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Biosensing with cell phones

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Continued progress in cell-phone devices has made them powerful mobile computers, equipped with sophisticated, permanent physical sensors embedded as the default configuration. By contrast, the incorporation of permanent biosensors in cell-phone units has been prevented by the multivocal nature of the stimuli and the reactions involved in biosensing and chemical sensing. Biosensing with cell phones entails the complementation of biosensing devices with the physical sensors and communication and processing capabilities of modern cell phones. Biosensing, chemical-sensing, environmental-sensing, and diagnostic capabilities would thus be supported and run on the residual capacity of existing cell-phone infrastructure. The technologies necessary to materialize such a scenario have emerged in different fields and applications. This article addresses the progress on cell-phone biosensing, the specific compromises, and the blend of technologies required to craft biosensing on cell phones.

Cell phones for biosensing

Modern cell phones are advanced multicore computers with sophisticated user interfaces and imaging capabilities. Default configurations include various physical sensors, such as magnetometers, accelerometers, and gyroscopes, which together with global positioning make smart phones a pervasively deployed physical-sensor platform. However, cell phones are not configured for chemical sensing or biosensing, which entail multivocal stimuli and reactions with target analytes that preclude a single permanent-sensor solution [1].

Biosensing [2] and diagnostics [3,4] typically involve detection of analytes in solution and sample conditioning, which can be integrated within lab-on-a-chip (LOC) devices [5]. The use of disposable fluidics with detection chemistry simplifies aspects such as periodic calibration [6] and can exploit strong chemical interactions that improve detection selectivity [7]. Although disposable devices are attractive for deployable solutions, the auxiliary systems for conditioning and readout [8] are typically dedicated, which limit their dissemination [9]. Biosensing with cell phones exploits the ubiquitous presence, physical-sensing capabilities, and processing power of phones to provide the auxiliary support required for advanced biosensing.

For more than a decade [10,11], consumer electronic devices (CEDs), such as flatbed scanners [12], CD units [11], and web camera–screen combinations [10,13], have been adapted for chemical sensing and biosensing. Cell phones are the latest CED platforms that offer the necessary resources to complement biosensing. Additionally, cell phones are disseminated at a scale unmatched by any other CED. They are also inherently part of the communication network, mobile, and continuously renewed by improved versions. The central challenge to exploiting this ubiquitous resource for biosensing is to craft smart interfaces between the biosensors and the phones.

Modern cell phones can be connected to digital acquisition boards (see the GitHub code repository, https://github.com/ytai/ioio/wiki) or dedicated electronics can be configured for interfacing to chemical sensors (see 'NASA Ames Scientist Develops Cell Phone Chemical Sensor', http://www.nasa.gov/centers/ames/news/features/2009/cell_phone_sensors.html). These approaches are equivalent to classical computer-controlled instrumentation and offer a vast range of possibilities, which fall outside the scope of this article. Here recent progress and perspectives on biosensing with minimal or no dedicated interfacing electronics are discussed, and in this context two strategies can be identified.

One strategy uses auxiliary reusable devices (ARDs) to link the biosensing assay to the cell phone [4,14]. ARDs can be of varied complexity and sophistication, and are specifically designed for certain phone brands and models. The second approach uses auxiliary disposable devices (ADDs), in which not only the biosensing part but also the coupling system is disposable. ADDs have generic designs that are compatible with diverse phone brands and models [10,15,16]. In this work, the different cell-phone biosensing strategies, target determinations, and detection principles in ARDs and ADDs are examined to address the feasibility and status of modern biosensing merged with cell-phone readouts.

Parallel history of cell phones and biosensing

The evolution of mobile phones has brought with it an evolution in their compatibility with biosensing (Table 1). The first consumer cell phones appeared in the 1980s, with the most iconic example represented by the bulky 1988 Motorola DynaTAC. CED chemical sensing emerged at the beginning of the 2000s [10–12], but popular and advanced phones at that time were unsuitable for biosensing. The diverse form factors and configurations that existed at the time, and the lack of generic operating systems (OSs), restricted potential biosensing solutions to specific advanced phones in the best case. The introduction of the iPhone in 2007 produced three important contributions to biosensing on cell phones. The iPhone had an OS that

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Table 1. Selection of cell-phone platforms for their historic relevance, and first configurations demonstrated for biosensing in ARD and ADD modes

Phones	Year	Price[a]	Front/rear camera	OS
Motorola DynaTAC[b] [18]	1988	9,337	No/No	–
Nokia 3310[c]	2000	278	No/No	–
Nokia 9210[d]	2001	1,321	No/No	–
Nokia N73[e] [15]	2006	750	0.3 MP/3.15 MP	–
iPhone 4[f] [22]	2010	599	0.3 MP/5 MP	iOS 4 to 7
Samsung Galaxy Note 3[g]	2013	730	2 MP/13 MP	Android 4.3

[a]Prices in US$ corrected for inflation to 2013.

[b]First consumer mobile phone (795 g, 30 min talk time).

[c]Representative popular model (126 million sold, 133 g), http://nds1.nokia.com/phones/files/guides/3310_usersguide_en.pdf.

[d]Representative advanced phone from 2001 (32 bit 66 MHz ARM9-CPU, 640×200 pixel display), http://nds1.nokia.com/phones/files/guides/9210_usersguide_en.pdf.

[e]First phone used for fluorescence microscopy.

[f]Representative contemporaneous smart phone with all capabilities for ADD, http://manuals.info.apple.com/MANUALS/1000/MA1565/en_US/iphone_user_guide.pdf.

[g]Representative smart phone from 2014 (32 bit, Quad-core processor 2.3 GHz), http://www.samsung.com/global/microsite/galaxynote3-gear/spec.html.

enabled the migration of applications to later models and upgraded OS releases. The iPhone also pioneered an influential design that standardized the appearance of subsequent smart-phone generations. The glass front encasing the screen and front camera combined the required mechanical and optical coupling of biosensing solutions, and allowed generic designs to be compatible with multiple brands and models. The introduction of touch-screen user interfaces (UIs) facilitated software UI configuration and created a vibrant market for third-party applications. In general, advanced phones from 2006 onwards were already capable of ARD biosensing [14], and front-camera phones from 2009 already sufficed for ADD biosensing [15]. The imaging of colorimetric devices without controlled illumination was achievable with even older phone cameras [6].

Interfacing biosensing

ARDs typically incorporate auxiliary light sources (Figure 1), which are necessary for fluorescence detection and microscopy. Most ARDs also provide mechanical support for the biosensing part, together with a well-defined configuration for aligning the sample. Although phone designs have converged to a glass-front configuration, the dimensions and optical specifications vary across brands and models, and ARDs are typically designed for specific phone models [15,17], allowing for dedicated solutions that can be developed relatively quickly. In recent years, numerous biosensing and diagnostic targets have been achieved with ARD systems [4,15,17], including viral imaging [18]. However, the major disadvantage of the ARDs is that they employ reusable accessories to complement the phone, which are scarcer than phones, and limit the reach of these solutions. By contrast, ADD systems (Figure 2) aim at developing deployable disposable devices able to match the diverse smart phone brands and models. Reusable accessories are excluded, and coupling and conditioning elements are integrated with the biosensor stage in a single disposable component. Achieving generic solutions of this type is demanding, and there are fewer examples of ADD systems [15,16,19].

A representative ARD system (Figure 1A), configured for rapid diagnostic test evaluation on a Galaxy SII smart phone [17], accommodates commercial immunochromatographic assays that respond with a test line, in which contrast is proportional to the analyte concentration in a blood sample. The system in this example was used to detect tuberculosis, HIV, and malaria [17], and the ARD provided mechanical fitting to the phone, a three-LED light source for reflection and transmission configurations, two AAA batteries, and a test cartridge securing the assay alignment within the ARD.

In a representative ADD system (Figure 2A,B), surface plasmon resonance (SPR), the benchmark for biosensing and for the study of biomolecular interactions [20], was implemented [16] with biosensing and coupling elements in a single disposable component. SPR experiments condition visible illumination for resonant energy transfer to plasmons on a thin metal film, which results in characteristic reflectance features that can be optically captured [20] and are sensitive to the metal surface conditions, where chemical detection takes place. The ADD-SPR concept used a disposable optical coupling element with embedded fluidics, in which the biosensing assay was implemented [16]. The coupler provided temporary optical and mechanical fitting to the phone front, conditioned the illumination (provided by the phone screen), and guided the reflection towards the front camera of the phone. The acquisition software was a time-lapsed image-capture program, and the system was tested on Nokia, Android, and Apple devices with a commercial β_2 microglobulin (β_2M) assay [16], an established marker for cancer, inflammatory disorders, and kidney disease.

Microscopy is relevant for the diagnosis of many diseases, and several cell-phone implementations focus on this technique. The first reported ARD example [14] was a compact bright-field and fluorescence microscope (Figure 1B), which had its own light source and was designed to couple to a Nokia N73 3.2 megapixel rear camera for image acquisition. This device was tested for the identification of tuberculosis, malaria, and sickle-cell anemia [14]. The ARD could be detached and the phone used for its original purpose; this could be considered an advantage over other ARD techniques that require removing the phone camera lens, such as lens-free microscopy [21]. However, although it is desirable to keep the phone intact, preserving the integrity of the phone is not a high priority for ARD systems. Because phones are constantly being replaced by newer models, thus providing a pool of unwanted, older cell phones for use with ARD systems,