Smartphones Democratize Advanced Biomedical Instruments and Foster Innovation

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From microscopy to diagnostics and monitoring of vital parameters, scientists, engineers, and educators have been making use of smartphones and smartphone components in various innovative ways, helping to democratize advanced measurement instruments used in research and education.

The use of mobile phones and their components as part of emerging imaging, sensing, and diagnostics tools has resulted in advances in measurement capabilities of researchers, educators as well as citizen scientists, opening up various new opportunities that were not possible before. For example, students can now conduct scientific experiments at home using mobile phones to image not only microscale objects like cells, but even individual DNA molecules after relatively simple fluorescent labeling protocols. This provides exciting opportunities for higher education, as it will significantly reduce financial and infrastructure-related barriers to hands-on experimental training at a global scale. At the same time, these emerging advanced mobile measurement capabilities enabled by smartphones will be quite useful for professionals in various fields, including, e.g., microbiology, telemedicine, epidemiology, among others. Some important examples of these have been demonstrated by various researchers within the last decade.[1]

One of the most significant drivers behind all these important advances is simply economies of scale. According to the International Telecommunication Union (ITU), there were ~7.7 billion mobile cellular phone subscriptions across the world by the end of June 2017. Around 10% of these subscribers are located in the least-developed countries, where resources are extremely limited. Another key driver for the use of smartphones for advanced measurements is that they are equipped with at least one high-end complementary metal oxide semiconductor (CMOS) image sensor. These image sensors are coupled with camera applications, which provide various adjustable settings, including, e.g., exposure time, frame rate, white balance, and focus. It is even possible to capture raw format images using smartphones, enabling more advanced computational imaging techniques, including, e.g., holography, to be implemented in a mobile device. This is also powered by another key attribute of smartphones: they also serve as personal handheld computers, where image reconstruction and processing algorithms can be integrated into custom-developed mobile applications and the results can be obtained locally without the need for data transfer, which is useful for point-of-care medicine applications in resource-constrained locations.

MOBILE PHONE-BASED MICROSCOPY

Recently, mobile phone image sensors with approximately one-micron pixel pitch have been released, facilitating the use of custom-developed opto-mechanical attachments to convert smartphones into field-portable and cost-effective microscopes. The opto-mechanical attachment to the smartphone camera is generally created using a 3D printer, which provides the flexibility of printing custom-made designs with a variety of polymeric materials and special features. The use of 3D printing is a cost-effective option for rapid prototyping of smartphone-based analytical tools to demonstrate their proof of concept; once the initial design is validated, other manufacturing approaches (e.g., injection molding) that are much cheaper and scalable can be used to create the same unit at large scale. Using these lightweight attachments, a variety of imaging modalities, including fluorescence microscopy[2,3] and brightfield microscopy,[4] have been incorporated onto smartphones to image various biological samples at the microscale (**Figure 1**). Some of these handheld microscope designs can be used as advanced analytical instruments for rapid and sensitive detection of parasites, cells, proteins, or even DNA molecules in, e.g., bodily fluids and tissue samples.

Image quality of these smartphone-based microscopes is in general comparable to that of standard benchtop microscopes equipped with, e.g., a 10× or 20× objective-lens. For

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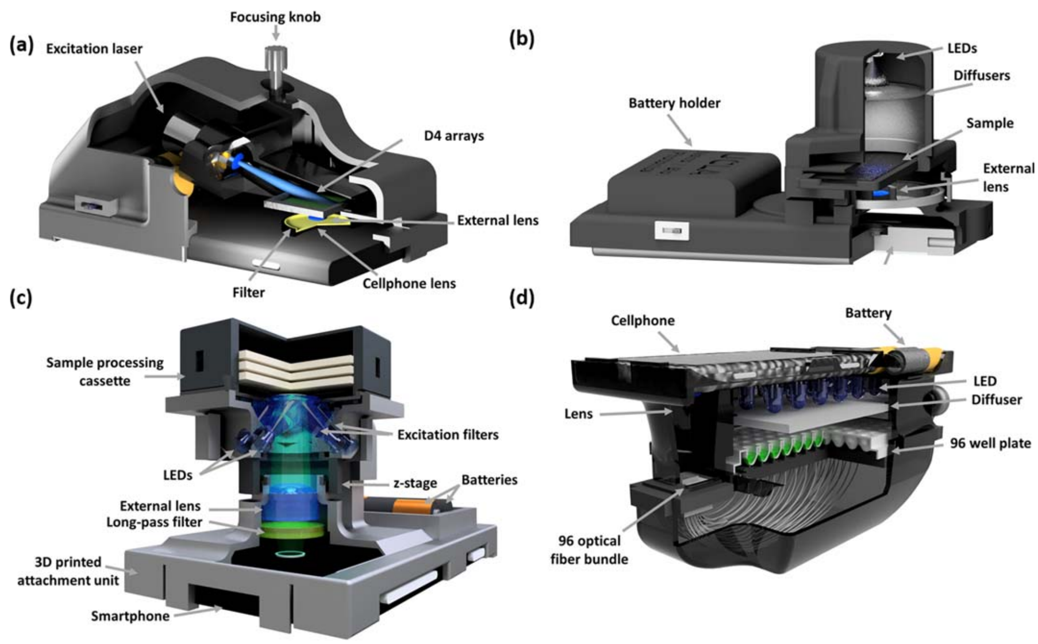

Figure 1 Optical designs of different mobile phone-based biomedical instruments. (**a**) A fluorescence microscope that can image individual double-stranded DNA molecules.[5] (**b**) A brightfield microscope with submicron spatial resolution.[4] (**c**) A mobile fluorescence microscope designed for detection of waterborne parasites.[2] (**d**) A colorimetric well-plate reader.

example, Bogoch *et al.*[4] demonstrated a mobile phone-based brightfield microscope that resolves submicron features of a sample. In another study, stretched, fluorescently tagged individual double-stranded DNA molecules were imaged and automatically sized using a mobile phone fluorescence microscope.[5] These mobile phone microscope images can be further enhanced by using machine learning, e.g., deep learning-based approaches that use neural networks to digitally correct various sources of spatial and spectral distortions (created by the inexpensive camera interface of a mobile phone) in order to match the performance of a high-end benchtop microscope.

CONNECTIVITY AND UBIQUITY OF MOBILE PHONE-BASED MEASUREMENTS

A key advantage of using smartphones as biomedical sensors, imagers, and diagnostic tools is that smartphones provide ubiquitous data connectivity and spatiotemporal labeling and sharing of the acquired information such as sensing or diagnostic data (**Table 1**). This simple and yet very important feature can be used to discover and monitor outbreaks by collecting and harnessing large datasets created by mobile phone-based measurement instruments from the regions and communities that are affected by, e.g., infectious diseases. These data and their analysis can be shared with public health authorities to coordinate staff, prevent transmission of diseases to other communities, and manage public health crises and emergencies.

So far, thousands of smartphone-based applications have been developed for healthcare practitioners and patients to help mainly in daily clinical practices, patient communication, education, and access to electronic health records. Some of these applications are being used for prescribing drugs, which help reduce prescription error rates and provide information on drug handbooks, drug formularies, as well as drug dose calculations. Another valuable use of the connectivity and ubiquity of smartphones in medical diagnostics is to monitor physical parameters of individuals using wearable technologies or peripherals through smartphone applications. Smartphones are being used as one of the major platforms to collect, display, and/or share biomedical data acquired by wearables.

There are also several smartphone connected or controlled sensors that secured US Food and Drug Administration (FDA) clearance. For example, Dario is an FDA-approved platform that is composed of a smartphone app and a glucose meter. Another example, among others, is a Wi-Fi-enabled thermometer, which uses 16 infrared sensors to measure the heat emitted from a person's head and the results are synced with the smartphone through a mobile application. In addition to optical imaging and sensing-related instrumentation, a smartphone-based ultrasound scanner has also been demonstrated by Philips. It uses a portable ultrasound transducer that is connected to and controlled by a smartphone (through a custom-designed mobile application) to capture images of deeper parts of the human body (e.g., kidney, aorta).

These and other innovative uses of mobile phone-based ubiquitous measurement instruments are enabling new applications for point-of-care and telemedicine, among other fields (**Table 1**). All these research and development efforts are helping us

Table 1 A brief summary of some of the key advantages, current limitations, along with possible solutions and some applications of mobile phone-based biomedical instruments

Summary of key advantages	
Cost-effectiveness (benefiting from economies of scale)	
Widespread global use and connectivity of mobile phones (providing spatiotemporal labeling and sharing of the acquired information)	
Ease of use	
Already equipped with various types of state-of-the-art sensors and imagers	
Computational power (including graphics processing units)	
Compactness and lightweight	
Some of the current limitations	**Possible solutions**
Rapid changes in mobile phone hardware and software, and related challenges in standardization of performance	Based on demand and broad consensus in standard features and needs of the industry and research labs, certain smartphone models can be selected as "platforms" for the development of mobile biomedical instruments, with a long-term regulated supply-chain. This will also help in standardization of performance.
Limited performance when compared to benchtop instruments	Machine learning-based computational methods can help close the gap between mobile phone-based instruments and their lab-grade counterparts.
Limited control and engineering of smartphone settings/features (e.g., camera features, etc.) using regular phone applications	Development of custom-made applications, ideally open-source, would help. The selection/creation of a standard mobile phone platform to regulate the supply and help with the long-term needs of the industry and research labs would also benefit from open-source application portals.
Some applications	
Monitoring physiological parameters, mobile sensing, and diagnostics	
Optical microscopy for detection, classification, and counting of biological analytes such as cells, parasites, and viruses	
Antimicrobial susceptibility testing	
Lateral/vertical flow test reading/quantification	
Point-of-care medicine and telemedicine (e.g., telepathology)	
Monitoring of the efficacy and safety of clinical trials	
Education	
Citizen science	
Diagnosis of infectious diseases	
Monitoring of chronic patients (e.g., detection of cholesterol levels)	
Sensing of allergens	
Electrochemical sensing of analytes	
Ultrasound imaging	
Detection of eye diseases (e.g., cataracts)	
Water and air quality measurements	

democratize advanced measurement instrumentation that is normally restricted for use in well-resourced institutions and will continue to create transformative opportunities to improve the practice of medicine, especially in resource-limited countries. Equally exciting is the plethora of opportunities that are being created by smartphone-based instrumentation to cost-effectively educate and train next generations through hands-on experimental curricula.

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CONFLICT OF INTEREST

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