, 2014; Morales-Narváez et al., 2015b) as well as for DCTs. For example, Petryayeva and Algar, 2014 performed RGB measurements on images taken with a phone camera in a multiplex assay in which they used QD bioconjugates as labels. The QD emission is reduced by quencher molecules in the presence of an enzyme that can be linked to the QD and to the respective quencher. Using this method, the authors were able to measure the activity of the enzyme in a range of picomolar to nanomolar concentrations.

Regarding the materials mentioned in point 3.1 to fabricate microfluidic channels on paper substrates (Wang et al., 2014; Chun et al. 2014; Zhang et al., 2015; Shafiee et al., 2015; Lopez-Ruiz et al., 2014), another option is the use of photoresists. For instance, Park et al., 2013 developed a paper-based system for the detection of Salmonella based on light scattering. This required a light

source and calibration of the angle between the source of light, the paper and the detector. However, the authors were ultimately able to reduce the device down to three components: the paper component, a fluorescent lamp and a mobile phone (which automatically performed all the calibration in less than a minute, using special software).

Paper-based biosensors can perform luminescence assays and, as mentioned above, can be coupled to mobile phones. For example, Roda et al., 2014b, 3D-printed an adapter for mobile phones (Fig. 8a, b, c) and reported proof-of-principle luminescence assays done on paper membranes coupled to the device. The membranes were introduced onto a cassette with an interesting design (Fig. 8 d). The reagents for the chemiluminescent reaction are pre-stored in the cassette, inside a reservoir that prevents them from mixing untimely; thus, field experiments can be performed using only the mobile phone and the cassettes. The sample is added onto the membrane, the cassette is introduced into the mobile phone (Fig. 8e) and, with a soft coup, the reagents should be liberated to react, and the measurement subsequently taken (Fig. 8f). There are also reports about the coupling of fluorescent (Lee at al., 2013b; Rajendran et al., 2014) or chemiluminescent (Zangheri et al., 2015) LF biosensors to mobile phones. Adapters for the former are wider and less portable than those for the latter, as they require insertion of LEDs, batteries and mirrors.

2.3. Surface Plasmon Resonance (SPR)

Surface Plasmon Resonance (SPR) is a physical phenomenon that occurs when the electrons of a conductive material oscillate due to the excitation provoked by a source of energy, which could be incident light, reemitting part of this energy. SPR has important implications for biosensing, as small changes on the surface of the material (e.g. a crystal or a nanoparticle with antibodies conjugated on its surface) will provoke detectable changes in the reemitted energy. In optics, this phenomenon is often identified by a shift in the maximum absorbance peak of the reflected light. SPR is advantageous in that it is a label-free technique that has high sensitivity yet requires only small volumes of analyte.

Nanoparticle surfaces are surrounded by strong electromagnetic fields that make the SPR effect stronger, especially for noble metals such as gold (Roche et al., 2011) or silver (Fu et al., 2016). This in turn facilitates measurement by mobile phone. Fu et al., 2016 developed a very small adapter for SPR measurements using AgNPs and AuNPs. The most interesting point of their device is that, instead of using the mobile phone camera as detector, they use the ambient light sensor (Fig. 9), a component that is integrated in most current mobile phones, where it regulates the intensity of the display according to the ambient light. They claim that using this sensor for their adapter obviates the need for a large dark room and for a lens to refocus the emitted light, thus providing a cheap sensor (less than $1). Gallegos et al., 2013 fabricated a mobile phone adapter with a photonic crystal fabricated on a plastic substrate attached to a lens system. To demonstrate the feasibility of SPR detection on mobile phones using crystals, they incubated a monolayer of proteins on the crystal and recorded the spectra variations.

Liu et al., 2015 created a quite interesting device that they fabricated with optical fibers to redirect light from a mobile phone flash (an LED light source) to its camera (Fig 10a, b, c, d). The device has

a flow cell (Fig 10a) into which samples and reagents are placed. The image obtained from glass fibers on the mobile phone can be observed on Fig 10d (measurement, control and reference channels) and its respective data processing. Another interesting device was reported by Preechaburana et al., 2012, who used the mobile phone screen itself as the light source (Fig 10e, f, g). An advantage of this method is that the emission wavelength can be easily controlled by simply changing the color on the display (in this case, between green and red).

When plasmons are excited by a stronger source of energy (e.g. a laser), the electric fields surrounding the metallic material are increased, resulting in Raman scattering, a spectroscopic technique named after the physicist Sir Chandrasekhara Venkata Raman. Ayas et al., 2014 applied Surface-enhanced Raman spectroscopy (SERS) to a mobile phone to count molecules in a sample. Although the experiment was performed with a non-portable Raman microscope, they proved that a phone camera could detect single sparkles related to individual molecule vibrations.

2.4. Microscopy

Optical mobile phone-based biosensing has yet another major application: microscopy. Even before the arrival of smart phones, there had already been a few reports of microscopes coupled to mobile phones (Breslauer et al., 2009; Tseng et al., 2010). Breslauer et al., 2009 designed a prototype of a portable fluorescence microscope (Fig. 11a) with the images obtained from 6-µm fluorescent beads. An LED was used as light source, and the condensing lens from a real microscope provided the imaging amplification. Tseng et al., 2010 developed a lens-free microscopy technique based on hologram production and interpretation. In this method, the light emitted by an LED is scattered by the sample, thus providing a hologram that is captured and translated by the mobile phone. Fig. 11b illustrates the design of the microscope as well as the comparison between a 10-µm bead observed on a real microscope and the corresponding hologram from the new technique (alongside its reconstruction, which closely resembles the original bead).

More reports about these optical devices have recently appeared, with several interesting applications in biosensing such as microbial detection (Kadlec et al., 2014), DNA imaging (Khatua and Orrit, 2013; Wei et al., 2014b), blood-cell characterization (Navruz et al., 2013), etc. Regarding the latter, Navruz et al., 2013 designed a device in which the sample was placed into contact with a glass tape that crossed two collimating lenses up to a mobile phone camera. If the glass tape manually rotated, but the sample is held fixed, the device can obtain images from different angles, which, when combined with a customized app, give high-resolution images such as that shown in Fig. 12a.

Digital diffraction is an interesting tool for performing microscopy measurements with a mobile phone (Im et al., 2015, 2016). This technique compares two light beams (one of which passes through the sample), and then constructs a diffraction scheme (Fig. 12b). The diffraction is normally applied on beads or nanoparticles, where the analyte is captured by bioreceptors. Comparison of the results to those from blank samples enables biosensing. Another interesting strategy for microscopy was implemented by Lee and Yang, 2014, who described a device that can work with only ambient solar light. In this device, the sample is placed just over the phone camera

lens, which detects the shadows under the object from the sunlight. The user has to move the mobile phone in order to obtain several pictures that are then combined (in specially designed software) to produce the imaging, similarly to in the previously described holographic technique of Tseng et al., 2010. Recently, Zhang et al., 2016 published a study on holographic microscopy, in which they measured tissue samples with a free-lens microscope and combined the images then with colored images taken with a mobile phone microscope. The combination provided high-resolution images with high color fidelity.

3. Electrochemical biosensors

Electrical measurements often permit sample quantification with higher sensitivity and reproducibility than do optical methods. Nevertheless, it is impossible to interpret electrical response without a device, and the assemblage of electrodes is complicated and is sensitive to environmental conditions. Fortunately, electrodes can now easily be miniaturized and produced at much lower cost than before, thus eliminating the assembly procedure and making them adaptable to mobile phones and other common portable devices (e.g. glucose detectors, wearable hear-rate monitors, etc.) In fact, electrodes can perform many functions. For example, Chen et al., 2014, in their previously mentioned ELISA assay using the Arduino controller, employed copper electrodes to control the flow rate in the microfluidics. The electrodes were powered by the mobile phone through the Arduino connection.

Among the different electrochemical detection techniques, cyclic voltammetry (CV) and chronoamperograms stand out for the simplicity of interpreting the results. Nemiroski et al., 2014 applied both techniques via a portable device compatible with several types of electrodes such as glucose tests (Fig. 13a) or SPCE (screen printed carbon electrodes). Their device takes advantage of mobile-phone connectivity to send the analytical data to a global network and subsequently relay a message with the results back to the user. Wang et al., 2015 developed a CV-based device for nitrate sensing in water that, curiously, is connected to the mobile phone via the audio jack (Fig. 13b). There are two main advantages of using the audio jack connection (Wang et al., 2015; Sun et al., 2014, 2016b): it can simultaneously send and receive information, and nearly all mobile phones have one (however, it has been omitted from some of the latest smartphone models, such as the iPhone 8 and Moto Z). Another connection option is the USB port. However, not all USB ports can simultaneously send and receive information (only the newest ones), and their design often differs with each mobile phone, meaning that a universal device would be difficult to create. Devices can also be powered by a USB connection. Lillehoj et al., 2013 reported a microfluidic system with integrated electrodes (Fig. 13c) connected to a mobile phone (Fig. 13d). Their system was able to perform the assay, run the fluidics and acquire the amperometric measurements in 15 min. The flow is moved by capillarity, so no pumps are required.

Impedance is an electrical technique that permits the detection of miniscule changes in a system, even if it is not conductive. However, this type of measurement is usually slower than other electrical measurements, as it requires a wide scan of different frequencies, whereby the system must be stabilized for each one. Jian et al., 2014 reported a device for bacteria pre-concentration and detection using microfluidics and impedance measurements, respectively. Their device

incorporates a Bluetooth generator for wireless connection with the mobile phone, enabling transmission of the results in real time.

Kim et al., 2015 have created a wireless oral device for detection of uric acid in saliva (Fig. 14), which is placed directly inside the mouth. It uses amperometric measurements to perform real-time monitoring of the uric acid concentration, and can send the data via Bluetooth to a mobile phone or other device. Nevertheless, their device is only a prototype, and it must be subjected to further studies on toxicity and biocompatibility.

4. Other biosensing methods and DCT-based devices

4.1. Other mobile phone-based biosensing strategies

Optical and electrochemical methods are well-known and highly applied biosensing techniques, but mobile phones offer new sensing possibilities such as sound-recording. A phone’s microphone can be used to perform spirometry (i.e. measurement of lung capacity) by measuring the sound of a patient blowing into it (Larson et al., 2012; Goel et al., 2016). To optimize performance of this assay, Goel et al., 2016 3D-printed a spirometry whistle that enabled enhanced recording.

Mobile phones can be coupled to several biosensing techniques, mainly as reader devices; however, they can execute even simpler tasks, serving, for example, as a simple display or network connector. Stedtfeld et al., 2012 fabricated a device for genetic testing based on fluorescence, using photodiodes for collecting the signal. They coupled their device to a mobile phone, which serves as a wireless interface to collect and send the data. Similarly, Choi et al., 2016 developed a giant-magnetoresistance biosensing platform in which a mobile phone serves both as display (to control the machine) and for sending data to the network.

As we previously mentioned, mobile phones, besides working as detectors, displays or network connectors, can also serve as signal producers. This occurs either via the current generated by the phone’s battery, or via the light emitted from the phone’s flash or screen. Surprisingly, mobile phones offer yet another integrated tool that can both produce and read signals: NFC. This technology is based on a device that can send energy to a nearby NFC tag (which does not require batteries) and read the signal that is bounced back. Azzarelli et al., 2014 reported the first NFC-based detector for chemical gas sensing. They modified an NFC tag by replacing part of the circuit with carbon nanotubes, whose interaction with ammonia and hydrogen peroxide is well known. In this case, this interaction gives a chemo-resistive response that works similarly to an on/off logic gate in the NFC tag circuit (Fig. 15a). Therefore, in relation to the presence of analyte, the energy transfer from the NFC to the mobile phone is decreased. Another interesting application of NFC technology has been reported by Kassal et al., 2015, who fabricated a smart bandage for monitoring skin wounds (Fig. 15b) and reporting, by wireless connection, on their status. As in their previous work (oral salivary device, Kim et al., 2015) they detected uric acid via electrochemical methods but in this case, instead of Bluetooth, they opted for NFC technology.

4.2. Other DCT-based devices

Indisputably, mobile phones have become the ideal tools for development of DCT devices. However, in the near future, will they remain the best option? Other devices could appear that

supersede mobile phones. A recent example that ultimately did not arrive to market is Google Glass, an eyeglasses-like device that was supposed to integrate AR in our life by displaying images (messages, maps, video chats, text, etc.) directly in front of our eyes. In terms of the potential of Google Glass, Feng et al., 2014 showed that LF strips could be read by simply looking at a quick response (QR) code stamped on the cassette (Fig. 16a), and then having Google Glass check the data base to determine the analyte that is being measured and its concentration relative to the intensity of the lines. Currently, Google is working on another wearable device, Google Lens (Google Official Blog), which can continuously monitor glucose levels in the user’s tears via integrated electrodes (Fig. 16b).

Drones, which have become a trending topic over the past few years, offer great potential as remote biosensing platforms: specifically, for transporting sensors to places that humans cannot easily reach. Priye et al., 2016 fabricated a lab-on-a-drone system able to perform several lab functions, including centrifugation (using the drone motors and 3D-printed structures), a polymerase chain reaction (PCR) in a portable heater, and sample-sensing (using a mobile phone). Thus drones, which offer impressively low weight (less than half a kilogram), could be used as portable labs.

Oxford Nanopore Technologies has reported a portable device for nanopore-based DNA sequencing that is small enough to be carried and used everywhere. Sample DNA sequences are passed through the nanopore, which has its own current that varies according to the DNA base passing through, which enables characterization of the DNA chain. In the future, these types of devices will surely be within reach of the common consumer, enabling anyone to readily detect the presence of bacteria in the environment—for example, to establish the freshness of food or in other areas concerning the user’s health.

5. Commercially available mobile phone-based biosensing systems

Although mobile-phone biosensing is still under development, several companies are already offering software and hardware to adapt phones for biosensing applications. One such company is Mobili, a company that develops sensors and software related to health, sports, safety, transport, education and research. They develop sensors for mobile phones that can measure parameters such as heart rate, skin temperature, acceleration, distance traveled, etc. There are emerging companies dedicated to developing software for reading and processing the data from LF strips using mobile phones, through personalized software in each case. For example, Novarum has created mobile phone apps that read a QR code integrated onto LF cassettes. The system knows how to scan and interpret the response by simply comparing pixel colors. The phone does not require any adapter. Continuing with optical sensors, there are also companies that are developing mobile phone camera lenses that offer enhanced zoom or image quality, or even enable true microscopy. For example, BLIPS Lenses is a crowd-funded project that offers cheap lenses compatible with any mobile phone. They work by simply being attaching onto the camera. The company Cellscope has developed another type of lens, Oto, for transforming mobile phones into otoscopes that are specially designed to examine children’s ears. Through special software, the images can be sent directly to a doctor.

iHealth is a company specialized in wearable devices (e.g. blood-pressure monitors) and analytical devices (e.g. glucometers) that employ mobile phones as displays via wireless connections. Another interesting device that can be coupled to mobile phones is the MobiUS System (sold by MobiSante), a portable ultrasound machine with a resolution comparable to hospital equipment (Wojtczak and Bonadonna, 2013).

Regarding electrochemical measurements, PalmSens sells the EmStat, a portable potentiostat with a wide working range (1 nA to 100 mA) and a resolution of 1 pA. This device is compatible with computers, tablets and mobile phones, and can perform several techniques, including CV and amperometry.

6. Conclusions and future perspectives

Mobile phone devices have been shown to offer great utility for biosensing applications and as DCT, whether in solution, on a substrate or even in gas. As summarized in Table 1, this has been made possible in part by a broad array of analytical techniques, including colorimetry, fluorescence, SPR, microscopy and electrochemistry. Also invaluable are the latest advances in mobile phone technology, including increases in memory and in processing power, the resolution of cameras powered by ambient light sensors, GPS, wireless connectivity (internet, Bluetooth and NFC technology), portability, apps, etc. Nevertheless, the success of mobile phone-based biosensing will strongly depend on biosensing technology, which still is the bottleneck of such impressive coupling.

Among various biosensing technologies, paper-based biosensing is very promising for coupling to smart phones. This is due to the advantages of paper, including its natural abundance, recyclability, low-cost and simplicity, both in its development and in its use. Furthermore, paper-based biosensors have proven to be truly portable: in most cases, they do not require additional reagents or devices, or any additional energy source beyond the mobile phone itself.

We strongly believe that mobile-phone biosensing is going to decentralize current healthcare systems and environmental, safety and security labs. We predict the rapid spread of POC (point-of-care) devices and other user-friendly monitoring devices for use at home or elsewhere. These developments will fall in line with the future development of Smart Cities, in which mobile phones will be crucial for network connections. In addition, other devices (e.g. smart glasses or dermal wearables) may soon appear that could co-exist with mobile phones for health monitoring.

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Abbreviations

AR, augmented reality; 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.

Highlights

- Mobile phone-based biosensing is a key tool which will permit the progress of society into smart cities: full connection everywhere.
- “Diagnostic and communication” technology will permit to any user to perform a quick assay and read the response with clarity either at home or in the field.
- Optical and electrochemical biosensors, among others, can be integrated into mobile phones with quite acceptable resolution and sensitivity.

Figures

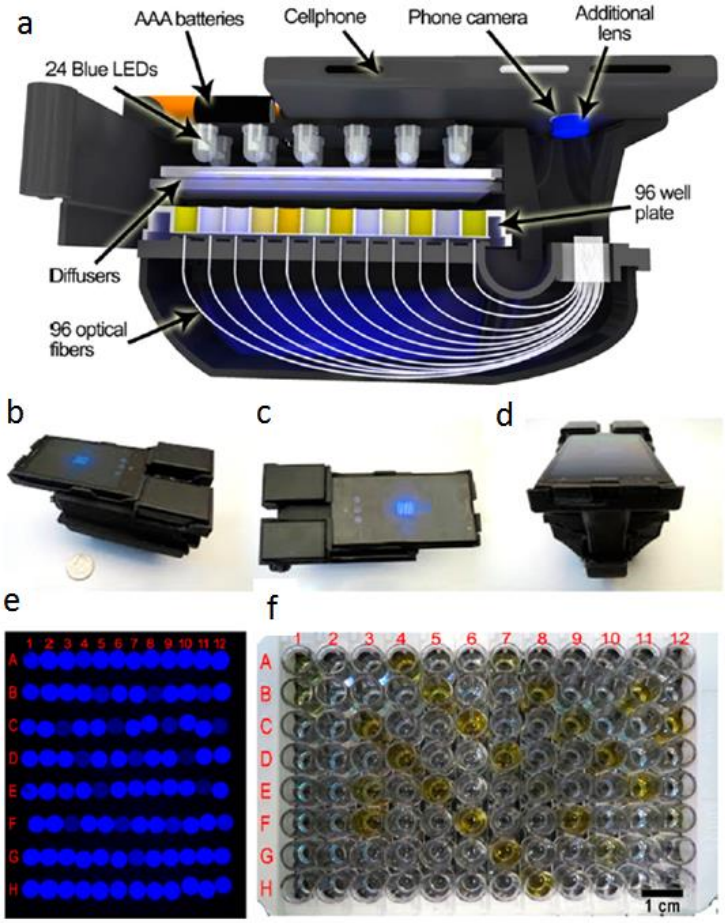

Fig. 1. Mobile phone adapter to perform ELISA tests. (a) Scheme of the device, (b) (c) (d) overview of the device and (e) image obtained from (f) ELISA plate. Adapted with permission from Berg et al., 2015. Copyright 2015 American Chemical Society.

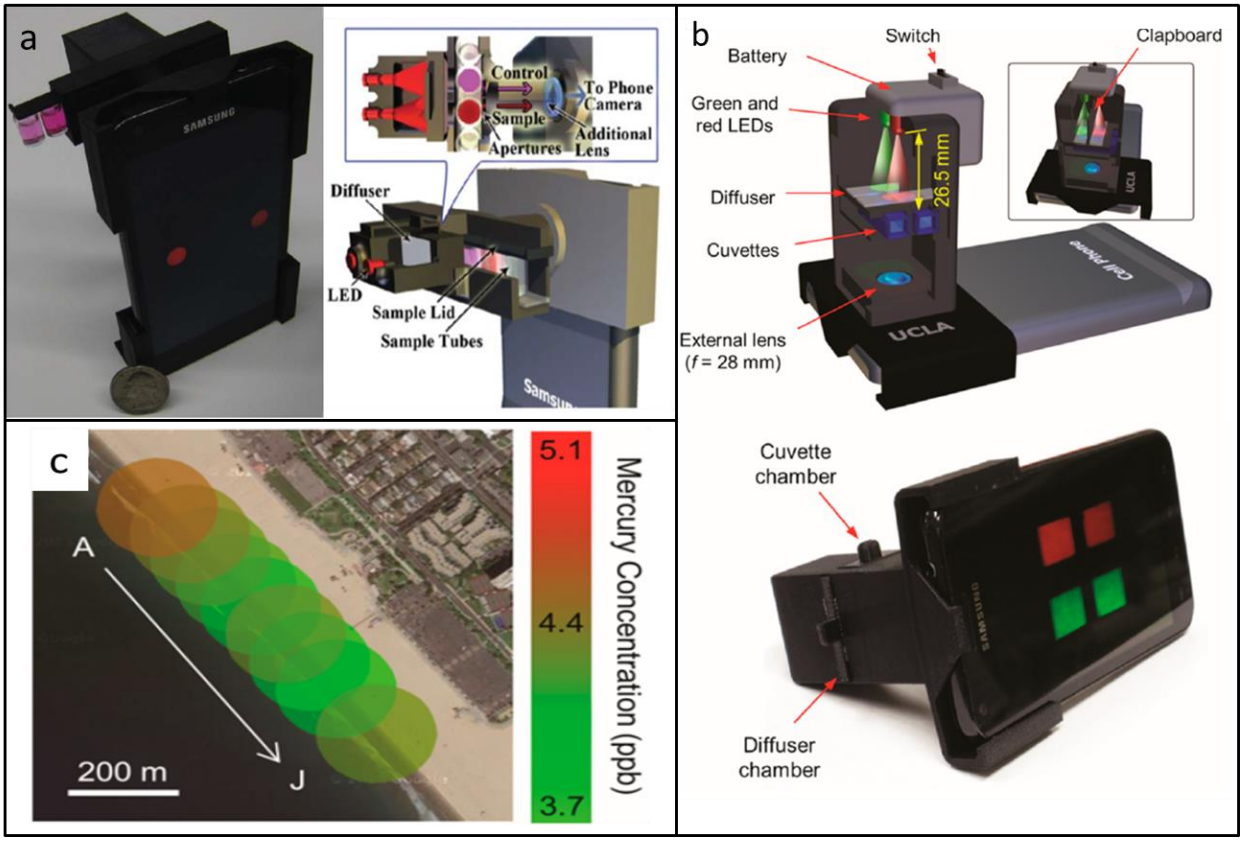

Fig. 2. Integration of different housings on mobile phones to perform colorimetric assays. (a) Colorimetric mobile phone reader for food allergens. Adapted with permission from Coskun et al., 2013a. Copyright 2013 Royal Society of Chemistry. (b) Colorimetric mobile phone reader for mercury detection and (c) spatial mapping of the contaminated areas registered with this device. Adapted with permission from Wei et al., 2014. Copyright 2014 American Chemical Society.

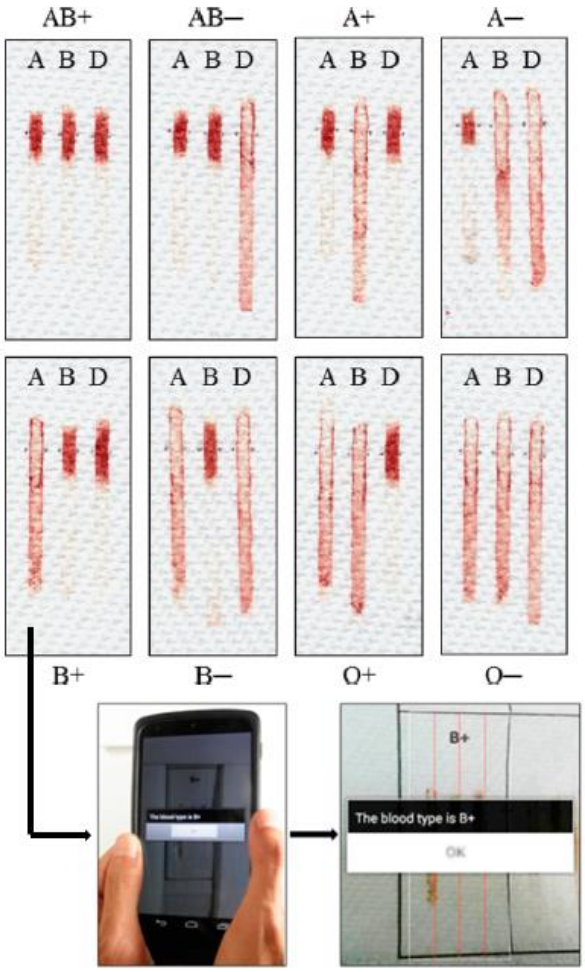

Fig. 3. Use of a mobile phone to interpret a paper-based biosensor for the determination of blood type. Adapted with permission from Guan et al., 2014. Copyright 2014 American Chemical Society.

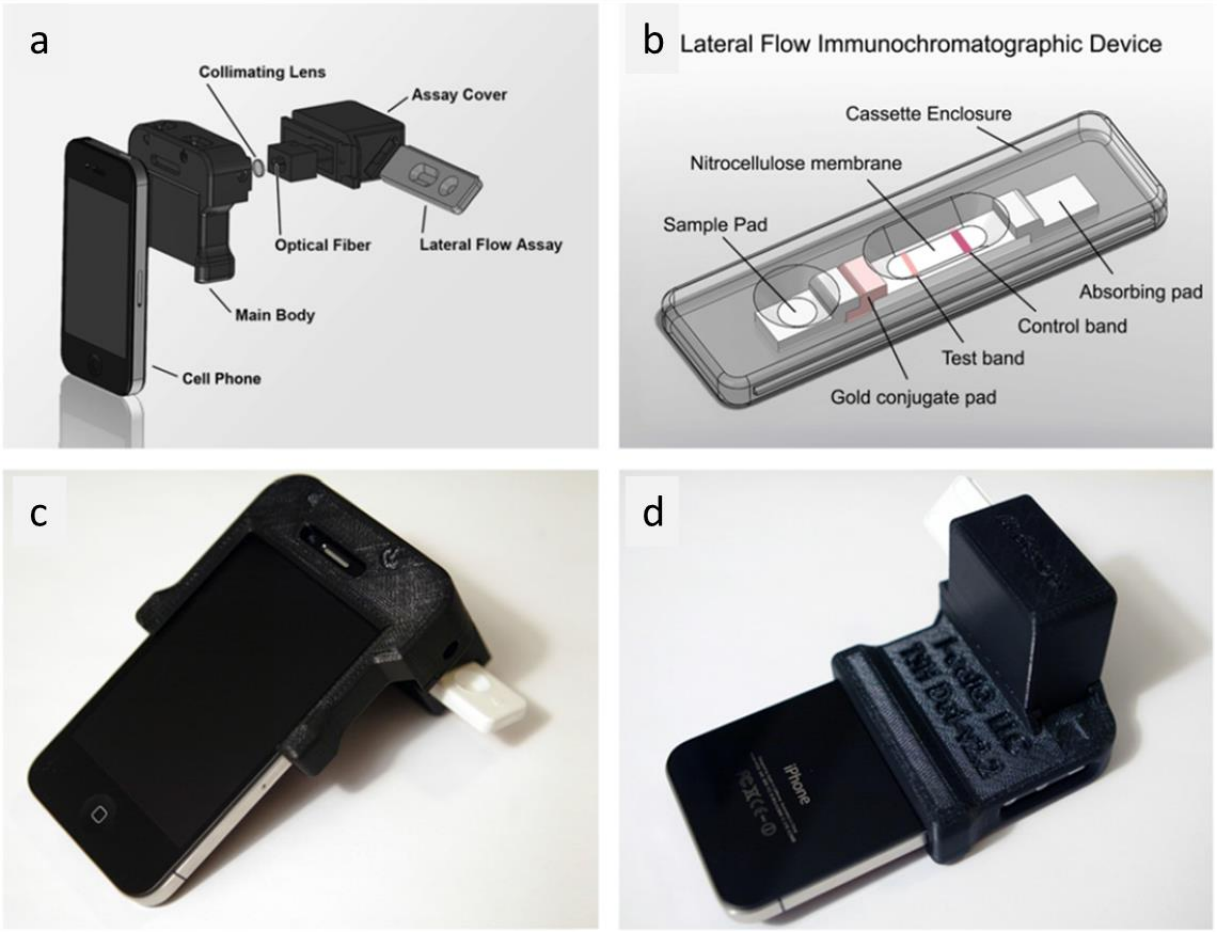

Fig. 4. (a) Schematic representation of LF adapter for mobile phones, (b) LF cassette composition and (c) and (d) images of the real adapter. Adapted with permission from You et al., 2013. Copyright 2013 ElSevier.

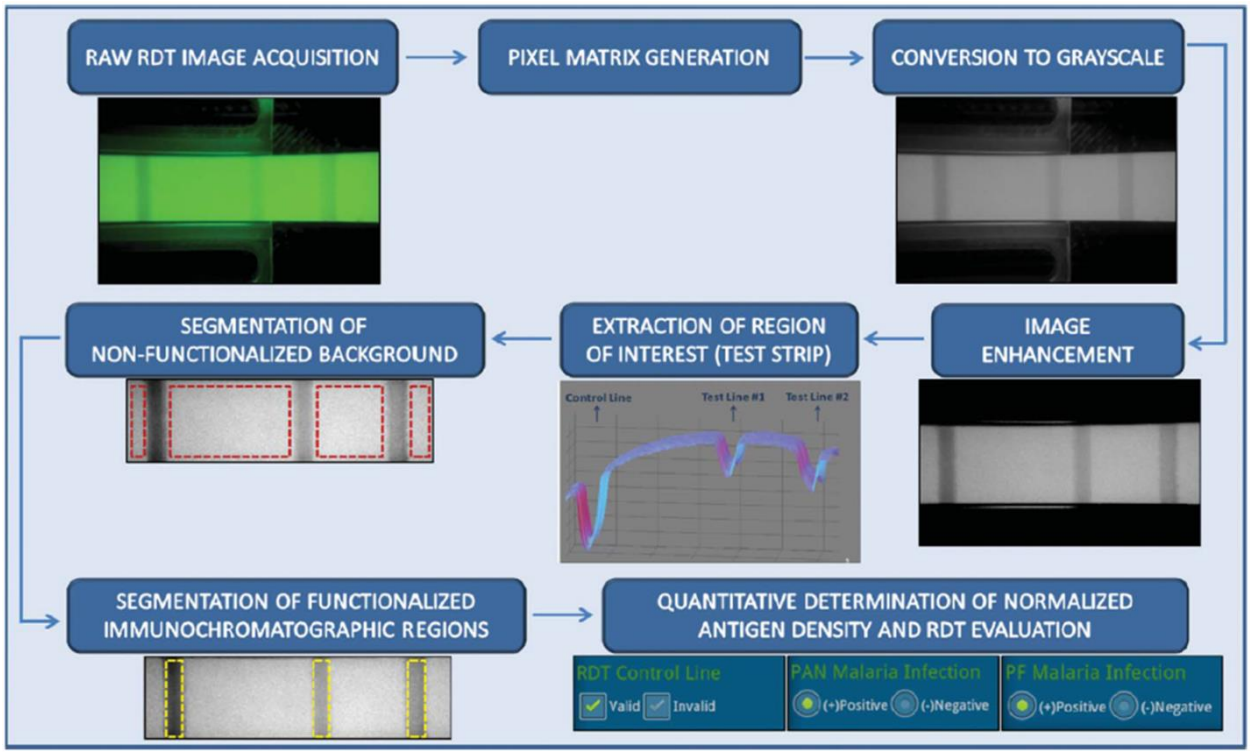

Fig. 5. Different steps during the image processing of a LF strip with mobile phone software. Adapted with permission from Mudanyali et al., 2012. Copyright 2012 Royal Society of Chemistry.

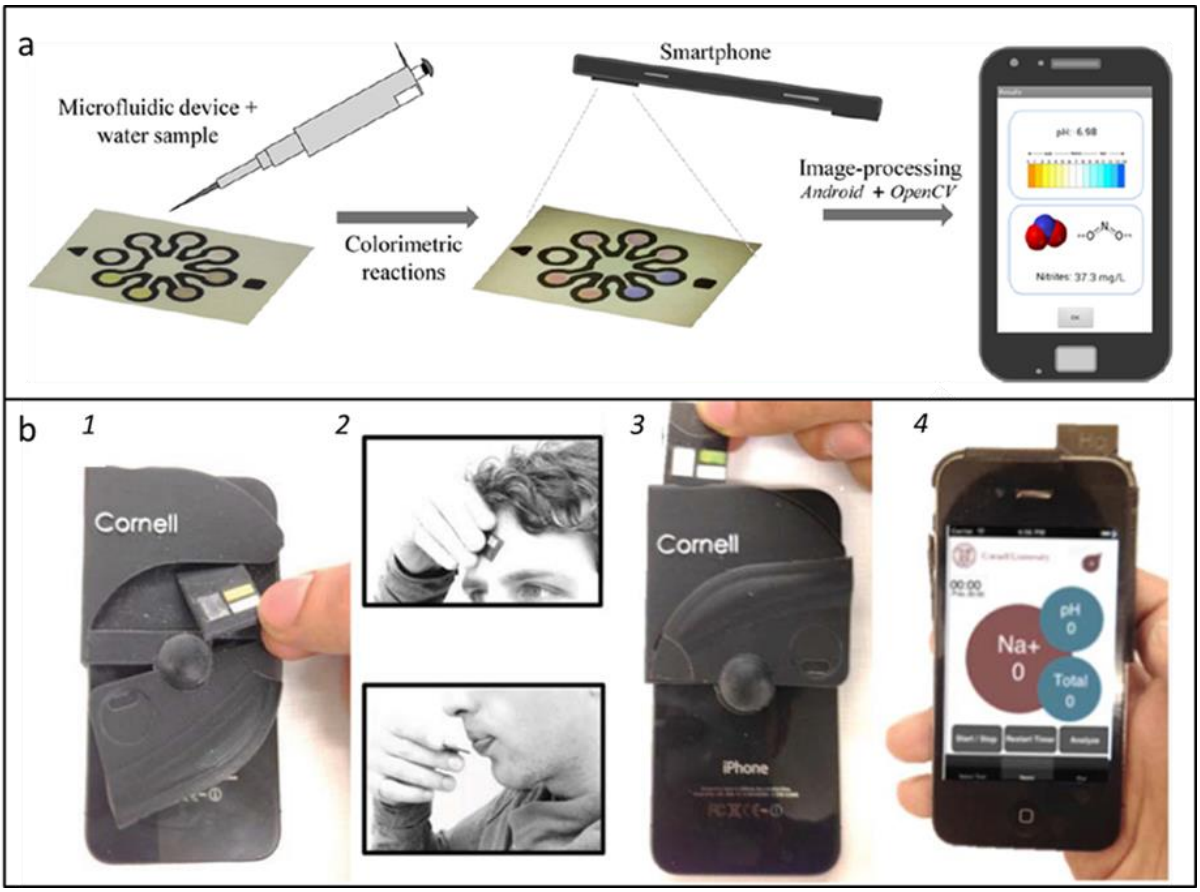

Fig. 6. pH detection by using mobile phones as colorimetric readers. (a) Detection on paper microfluidic system. Adapted with permission from Lopez-Ruiz et al., 2014. Copyright 2014 American Chemical Society. (b) Detection by using test strips: (b1) Strip is removed from storage compartment, (b2) sample, sweat or saliva, is applied, (b3) the strip is placed on the adapter, in front of the camera and (b4) response is obtained. Adapted with permission from Oncescu et al., 2013. Copyright 2013 Royal Society of Chemistry.

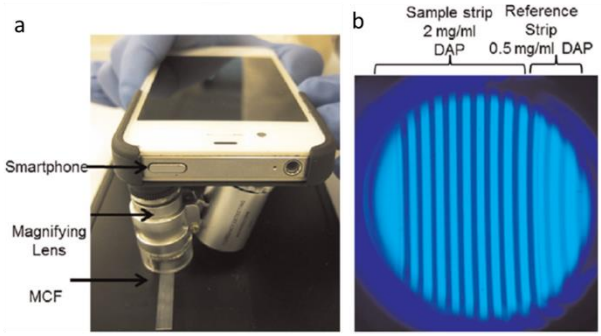

Fig. 7. (a) Magnifying lens used to read the fluorescence on a microfluidic system (b). Adapted with permission from Barbosa et al., 2015. Copyright 2015 ElSevier.

Fig. 8. Adapter for chemiluminescent strips reading. (a), (b), (c) images of the devices, (d) scheme of the cassette for the strips, (e) coupling of the cassette on the mobile phone and (f) signal procurement. Adapted with permission from Roda et al., 2014b. Copyright 2014 American Society of Chemistry.

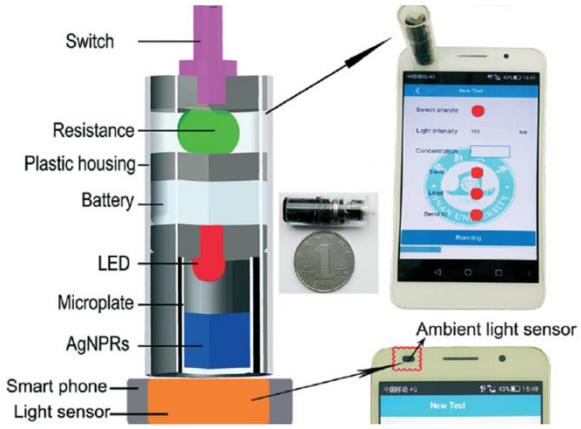

Fig. 9. Tiny SPR adapter using the ambient light sensor present in the mobile phone as reader. Adapted with permission from Fu et al., 2016. Copyright 2016 Royal Society of Chemistry.

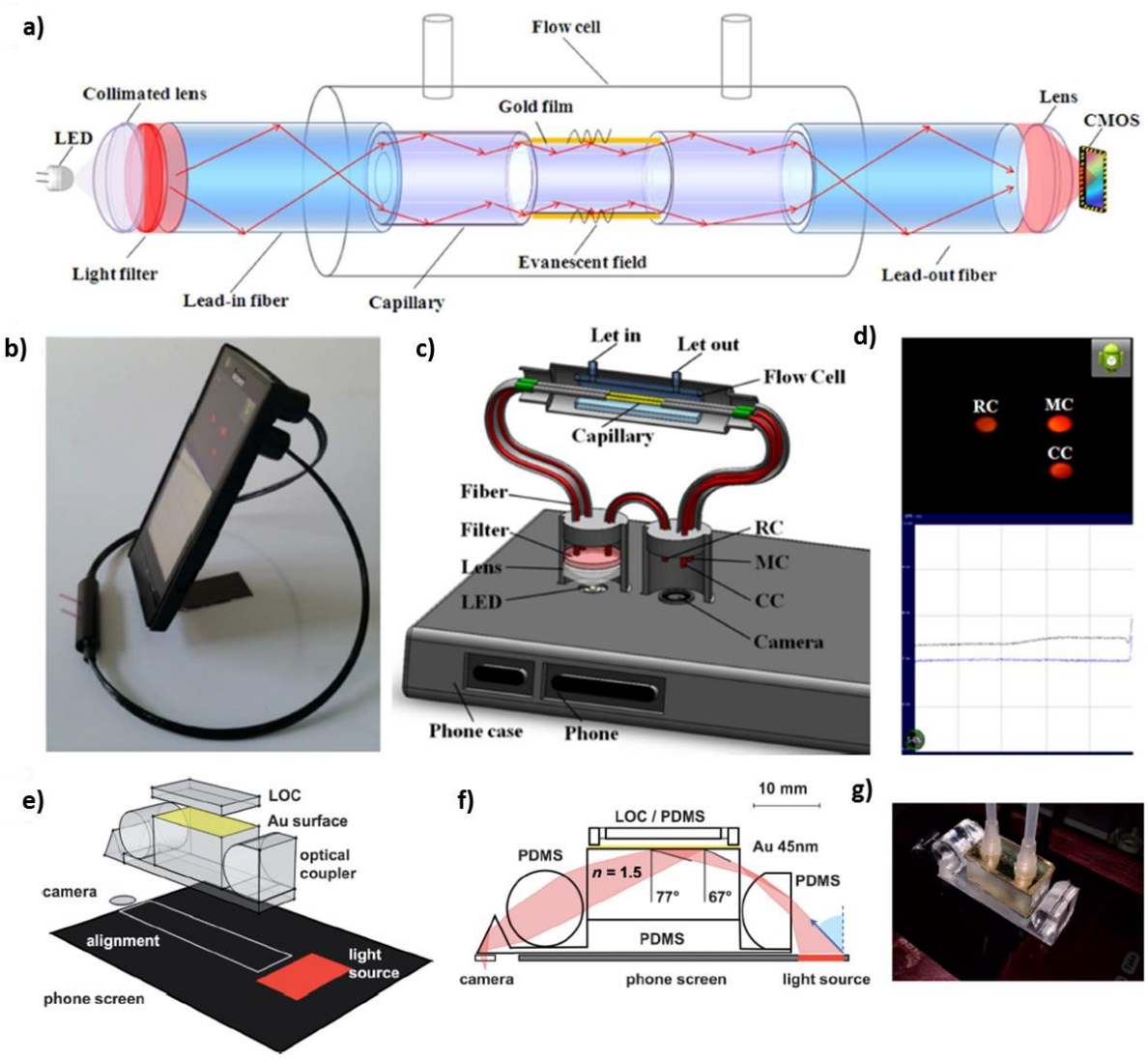

Fig. 10. SPR-based mobile phone biosensor: (a) scheme of the device, which is integrated (b) on the mobile phone (c) connecting the flash camera and the camera with optical fibbers; (d) response registered. Adapted with permission from Liu et al., 2015. Copyright 2015 Nature. (e) Scheme of SPR biosensor that uses the screen as source of light: (f) explanation mechanism, (g) image of the device. Adapted with permission from Preechaburana et al., 2012. Copyright 2012 Wiley-VCH.

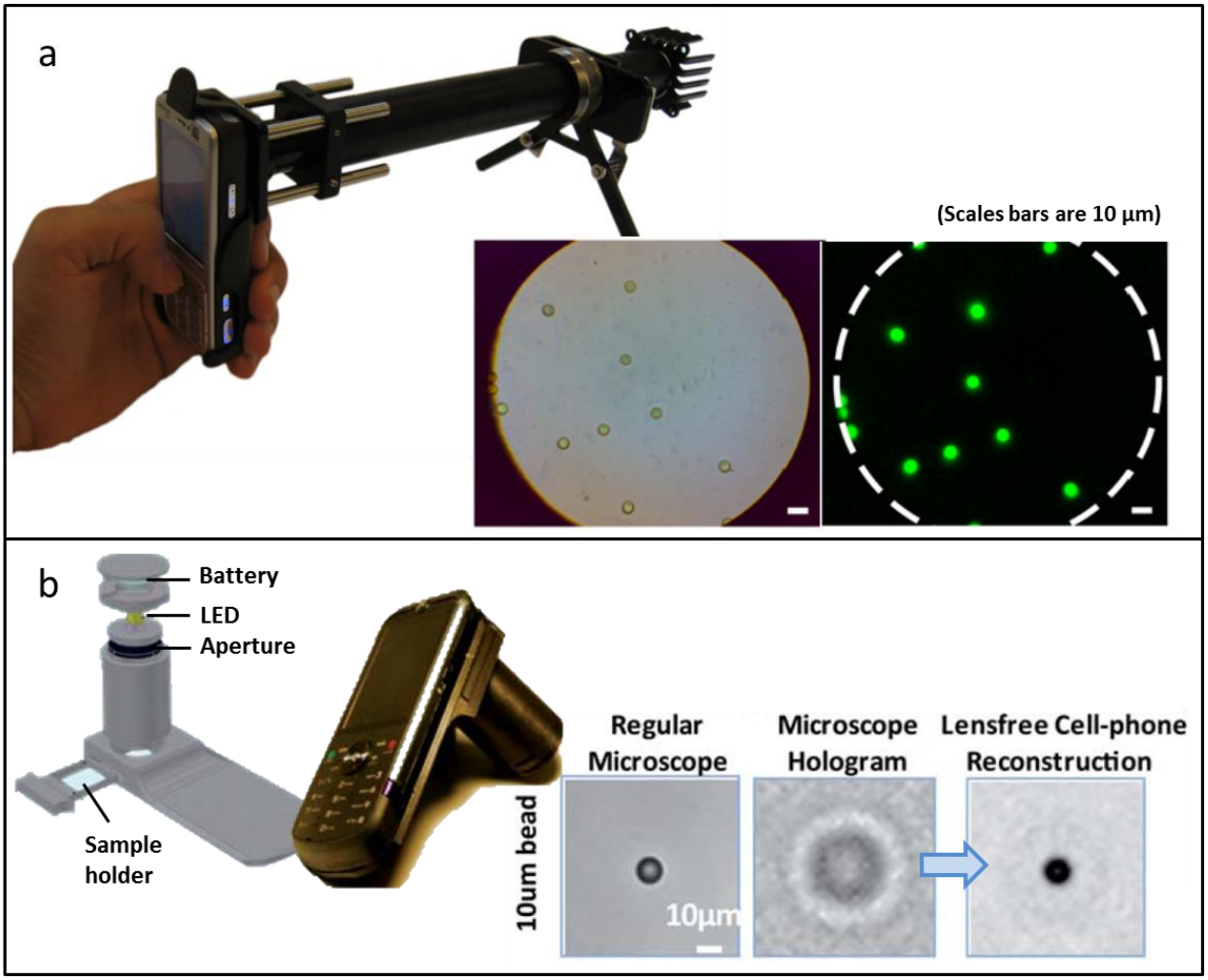

Fig. 11. (a) Fluorescent microscope adapted for its use on mobile phones. Brightfield (on the left) and fluorescent (on the right) captures of fluorescent beads are shown. Adapted with permission from Breslauer et al., 2009. Copyright 2009 Public Library of Science. (b) Free-lens microscope based on hologram imaging. Adapted with permission from Tseng et al., 2010. Copyright 2010 Royal Society of Chemistry.

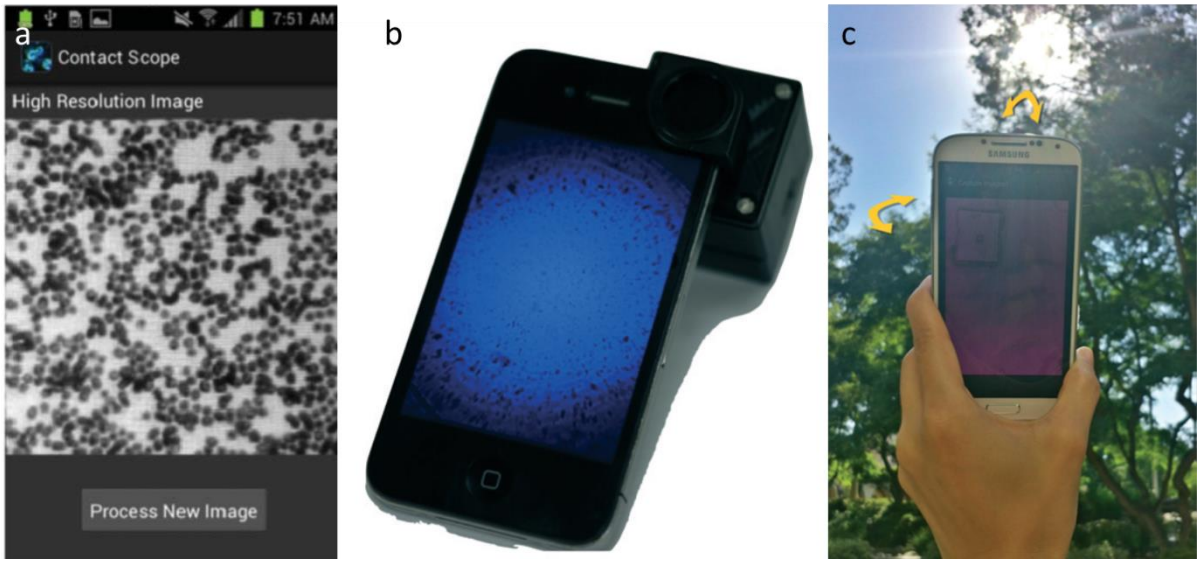

Fig. 12. (a) Image of blood cells obtained with a mobile phone microscope. Adapted with permission from Navruz et al., 2013. Copyright 2013 Royal Society of Chemistry (b) Digital diffraction scheme obtained from a sample of beads. Adapted with permission from Im et al., 2016. Copyright 2016 National Academy of Sciences. (c) Microscopic imaging with just ambient light. Adapted with permission from Lee and Yang, 2014. Copyright 2014, Royal Society of Chemistry.

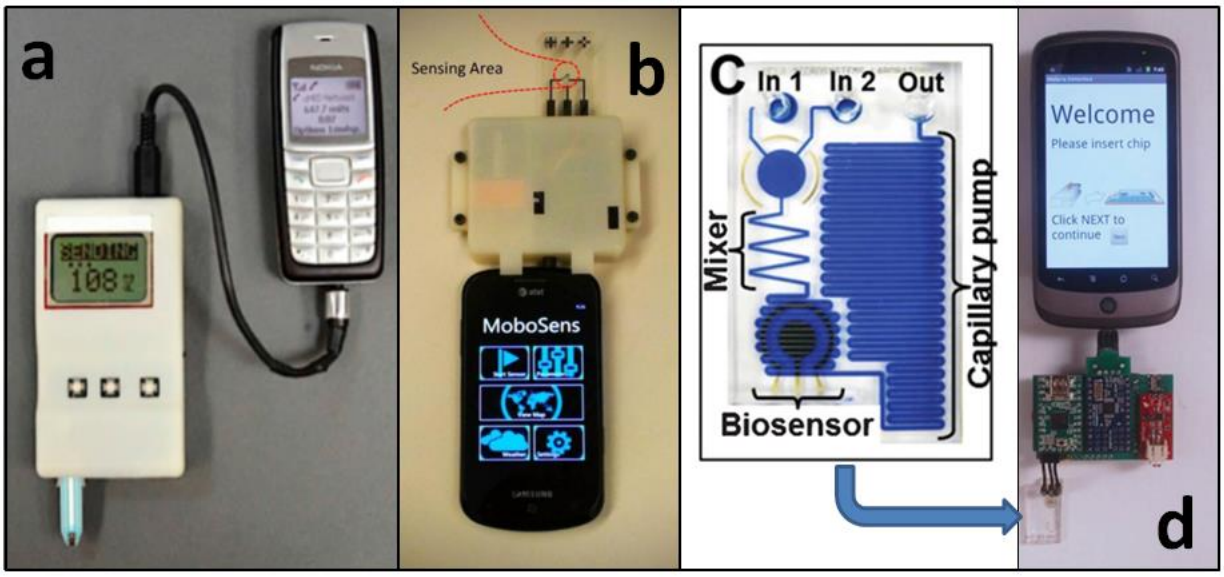

Fig. 13. (a) Portable device to read different types of electrodes with a mobile phone. Adapted with permission from Nemiroski et al., 2014. Copyright 2014 National Academy of Sciences. (b) Device for CV measurement coupled on the headphone jack of a mobile phone. Adapted with permission from Wang et al., 2015. Copyright 2015 ElSevier. (c) Microfluidic system with electrodes that can be connected to (d) a mobile phone. Adapted with permission from Lillehoj et al., 2013. Copyright 2013 Royal Society of Chemistry.

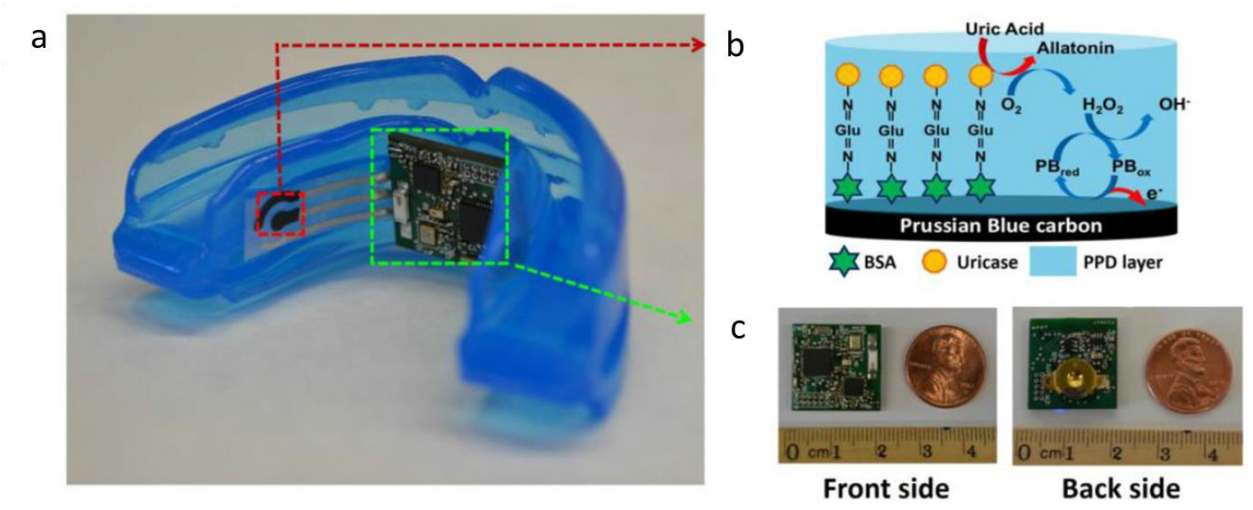

Fig. 14. Wearable salivary device for uric acid control. (a) The device. (b) Electrodes reaction. (c) Wireless amperometric chip. Adapted with permission from Kim et al., 2015. Copyright 2015 ElSevier.

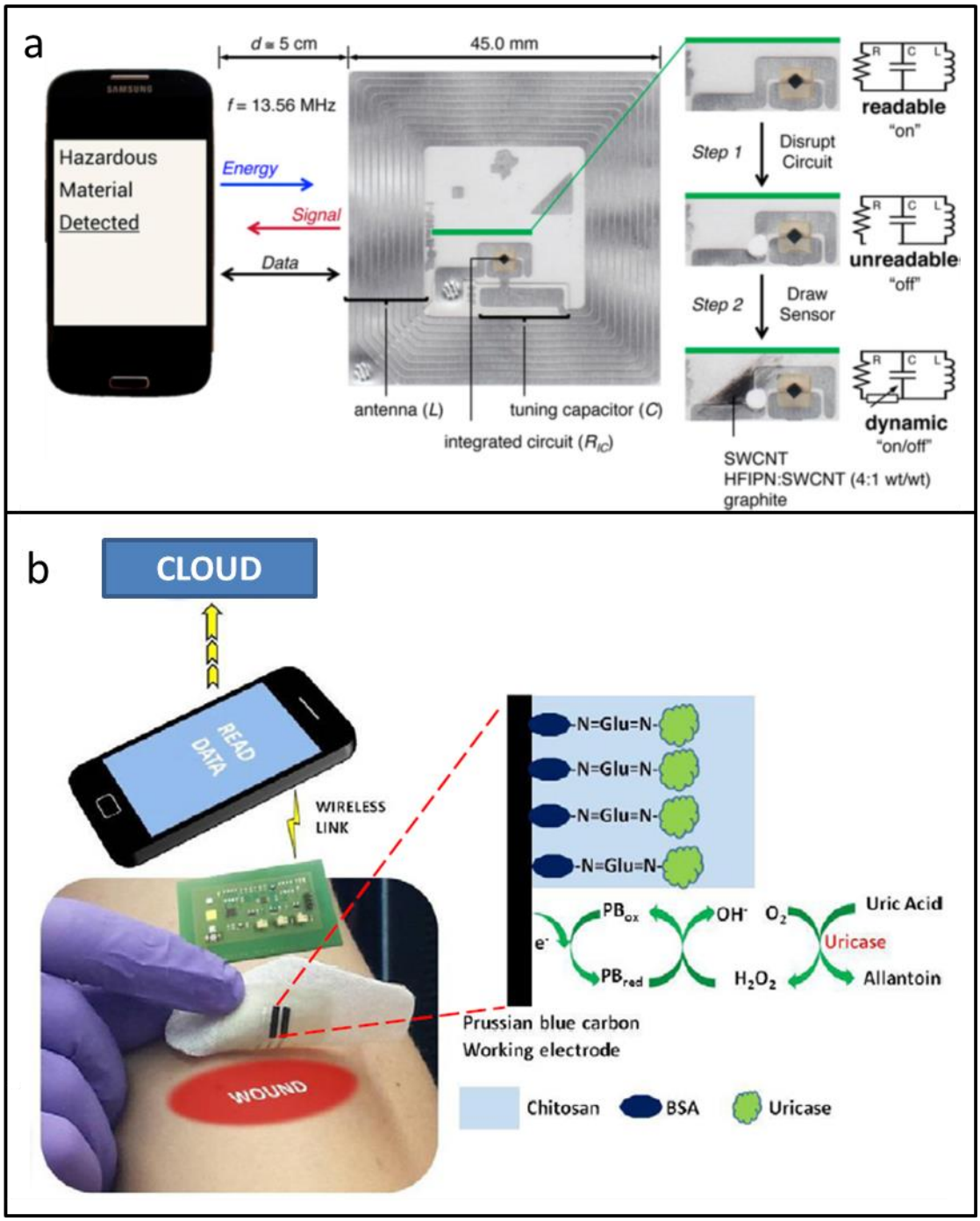

Fig. 15. (a) NFC-based sensor for gases. Adapted with permission from Azzarelli et al., 2014. Copyright 2014 National Academy of Sciences. (b) Sensor on a bandage. Adapted with permission from Kassal et al., 2015. Copyright 2015 ElSevier.

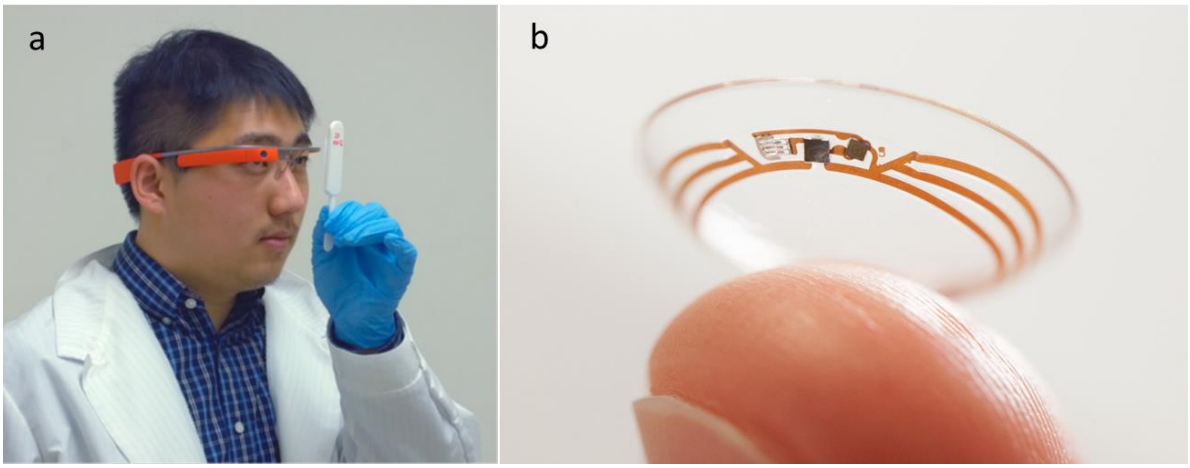

Fig. 16. (a) Using Google Glass to translate the response of LF strip. Adapted with permission from Feng et al., 2014. Copyright 2014 American Chemical Society. (b) Google Lens, for glucose sensing. Adapted with permission from Google Official Blog. Copyright 2014 Google.

Table 1: Comparison of different detection methods applicable on mobile phones.

Detection method	Signal generation	Transducers	Comments
Optical • Colorimetric • Luminescent • Fluorescent • SPR • Microscopy	• Ambient light • LEDs • Laser • Mobile phone screen • Chemical reaction	• Camera • Additional lens • Ambient light sensor • External devices	Assay performed on: • Paper • Cuvettes • ELISA • Microfluidics • Skin
Electrochemical • Cyclic voltammetries • Chronoamperograms • Impedance	Current from: • External batteries • Mobile phone battery	• Earphone jack • USB port • External devices	Connection: • Direct • Bluetooth • Wi-fi • NFC
Other • Sound recording • Magnetoresistance • NFC interference • Other devices connection (e.g. ultrasound scanner)	• Mobile phone features • External devices	• Mobile phone • External devices	Interaction with: • AR devices • Drones • Portable laboratory systems