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Mobile phones create new opportunities for microbiology research and clinical applications

“...mobile phones have the potential to transform traditional uses of imaging, sensing and diagnostic systems, especially for point-of-care applications and field settings.”

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Mobile phone-enabled measurement tools for research & clinical use

Smartphones have been in our lives since the beginning of 2000s. By the end of 2015, 2 billion people across the world had a smartphone and the penetration rate of smartphones is expected to further increase to cover approximately 80% of the world population by 2020 [1]. Smartphones are equipped with a variety of advanced sensors such as digital cameras, microphones and accelerometers, among others [2]. Together with their cost-effectiveness, wide-spread use, computational power and connectivity, mobile phones have the potential to transform traditional uses of imaging, sensing and diagnostic systems, especially for point-of-care applications and field settings.

In fact, mobile phone-based imaging and sensing platforms have already been used in a variety of applications,

including clinical chemistry, biomedical and environmental monitoring [3–5], food analysis [6–8], detection of different types of chemical and biological analytes such as cells, parasites [9], bacteria [10], eggs [11], proteins [12], various biomarkers [6,7], nanoparticles [13] and even nucleic acids [14–16]. In many of these platforms, processing of the acquired data and the resulting computational analysis are done either on the smartphone or over a local or remote server using a custom-developed smartphone application. In some cases, subcomponents of the mobile phone peripherals, for example, the complementary metal-oxide-semiconductor (CMOS) imager chip of the camera module, can also be used for advanced microscopy and cytometry applications [17–19], in which case a laptop computer or a tablet can be used for image reconstruction and related analysis.

KEYWORDS

- biosensors • flow cytometry
- fluorescence microscopy • imaging
- mobile-phone microscopy • sensing
- smartphone-based instrumentation

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“Different microscopic imaging modalities have been incorporated with mobile phones to provide field portable sensing platforms that can potentially be used for early detection and prevention of a variety of health problems.”

Mobile phone-based microscopy, sensing & diagnostics

Different microscopic imaging modalities have been incorporated with mobile phones to provide field-portable sensing platforms that can potentially be used for early detection and prevention of a variety of health problems. Among these, smartphone-based fluorescence microscopy is one of the most commonly used imaging methods. The design of these compact, mobile phone-based microscopy tools generally contains a 3D printed opto-mechanical attachment unit, an external lens for magnification, an excitation filter and/or an emission filter, light-emitting diodes (LEDs) or laser diodes forming the excitation source, a translation stage to adjust the field-of-view and focus, and a sample tray. As an example, using a mobile-phone fluorescence microscope Zhu *et al.* [10] reported a quantum dot-based *Escherichia coli* detection platform integrated with glass-based capillary channels that were coated with antibodies specific to *E. coli*. This platform provided a limit of detection of 5–10 CFU per ml for fat-free milk samples contaminated with *E. coli*. In another study, a mobile phone-based fluorescence microscope was used as an imaging flow cytometer to analyze blood samples and biological contamination levels of drinking water samples [20]. In this design, the excitation of the fluorescent tags was done using LEDs and video capturing feature of the mobile phone was used to image fluorescently-labeled particles flowing in polydimethylsiloxane-based microfluidic channels. Another mobile phone-based imaging platform enabled rapid and sensitive detection and automated counting of waterborne pathogens (e.g., *Giardia lamblia* cysts) in large volume water samples (e.g., 10 ml) using image-processing algorithms and machine learning [4]. This design is composed of a smartphone-based fluorescence microscope, a disposable sample-processing cassette and a custom-developed smartphone application. Total time to result, including sample collection, labeling, filtration, optical detection and automated counting, is approximately 1 h, which is significantly shorter compared with conventional methods [21] which can take more than 24 h. This handheld and cost-effective platform weighs only approximately 205 g and provides a limit of detection of approximately 12 cysts per 10 ml with a *G. lamblia* cyst classification accuracy of approximately 95% for nonpotable, pond, tap and reagent grade water samples.

Smartphone-based fluorescence microscopes have also been used for imaging nano-sized biological specimen [13,15,16]. In the design of these microscopes, a laser diode-based illumination with a highly-oblique incidence angle (e.g., $\sim 75^\circ$) is used for excitation of target fluorescent tags and particles, which provides a strong rejection of the excitation beam due to the low numerical aperture of the mobile phone camera system. Based on this design, isolated 100 nm fluorescent particles and human cytomegaloviruses were imaged using a cost-effective smartphone attachment weighing only approximately 186 g [13]. A similar design makes it possible to image and measure the lengths of individual double-stranded DNA molecules with a sizing accuracy of <1000 base pairs (stretched on a surface and labeled with YOYO-1 iodide) using a smartphone [15]. This mobile phone-enabled DNA imaging and sizing platform can serve as a useful point-of-care tool to detect antimicrobial drug resistance related genes that cause difficulty to treat infections in humans.

Smartphones have also been used as colorimetric readers [3,7,22], for example, to test antimicrobial drug susceptibility [23] and analyze ELISA-based tests, such as mumps immunoglobulin, measles IgG and herpes simplex virus IgG tests, with a very similar level of performance compared with US FDA-approved clinical well-plate readers [3]. This mobile phone-based 96-well reader design [3,7] is composed of a 3D printed opto-mechanical attachment unit that houses 96 multi-mode plastic fiber-optic cables that are each coupled to individual wells of a disposable well plate, enabling the measurement of the transmitted light from the wells, all in parallel and without the need for any mechanical scanning. In this handheld well-plate reader, the wells are illuminated using an array of LEDs and the uniformity of the illumination is ensured using an optical diffuser. Quantified analysis of the optical signal that is carried with the fiber-optic array is rapidly performed over a server (e.g., a simple laptop) using a machine learning-based image analysis algorithm without the need for an expert reader. This mobile phone and cost-effective well-plate reader enables high-throughput analysis of biological samples for many patients at once.

Another important imaging modality that is integrated with smartphones is bright-field microscopy. In this mode of imaging, a sample of interest is illuminated uniformly using white light (e.g., a broadband LED) and imaged through the

camera of a smartphone together with an external lens that is used for magnification. This low-cost design can be used to detect pathogens of a variety of diseases, even at low-resource settings. For example, D'Ambrosio *et al.* [9] developed a mobile phone-based video microscope to detect and automatically quantify *Loa loa* microfilariae in whole-blood samples without any labeling steps. In this design, an LED array illuminates the whole-blood sample in capillaries and the microfilaria in blood are then detected by processing the acquired sequential frames of each field of view of the sample, with the results provided in less than 2 min. Field testing of this prototype was conducted in Cameroon, Central Africa using 33 *Loa*-infected patients, demonstrating 94% specificity and 100% sensitivity in comparison to manual thick smear counts. Another recent study [11] evaluated the performance of a smartphone-based bright-field microscope for label-free detection of *Schistosoma* spp. eggs in urine samples in rural areas of Accra, Ghana, Africa. This cost-effective and field-portable smartphone-based microscope has a spatial resolution of approximately 0.87 μm and uses a translation stage to scan a microscope slide for the presence of *Schistosoma haematobium* eggs. The field experiments conducted with this mobile phone microscope revealed a sensitivity of 72.1%, a specificity of 100%, a positive-predictive value of 100% and a negative-predictive value of 57.1% [11].

Commercialization of mobile phone-based measurement tools

In addition to these proof-of-concept experiments as well as clinical validation and related testing, there are several smartphone-based biomedical measurement tools that are commercially available. As an example, Mudanyali *et al.* [5] devised a mobile phone-based transmission and reflection imaging system to provide a field portable and cost-effective rapid diagnostic test reader. Using this mobile reader, an image of a rapid diagnostic test is captured and digitally processed on the phone for automated reading and quantification of the test results through a custom-developed smartphone application. This mobile phone-based imaging platform has been commercialized by Holomic/Cellmic, LLC (CA, USA), and is currently in use in several countries for quantification of various colorimetric and fluorometric tests. Another commercially available mobile phone-based reflection microscope is released by MetaOptima Technology, Inc. (Vancouver,

BC, Canada) under the name of MoleScope [24]. This mobile phone-based imaging device enables capturing of high quality images of the skin (e.g., moles) and share them with medical professionals through an application.

Future perspective

The above outlined mobile phone-based imaging, sensing and diagnostic tools, together with many others, might be transformative to bring advanced biomedical measurements and testing to resource poor settings, point-of-care offices and even to our homes, and will get more and more powerful with the emergence of internet of things, 5G networks and edge computing. All of these will provide extreme connectivity and access to advanced computational resources, including machine learning-based data analytics that will be used to harness the resulting microscopic imaging, sensing and diagnostics data generated by such mobile measurement tools. These capabilities will provide unique opportunities and a much needed toolset especially for microbiology research, preventive and precision medicine as well as microbiome initiatives.

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