The Potential of Smart-phones as a Portable Diagnosis Tools

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***Abstract*:** **Mathematical algorithms of smart phone applications have rapidly growing, transforming smart phones into optical readers to quantify and measure colorimetric changes occurred at different type of colorimetric test strip as well as portable lens or lens free microscope . Making it an inexpensive and accessible alternative diagnostic tool to replace more costly commercial systems. This paper presented the global trend of using smart-phone platform based on optical theory.**

Keywords: Smart-phone algorithm, lens free microscope, colorimetric detection, POCT, optical biosensor.

1. Introduction

The wide utilization of smart phone has been growing rapidly in the last five years, the global subscriptions raised up to 70% reaching around 6.8 billion at the end of 2013 [1]. Therefore, exploiting the available smart phone mobile's infrastructure in health care management will accelerate health procedures toward disease monitoring and diagnosis. As well as reduce the cost of health care management for existing and emerging diseases. Smart phones camera's have been suggested to be use as diagnosis tool based on their ability to work as image sensor and visible-light spectrometer. These principles are utilized in a wide field of medical application including chemical analysis for laboratory tests [2]. Recently, smart phones applications have been showed a great potential for point of care diagnostics, which can be coupled with dipsticks, lateral-flow strip and colorimetric tests in solution that are typically read by spectrophotometers or micro plate readers [3]. Many studies demonstrated the utilization of smart phone's algorithm to achieve quantitative measurement of point of care strips through quantifying pathological indicators or concentration of biomarkers in samples such as urine sample, blood sample or salvia sample. Yetisen et. al 2014 showed the potential of smart phone algorithm to quantify the concentration of protein, glucose and pH in artificial urine samples. Resulting high sensitive and reproducible measurements [4]. The capability of smart phone functioning as spectrophotometer was reported by Gallegos et. al 2013, customized software application was developed to convert smart phone camera image's into photonic spectrum in the visible wavelength rang in combined with curve fitting to detect the immobilized protein [5]. Moreover, JUNG et. al 2015 showed the potential of smart phone to detect alcohol in saliva sample by developing an integrated optical attachment based on smart phone camera. Enzyme reaction producing a gradient of color intensity at test kit from light to dark green proportional to ethanol concentration, matching the concentration of alcohol with light intensity by curve fitting, then an algorithm used to calculate the concentration of alcohol and display the result by Smartphone along the web according to geo-location at which the test was made [6]. Connecting the smart phone to the internet via telecommunication network enable the user to share their test result with consultant centre or hospital which play a significant role in health care management especially for patients at remote area.

2. Methodology and Principle of Operation

The utilization of smart phone application as portable clinical diagnostic tools based on point of care test (POCT) has been rapidly increasing and become a global trend. However, there are many platforms used by Smartphone application to detect different biological indicators such as enzymes, cells, nucleic acids, antigen–antibodies and microorganisms. The detection methodology could vary depending on the biological derived materials including optical-based testing methods such as optical reader, imaging, absorbance, reflectance, fluorescence and colorimetric analysis.

2.1 Smart–phone based microscope

Generally, many diseases can be diagnosed in laboratory under the utilization of microscopes such as bacterial infections, blood-borne diseases and tumor cell detection. The obtained image by microscope is magnified by a series of lenses enabling the operator to see clearly small microorganism by naked eye. In 2007, Frean et al showed that mobile phone camera's has the potential to capture images from the eyepiece lens of a microscope and can be used for bio-detection of microorganisms. Inspired by Frean's work, many research groups began to use imaging systems based on smart-phones camera for bio-detection such as Zhu et al.2013 and Meng et al.2017 [7,8]. The smart-phone based microscope has an extra attachment consists of a series lenses and other optical components coupled with CMOS components working as microscope which obtain an image of analytes. More advanced effort have been developed to improve the image quality of smart-phone based microscopes.

Breslauer et al. 2009 developed a smart-phone based microscope with long lens system as an attachment to phone camera. The attached lens system shown in figure-1 simulates all typical components of microscope including a light-emitting diode (LED) as a light source, condenser lens, a sample stage, an objective, an eyepiece and several filters which are used for fluorescent detection of microorganisms [9].

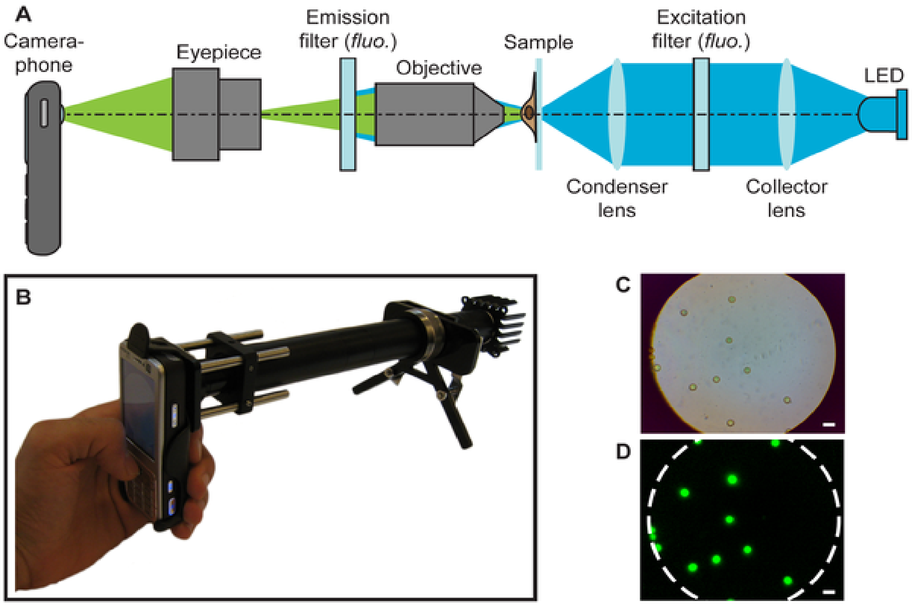

Figure 1: Mobile-Phone based Microscopy

Part (A) of figure-1 shows optical system of mobile-phone based microscopy which is necessary for fluorescence imaging and consist of optical eye piece, filter, objective, excitation filter and LED light source. Part(B) is the developed prototype device by Breslauer and his coworkers where the sample is adjacent to the focusing knob. Parts (C and D) represent bright field and fluorescent image. The prototype device was characterized for clinically relevant applications by using bright field illumination to capture high-resolution images of both thin and thick smears of malaria-infected blood samples, as well as of sickle cell anemia blood samples [9].

Oh the other hand, many researchers have performed studies on mobile-phone based lens free microscopes to reduce the cost, size and the weight of diagnostic tool. Tseng et al. 2010 demonstrated the use of lens free microscope shown in figure 2, where the samples are loaded from the side and are vertically illuminated by incoherent LED light coupled with lens free imaging platform. The scattered incoherent light from each micro object in the sample area interfere with background light, enabling lens free hologram of each object to be detected at an array detector at platform. The holographic signatures captured by phone camera's to reconstruct microscopic image of tested object. Clinically, Tseng et al. utilized mobile-phone based lens free microscope successfully in various size micro-object such as red blood cells, white blood cells, platelets and water born microorganisms such as *Giardia lamblia* [10].

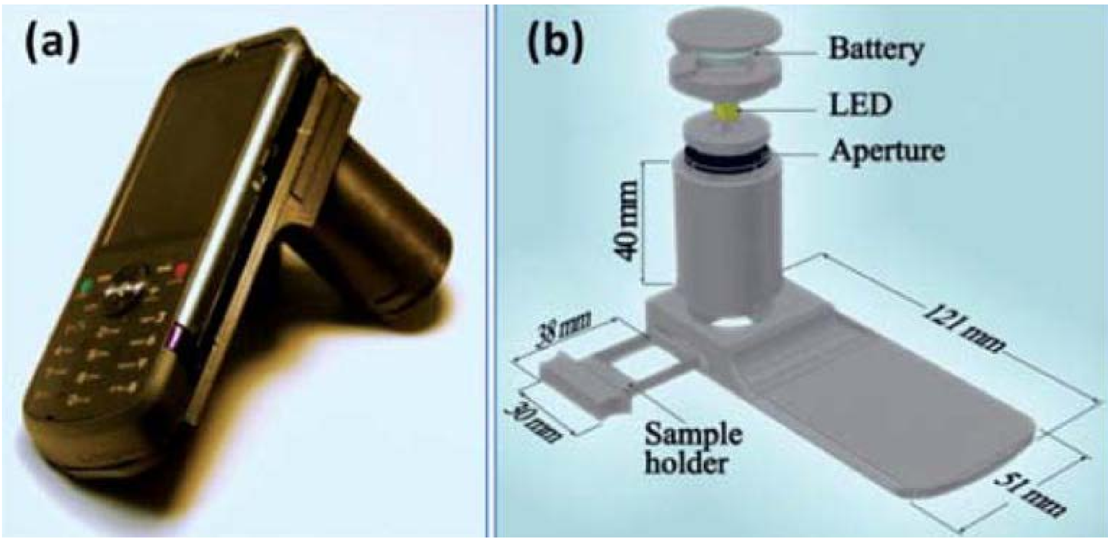

Figure 2: a- Mobile-phone based lens free microscopes, b- Schematic diagram

Tseng and his colleges found that computing power of old mobile phone not compatible to proceed calculation algorithm for mobile-phone lens free microscope and reported that as a significant limitation. Therefore they used a desktop PC to achieve calculation and analysis. Other study used a smart-phone with high processor efficiency to develop mobile lens free microscope and overcome the previous limitation as shown in figure 3. Lee and Yang et al. 2014 who used a technique based on replacing lens module and placing the sample directly at image sensor to obtain direct shadow image of object under ambient light source such as lamp, LED or sun light. Then, multiple images at various angle of illumination were captured to improve image reconstruction. This technique of smart-phone based lens free microscope improving imagining quality over a wild range field of view, and enabling image acquisition and reconstruction to be perform on smart-phone device by an algorithm compatible with commercial android system [11].

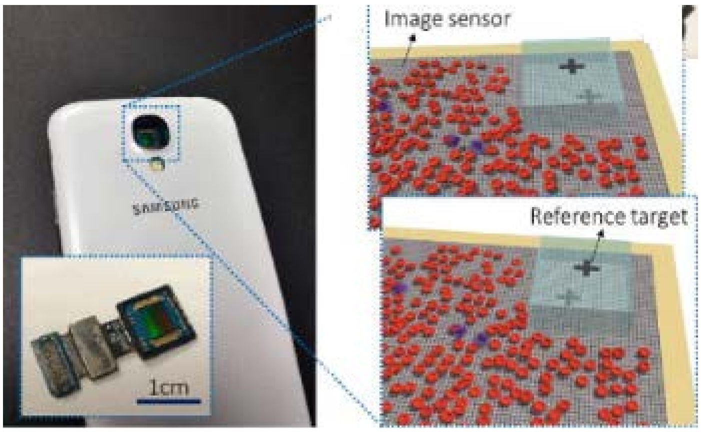

Figure 3: Smart-phone based lens free microscope, by Lee and Yang.

Clinically, Lee and Yang used the prototype smart-phone based lens free microscope to examine blood smear and fresh water microorganism for water quality monitoring. The obtained results demonstrated high capability of smart-phone based lens free microscope to capture high resolution images for microorganisms as well as image acquisition, analysis and reconstruction can be achieved by smart-phone processor coupled with certain mathematical algorithm.

2.2 Smart–Phone based Colorimetric Analyzer

Nowadays, Smart-Phone based colorimetric analysis is a global trend due to its simplicity and low cost. The innovating technology of smart-phone based colorimetric analysis mainly focusing in lateral flow immunoassay (LFIA), enzyme-linked immunosorbent assay (ELISA), chemiluminescence and electro-chemiluminescence as a detection method coupled with smart-phone's camera to obtain accurate results. The phone camera is significant part that used to capture images of the reference sample and the target sample, respectively. Comparing color changing between reference sample color and target sample color to obtain the test result. In fact, color in captured images is very sensitive to the light conditions and the quality of used camera, therefore the reference sample color should be obtained under that same condition as the target sample to avoid any effect of light. Colors with electromagnetic radiation wavelength between 380 to 780 nm can be seen by human eye. However, the light transmitted or reflected from the object depends on its spectral characteristics (light absorbed by an object at different wavelength) as shown in figure 4. Regarding an image, each spatial point has its own color stimuli in the form of a spectral power distribution, color stimulus values produce the incoming or measured signal to the imaging device and then quantified as a numbers in digital imaging reconstruction system.

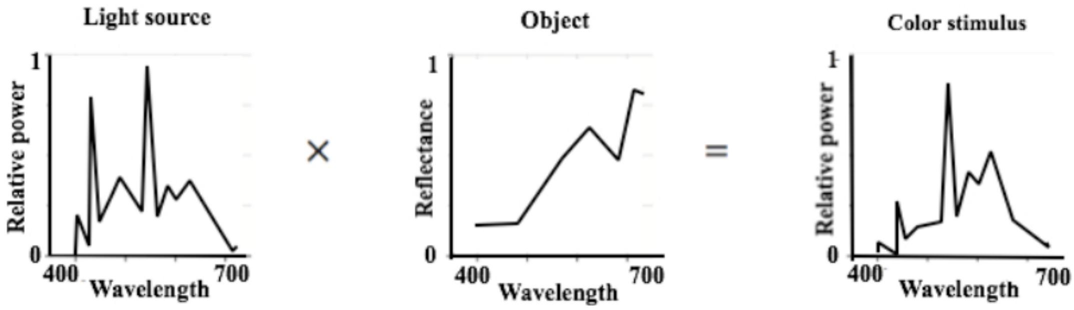

Figure 4: Color stimulus from an object and production of the relative power distribution

Smart-phone cameras made of complementary metal-oxide semiconductor (CMOS) which is consider as digital image sensors, detecting light as an arrays consisting of small detection sites (pixels), each pixel producing a signal proportional to the number of detected photons and generate only one of the three primary colors red, green or blue, enabling smart-phone cameras to work as digital image detector.

Jong II Hong and Byoung-Yong Chang et al. 2014 developed digital colorimetric detector using a smart-phone camera to report the result of urine test strips in term of color change. Urine test strips was examined visually by naked eye to determined abnormal level of leucocytes, specific gravity, pH, glucose, nitrite, protein, ketones, bilirubin and red blood cells (RBC) in urine. Then smart-phone camera used to obtain digital image of tested urine strip. The measured color at each pixels are digitalized using special correction algorithm, then the corrected color measurements converted into its related concentration value according to preloaded calibration curve. Finally, the results showed that ability of smart-phone camera to detect colorimetric change at urine dipstick and determined the abnormal value of tested pathological indicators [12]. In addition to that, Oncescu et al. 2013 suggested a rapid detection method for colorimetric changes based on smart-phone coupled with accessory strip to detect pH level in sweat or saliva samples. Reference strip was made of white plastic material, comparing the resulted capture image from pH test strip with reference one, showing the changes in white balance color on the camera during colorimetric detection [13].
Also, Shen et al. 2012 introduced a novel method to quantify colorimetric changes in assay by smart-phone coupled with disposable urine strips. Colorimetric reference values was used to obtain calibration curve that describes high accuracy pH measurement with linear response [14]. In addition to that Yetisen et al. 2017 showed a fluorescence biosensor based on point of care technology (POCT) to analyze tear significant components related to ocular disorder such as Na , K , Ca and pH. The POC micro-fluidic strip was placed at portable readout device consisting of series of LEDs illuminating at different wavelength to obtain fluorescence excitation. After that, smart-phone camera was used to capture fluorescence image for POC strip which were analyzed and digitalized by smart-phone application to obtain associated concentration value for quantitative test of tear fluid [15].

3- Conclusion

Smart-phone algorithms are playing a significant role in global trend to improve and develop new methodology of portable diagnostic tools. Smart-phones are showing a great potential as consistent and reliable diagnostic reader coupled with algorithms allowing smart-phone's camera to read quantitative measurement and detect analyte or microorganisms. The new technique platform has been widely used smart-phone based optical bio-sensing due to the high quality of the built-in camera serving as a detector, usually a spectrometer or a microscope in the laboratory applications. In parallel, the improvement of POCT has been an emerging subject in the medical field to reduce the cost and the working time, assisted by smart-phone algorithm to digitized values for more accurate and versatile measurements. Recently, global specialists believe that the utilization of smart-phone algorithms will become more and more convenient and usable in the near future. Especially, for the optical biosensors based on smart-phone platforms allowing rapid, low cost and portable diagnostic tool connected with telecommunication network to share the obtained results.

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