Smartphone supported backlight illumination and image acquisition for microfluidic-based point-of-care testing

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Abstract: A smartphone-based image analysis system is advantageous for point-of-care testing applications. However, the processes of observation and image recording rely heavily on an external attachment that includes additional light sources. Moreover, microfluidic point-of-care devices are highly miniaturized, and can be clearly observed only under magnification. To address these issues, the present work proposes a novel imaging box for converting the built-in light source of a smartphone into uniform backlight illumination to avoid interference arising from reflections. A multi-piece orthoscopic lens is embedded in the imaging box to enable the imaging of micro-sized samples. As such, the colorimetric signal of a microchannel with a width as small as 25 µm can be faithfully recorded. Protein concentration quantification based on the bicinchoninic acid assay method was demonstrated with the proposed smartphone/imaging box system from an analysis of colorimetric signals. In addition, a microfluidic chip for conducting ABO blood typing was fabricated, and the microscopic imaging of induced blood coagulation can be clearly observed in a 3 µL sample using the proposed system. These results highlight the potential for adopting smartphone-based analysis systems in point-of-care testing applications.

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1. Introduction

Point of care testing (POCT) has received increasing attention due to increased demand for on-site fast detection, particularly for food safety supervision, sanitation, and pre-clinical biochemical analyses [1–4]. POCT can serve as a substitute for large-scale analytical equipment in areas of limited economic development. Therefore, POCT is an especially important candidate to fulfill the basic need for biochemical analytic testing in rural areas or under resource-limited conditions. POCT incorporates two primary features. One feature is represented by disposable low-cost sensing strips/testing devices, and the other is represented by portable devices for signal acquisition and analysis. The rapid development of microfluidic technology achieved in the past decades has provided versatile microfluidic devices for potential use in POCT analyses that greatly reduce sample and reagent consumption [5–8]. However, the need for interfacing microfluidic devices with expensive specialized equipment, such as microscopes and spectrometers, significantly compromises the potential of microfluidic devices for use in POCT applications. This drawback has been potentially alleviated by the telecommunications revolution occurring over the past decades, which has produced smartphones that include a camera, a personal computer, and an interface with the internet. This multiple functionality of smartphones provides intense incentive for the development of POCT schemes that take full advantage of smartphones for interfacing with miniaturized sensing units/microfluidic devices [9–12].

Colorimetric-based biochemical detection is one of the most common assays employed in biological and chemical experiments. In the standard approach, a spectrometer is utilized to determine the colorimetric changes in a sample according to optical absorbance. However,
the colorimetric content of color digital images can be numerically analyzed by retrieving pixel intensities, and several color models, such as red-green-blue (RGB) and the hue-saturation-value [13–15], have been proposed to quantitatively compare different color signals. As such, the built-in camera of a smartphone can effectively capture color and structural information on microfluidic devices, and the integration of a smartphone camera and a microfluidic chip effectively reduces the complexity and cost of a POCT system [16, 17]. However, the direct use of smartphones for imaging suffers from non-uniform illumination caused by the light source and the surrounding environment [17]. Meanwhile, the relative positioning between the sample and the smartphone also introduces bias into colorimetric analyses. For this concern, Jung et al. developed a miniaturized attachment to provide stable illumination conditions, as well as to provide a uniform positioning between the sample and the smartphone [18]. Two types of external lighting have been adopted in imaging boxes. The first type arranges an external light source above the sample [1, 5, 9, 17]. However, this approach results in image exposure problems associated with light reflection from the sample. The second type supplies a backlighting source that illuminates the sample from the bottom, which can eliminate exposure problems caused by light reflection [10, 15]. An additional advantage of backlighting is that it enables capture of the transmission signals of light passing through colorimetric samples. Venkatesh et al. designed a detection device containing an array of light emitting diodes (LEDs) to provide uniform illumination of samples, and enzyme-linked immunosorbent assay (ELISA) was conducted based on the colorimetric information of microplate images retrieved from the smartphone. However, past efforts at developing smartphone-based POCT systems have uniformly neglected the convenience of the light source installed on the smartphone itself. A miniaturized device that can be docked on a smartphone, and which utilizes the light source of the smartphone itself to provide backlighting illumination would be most favorable owing to its greater simplicity and portability. In addition, the micro-size structures of microfluidic devices cannot be clearly imaged by the built-in camera of a smartphone. Therefore, smartphone-based POCT systems must also provide for enhanced magnification of device structures.

To address these issues, we designed a miniature imaging unit that can be docked onto a smartphone. We adopted an optical configuration consisting of an optical fiber, a mirror, and a light guide plate (LGP) to convert the built-in smartphone light source into a planar backlighting source. In addition, a set of orthoscopic lens was assembled to facilitate the clear imaging of small-sized devices. The two functional units were assembled in a three-dimensional (3D) printed epoxy box. The viability of the proposed smartphone/imaging system was demonstrated by conducting on-chip protein concentration measurements based on the bicinchoninic acid (BCA) method and ABO blood typing. The reduced sample volume employed in the system enabled the successful measurement of protein concentrations and the conduct of ABO typing without special equipment. These results highlight the potential of for adopting smartphone-based analysis systems in POCT applications.

2. Experimental

2.1 Design and fabrication of the imaging box and different microfluidic chips

The imaging box consists of an illumination system, a magnification module, and a mechanical adaptor. The top plate includes two circular apertures for docking the camera lens and the LED light source of the smartphone, which were positioned according to the geometrical layout of the camera. The present study employed an Apple iPhone 6s smartphone. Therefore, the camera lens and light source apertures were 8 mm and 5 mm in diameter, respectively, as shown in Fig. 1(A). The microfluidic stage was designed at the bottom of the imaging box under the imaging system, and a sliding gate on the side of the box allows for sample input and output. The individual systems are discussed in detail as follows.
Illumination system: The novel optical light module shown in Fig. 1(B) was developed to re-direct the smartphone light source as backlight illumination. The optical fiber was composed of polymethyl methacrylate (PMMA), and had a diameter of 5 mm and a length of 15 mm. To avoid unwanted illumination, the exterior of the optical fiber was covered with black tape, and directly connected with the light source aperture. The other end of the fiber was connected with a section containing a mirror set at 45° relative to optic axis of the fiber to redirect the light and form an edge-type light source (Fig. 1(C)). Finally, the light rays enter an LGP composed of polycarbonate (PC) with dimensions 21 mm × 16 mm × 2.8 mm to produce evenly distributed backlight illumination. The LGP is illustrated schematically in Fig. 2(D). The working principle of this LGP is that the refractive index of the LGP employed in this study is $n_1 = 1.49$, and the refractive index of air is $n_2 = 1.0$, which permits total internal reflection (TIR) of the light in the LGP. Thus, uniform backlight illumination is produced by the raised scattering points. Also, to reduce the loss of light, the sides and bottom of the LGP are covered with a reflective film. Individual microfluidic chips were mounted on the light guide plate, directly under the camera lens for imaging.

Magnification module: The magnification system was composed of four lenses in two groups with an equivalent focal length $f = 10.5$ mm. The four-element system consisted of a single plano-convex lens and three cemented convex-convex achromatic lenses designed to reduce lens distortion. The configuration of the magnification module was employed to alleviate chromatic aberration and distortion in the central imaging region. The multiple lenses were assembled and fastened in a 3D-printed holder with a diameter of 11 mm and a length of 13 mm. The lens holder was vertically assembled directly under the camera lens according to the schematic illustrated in Fig. 1(B). The magnification modular is illustrated in Fig. 2(E). According to the magnification factor formula $Γ = 250/f$, $Γ$ is calculated to be about 25. Meanwhile, the working distance of the magnification module is 5 mm, which satisfies the limitations associated with most disposable polydimethylsiloxane (PDMS) micro-devices, flexible thin film devices, and paper-based microfluidic devices.

![Fig. 1. Design and fabrication of the smartphone-based imaging box: A) dimensions and components of the imaging box; B) schematic of the internal backlighting and magnification systems of the imaging box; C) schematic of the converting of smartphone light source to backlight illumination; D) schematic of the guide light plate; E) the magnification module; F) interface between the imaging box and the smartphone via a cover-like adapter.](image)

Mechanical system: The configuration of this system is illustrated in Fig. 1(F), and is composed of the cuboid imaging box connected to the smartphone via a cover-like adapter with which the smartphone is mounted. Inserting the phone into the adapter properly aligns the camera and light source with the corresponding apertures in the imaging box, which
greatly simplifies the image capture process. Hence, the smartphone can be easily connected to the imaging box through the smartphone cover-like adapter.

The imaging box and smartphone cover-like adapter were printed using a MoonRay 3D printer (SprintRay Inc., USA). The lenses, optical fiber, mirror, and LGP were then assembled in the imaging box.

Two types of miniaturized devices were tested to demonstrate the image capacity of the box. For smartphone imaging, the light source was set in its continuous operation mode, the camera was focused on the target chip, and then the image was captured according to standard procedure. First, Formvar/carbon film coated grids used in transmission electron microscopy (TEM) analysis were imaged to test the magnification effect and imaging quality of the imaging box. The mesh size of the carbon coated grids was 230, while the bar width was 25 μm, the pitch was 110 μm, the grids number of the mesh was 500 and the hole size was 85 μm. In order to compare the quality of photographs taken with and without the image box, Image Pro plus (version IPP6.0, MediaCybernetics, USA) was applied to count the number of grids. Specifically, particle counting and measurement function was applied to analyze the image to automatically extract and count the grids. Second, a PDMS device was fabricated following standard lithography and replication techniques [19]. Structured PDMS was replicated from a photoresist mold, and assembled with an adhesive film to form the microchannels. A color solution composed of food additive dye and water in a 1:20 v/v mixture was injected into the microchannels. To compare the quality of photographs taken with and without the image box, Plot Profile function of ImageJ software (NIH, USA) was used to analyze the grayscale along the edge of the channel.

2.2 Testing the colorimetric analysis abilities of the imaging box

As discussed, the potential of the proposed imaging box in POCT applications was demonstrated by conducting colorimetric-based protein detection and ABO antigen-based blood typing using microdevices. These analyses are discussed in detail as follows.

**Bicinchoninic acid (BCA) protein detection**: BCA protein detection is a standard colorimetric assay conducted in laboratories. The working principle of the assay lies in that monovalent copper ions (Cu⁺) interact with a BCA reagent to form a purple reactive complex, which exhibits a strong absorbance at 562 nm. Because the peptide bonds in protein molecules reduce Cu²⁺ ions from copper (II) sulfate to Cu⁺, the amount of Cu²⁺ reduced is proportional to the amount of protein present in the solution. Thus, the colorimetric changes (absorbance value) would reflect the protein concentration in a sample. For conducting BCA protein detection, different concentrations of bovine serum albumin (BSA) solution (0, 0.05, 0.1, 0.2, 0.3, 0.4, and 0.5 mg/ml) was added into the BCA reagent according to instructions (BCA protein kit, Beyotime Biotechnology, China), and 20 μL samples were incubated at 37°C for 45 min in compartments with a diameter of 3 mm and a depth of 1.5 mm that were fabricated by 3D printing. The colorimetric variation was imaged by the smartphone/imaging box system, and the captured images were quantitatively analyzed using ImageJ software according to the G channel intensities based on the RGB model in the detection zone. Next, the pixel intensity of G channel was direct read by the smartphone APP color name (Softporek BG Ltd.). In addition, the same BCA solution samples were analyzed using a spectrophotometric microplate reader (ELx800TM, Gene Company) at 570 nm. The signal (intensity of G channel or absorbance) to protein concentration curve was plotted. All experiments were repeated for three times.

**ABO blood typing**: The ABO blood type system is classified according to whether specific antigens (agglutinogens) A and B exist on the surface of red blood cells [20]. Blood is then divided into four types: A, B, AB, and O, according to the relative distributions of A and B. First, the flexible thin film device shown in Fig. 5(A) was fabricated using shaped Parafilm and thermal lamination with two transparent PET films to form micro-channels [21]. The chip is a tridentate structure containing three reaction zones, each of which is a
circle with a diameter of 1.5 mm. The width of the main channel is 1.7 mm, the width of each sub-channel is 600 μm, and the channel depth is 100 μm. Prior to sealing the upper PET layer, which included four holes that can connect the inlet and outlets, 0.7 μL of anti-A antibody, anti-B antibody, and distilled water were respectively added to the three reaction zones and incubated at 37°C for 30 min. Then, the device was sealed with the upper PET sheet. Blood was obtained from a health volunteer under the regulation of Southwest University Hospital. The blood was diluted five-times with saline and only 3 μL of the diluted blood was pipetted into the inlet of the device, which flowed through the main channel and reached the reaction zone. According to the principle of ABO blood typing, the corresponding antigen causes blood cells to flocculate, producing a visible agglutination. Images of the microfluidic device were then captured with the smartphone/imaging box system. In the analysis, changes in the color and appearance within the detection zone were considered.

3. Results and discussion

3.1 Image quality characteristics of the smartphone/imaging box system

Figure 2A shows the prototype of the image box. The smartphone can be stably docked on the image box. As shown in Fig. 2(B), the smartphone light source was converted to a flat backlight illumination by the optical fiber-mirror-light guide plate configuration. The changing of top direct illumination to a backlight illumination could avoid specular reflection, especially when image a smooth and transparent surface. In previous studies [7, 10, 15], external light sources were utilized to establish backlight illumination for smartphone-based testing. While, the light source of smartphone itself has not been fully taken advantaged. The proposed power-free image box converting the light source of the smartphone to a plat backlight illumination would be favorable owing to its greater simplicity and portability.

Fig. 2. Prototype of the image box (A); backlight illumination (B).

The image quality obtained by the smartphone/imaging box system was demonstrated by imaging a carbon coated grid. As shown in Fig. 3(A), it is not possible to clearly observe the structure of the carbon coated grid with the smartphone alone unless the digital zoom in function of the camera is used. Yet, employing the digital zoom function of the camera would compromise the pixel quality of the image. However, the structure of the carbon coated grid is clearly observable in the image captured with the smartphone/imaging box system. The two photographs were further analyzed by using Image Pro plus. As compared in Fig. 3(A), it is difficult to depict individual grids of the carbon mesh imaged by the digital zoom in function of the camera. While the edge of each grids can be clearly observed from the image taken with the proposed image box. The improved image quality also permits the automatic counting of the grid by using particle analysis function of Image Pro plus. There are 500 grids in each mesh. The software picked grid number from image taken with and without proposed image box are 500 and 369, respectively, demonstrating the potential of the image device for recording micro-sized samples. Next, a PDMS device including
microchannels with different widths was fabricated, and the device was imaged by the smartphone/imaging box system. As shown in Fig. 3(B), channels with widths as small as 25 μm are clearly observable. While without the assist of the image box, the digital zoom in function of the smartphone can barely show the image of the channel down to micro-size. The edge of the channel was analyzed by the profile function of Image pro plus. The side of the channel is blur because of the compromised pixel quality. From the profile analysis, the blur image is characterized by a bumpiness profile line. While, channel imaged with the image box has a relative flat profile line. Figure 3(A) and (B) demonstrate that magnification module of the image box enable observation and capture the micro-size sample by using smartphone. As compared in Table 1, the proposed image box can achieve uniform illumination without external light source. The illumination module empowered image box can provide backlight illumination, while the orthoscopic lens enabled magnification permits observing of structures at micro-meter size. The all-in-one image box would benefit the POCT applications.

Fig. 3. Comparison of image quality. A) Carbon grid captured with smartphone zoom in function and smartphone-docked with image box; particle counting by Image Pro Plus; B) Microfluidic channels captured with smartphone zoom in function and smartphone-docked with image box; the Gray intensity variation at the right edge area of the 250 μm channel (width: 250 μm) imaged with different model.

Table 1. Comparison of smartphone based image acquisition and analysis

| Backlight illumination | Smartphone light source | Magnification | Ref | Backlight illumination | Smartphone light source | Magnification | Ref |
|------------------------|-------------------------|---------------|-----|------------------------|-------------------------|---------------|-----|
| No                     | Yes                     | No            | [1] | Yes                    | No                      | Yes           | [2] |
| No                     | No                      | Yes           | [3] | Yes                    | No                      | No            | [6] |
| No                     | Yes                     | No            | [5] | Yes                    | No                      | No            | [7] |
| No                     | Yes                     | No            | [17]| Yes                    | No                      | Yes           | [9] |
| No                     | No                      | No            | [13]| Yes                    | No                      | No            | [10]|
| No                     | Yes                     | Yes           | [18]| Yes                    | Yes                     | Yes           | This work |

3.2 Accuracy of the smartphone-based colorimetric assay

Colorimetric images of solutions with different BSA concentrations were captured with the smartphone/imaging box system, and the results are presented in Fig. 4(A). A visual change from colorless to a purple color can be observed with increasing BSA concentration from 0 to 0.5 mg/mL. First, the color image taken with the image box was analyzed by computer-based ImageJ software. The average results of image analysis (ΔGreen channel intensity) for each of the three samples are plotted in Fig. 4(B) versus BSA concentration, and the results were subjected to linear fitting (ΔGreen Intensity = 78.27x – 2.1571). The goodness of fit was determined by the correlation coefficient (R²), which is 0.9944. While, the detection
limit of 0.0413 mg/mL was calculated from 3 times the standard deviation of blank sample signal divided by slope of the regression equation [6]. Furthermore, the protein BCA detection samples were imaged with smartphone and direct analyzed by the smartphone APP color name (Softporek BG Ltd.). The retrieved Green intensity was plotted against the protein concentration. As shown in Fig. 4(C), the linear dose-signal relationship is within the range of 0-0.5 mg/mL (ΔGreen Intensity = 97.98x – 0.0034, R^2 = 0.9903, n = 5) for BSA, and the calculated detection limit is 0.0467 mg/mL. In addition, the optical absorbance obtained by the spectrophotometric microplate reader at 570 nm is given on the right side of Fig. 4(D), which presents a linear fitting characterized by R^2 = 0.9993. The detection limit of spectrometer measured absorbance method is 0.0284 mg/mL. The better performance in detecting lower concentration of BSA could because 200 µL BSA solution was placed into the microplate and the depth of the solution is 7 mm. While for smartphone-based image acquiring, the depth of the measured solution is only 1.5 mm. According to Beer-Lambert Law, the absorbance of the sample is determined by both the concentrations of the attenuating species as well as the thickness of the sample. If the sample is thicker, the light has to pass through more sample molecules and more is adsorbed [5]. In a microfluidic based analysis, the colorimetric signal intensity would be sacrificed because of the significantly reduced sample volume or thickness. Next, the analytical recovery of the BSA concentration measurement was calculated by comparing the spiked and detected protein concentrations to evaluate the reliability of the image-based colorimetric detection. As shown in Table 2, the recovery rates calculated from Image J-based analysis is in the range of 95.6% - 108.5%, and the number obtained from smartphone APP color name-based analysis is in the range of 99.3% - 107.8%. The recovery rate obtained with the image taken with image-box docked smartphone is comparable to the performance of spectrometer-based absorbance measurement (Table 2), demonstrating the potential of the proposed smartphone/imaging box system in POCT applications. Moreover, the convenience of smartphone APP-supported colorimetric analysis would further strength the image-box for on-sit detection.

Fig. 4. Colorimetric analysis of bicinchoninic acid (BCA) protein detection assay: A) images captured via the smartphone/imaging box system with increasing BSA concentration from 0 to 0.5 mg/mL; B) analysis of images captured via the smartphone/imaging box system by Image J (ΔGreen channel intensity); C) analysis of images captured via the smartphone/imaging box system by smartphone APP color name (ΔGreen channel intensity); D) dose-signal curves obtained from optical absorbance obtained by a spectrophotometric microplate reader at 570 nm (A_{570nm}).
Table 2. Determination of BSA concentrations by the Smartphone-based colorimetric analysis and conventional spectrometer microplate reader

| Added con.(mg/mL) | Smartphone image - A | Smartphone image - B | Microplate reader |
|------------------|----------------------|----------------------|-------------------|
|                  | Measured con. (mg/mL) | Recovery rate (%)    | Measured con. (mg/mL) | Recovery rate (%) | Measured con. (mg/mL) | Recovery rate (%) |
| 0.15             | 0.163 ± 0.019         | 108.5                | 0.154 ± 0.082      | 102.8             | 0.153 ± 0.003         | 101.9             |
| 0.25             | 0.239 ± 0.011         | 95.9                 | 0.269 ± 0.074      | 107.8             | 0.256 ± 0.003         | 102.6             |
| 0.35             | 0.342 ± 0.013         | 97.6                 | 0.347 ± 0.015      | 99.3              | 0.345 ± 0.005         | 98.6              |

Smartphone image – A: image taken with image box was analyzed by computer-based software ImageJ
Smartphone image – B: image taken with image box was analyzed by smartphone-based software Color name

3.3 On-chip ABO blood typing from smartphone-captured images

An image of the ABO blood typing test chip captured by the smartphone alone is shown in Fig. 5(A). We note from this image that it is difficult to determine the occurrence of blood coagulation because the size of the chip is very small. However, the image captured by the smartphone/imaging box system presented in Fig. 5(B) clearly shows the differences between detection zones, demonstrating the capability of the proposed smartphone/imaging system for blood typing analysis.

![Fig. 5. On-chip ABO blood typing and observation. A) blood typing results taken by smartphone; B) blood typing results taken by smartphone/imaging box.](image)

4. Conclusion

The present work developed a smartphone/imaging box system for POCT applications that could take full advantage of the multiple functionality of smartphones for interfacing with miniaturized sensing units/microfluidic devices. To ensure reproducible lighting conditions, the LED light source of the smartphone was converted into backlight illumination by a system consisting an optical fiber, a mirror, and a light guide plate. A multi-piece convex lens was assembled in the imaging box to effectively and faithfully magnify the central region of microfluidic chips. The proposed smartphone/imaging box system was applied for colorimetric-based BCA protein detection and ABO blood typing. The results verified that the colorimetric signals obtained from very small samples in microfluidic devices can be clearly recorded, and that the magnified images support ABO blood typing analyses. These results highlight the potential of smartphone-based analysis systems for POCT applications.

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