mHealth Dipstick Analyzer For Monitoring of Pregnancy Complications

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***Abstract*— Dipstick-based urinalysis is routinely used for detection of early signs of such pregnancy complications, as preeclampsia and gestational diabetes. Usually it is done in doctor's office using an automatic dipstick analyzer. Here we present a novel smartphone-based colorimeter and demonstrate its application to the measurements of glucose and protein concentrations in biological samples. The key innovations of our approach was to combine powerful image processing encoded into a mobile phone application with a low cost 3D printed sample holder that allowed to control lighting conditions and significantly improved sensitivity. Different solutions with protein and glucose concentrations ranging from 0 to 2000 mg/dL were prepared and analyzed using our system. The smartphone-based colorimeter always correctly classified the corresponding reagent strip pads, what confirms that it can be used as a low cost alternative for commercial dipstick analyzers.**

Keywords*— *pregnancy complications, preeclampsia, glucose and protein detection, mHealth, urinalysis

I. Introduction

Recent advances in smartphone technology, such as greatly enhanced processing power, storage capability and wireless connectivity turned mobile phones into powerful computers integrated with high quality cameras and numerous sensors. Additionally, the price and size of the mobile phones have decreased so much, that they became available even in the countries with the lowest income. The worldwide mobile phone subscription recently reached close to 7 billion users [1]. Some of the applications of the mobile phones in healthcare and biomedical fields include weight management [2], lens-free microscopy [3], hypertension monitoring system [4], label free immunoassays [5], monitoring system for Parkinson's disease patients [6], retinal disease diagnostic device[7], system for monitoring kidney metabolomics [8], flow cytometry [9] and many others [10].

There are colorimetric smartphone software applications that determine a concentration of an analyte in a biological sample by conducting color analysis [11]. Similarly to traditional colorimeters, they are based on Beer-Lambert's law relating absorbance of collimated monochromatic beam in a homogeneous medium to the concentration of the absorbing species and the propagation distance through the absorptive medium [12]. Alternatively, mobile phone based colorimeters can use color analysis to determine a concentration a colored substance. For example, there was a smartphone based colorimetric reader for quantitative analysis of direct enzyme-linked immunosorbent assay (ELISA) for horse radish peroxidase (HRP), rapid sandwich ELISA for human C-reactive protein (CRP) and commercially available BCA protein estimation assay [13].

Smartphone based colorimeters are broadly classified into two categories: stand-alone applications and applications combined with different hardware components. Mobile phone colorimeters with designated app to process the color information are excellent low cost alternative for expensive commercial colorimetric readers [11]. The main limitation of this approach is that the user needs to calibrate with a set of reference images whenever there is a change in ambient light conditions.

Colorimetric app with a dark hood and external lighting setup works great in controlling the ambient lighting condition. This hood setup can be an ideal choice for holding the sample at constant position for continuous tracking of color change at particular location on the sample. Building a hood for the colorimetric application requires accurate dimensions of the mobile phone and specific design based on the position of the camera. In addition to this, it requires battery powered light source like LED array to keep the illumination constant. Assembling the setup is one of the main limitations with this method that led us to develop a simple and cost effective hybrid point-of-care mobile phone based colorimeter. This device overcomes the limitation of both types of mobile phone based colorimeters and demonstrates great performance, high reproducibility, accuracy and stability under varying lighting conditions.

II. MATERIALS AND METHODS

In order to make a precise and reproducible mobile phone based colorimeters, we need to fix a number of hardware parameters like distance between a mobile camera and an object, multiple camera settings and use a stable light source [14]. In order to keep a sample at constant distance from the camera, we introduce a 3D printed sample holder (Chroma-dock). The Chroma-dock, as shown in Fig. 1 (c) and (d), consist of a back box attached to a mobile phone and a removable cassette serving as a sample holder. This structure not only allows keeping the sample at constant distance from the camera, but also creates a controlled-light environment. This allows capturing very reproducible images and eliminates the background noise.

Another important set of hardware parameters that have to be fixed, is camera settings, such as exposure rate, ISO setting, white balance, sharpness, hue, saturation and gamma. In a case of a stand-alone application-based colorimeter that does not include any additional hardware, these settings have to be dynamically changed, according to varying environmental conditions, what introduces additional noise.

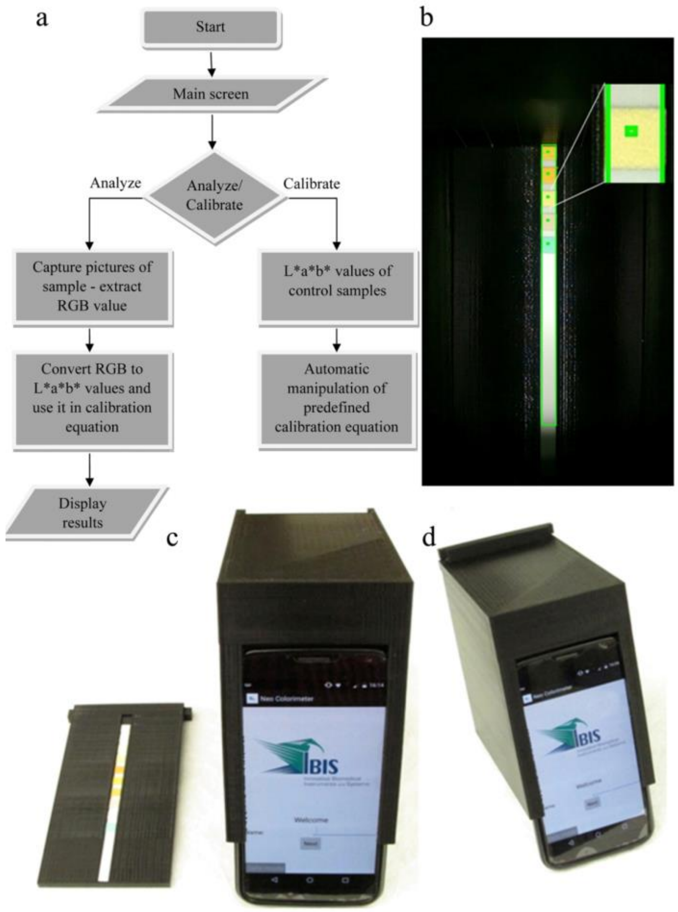

Fig. 1. (a) Algorithm used for colorimetric measurement, (b) camera preview with region of interest (ROI) over the reagent pads of the test strip (c) Mobile phone based colorimeter with a cassette and a holder, (d) the cassette is inserted.

Finally, another important component of a stable mobile phone colorimeter is a high quality light source. While an external LED can be used for mobile colorimetric measurements, it would require an external power supply and wiring, what adds complexity to the system. Fortunately, contemporary cellphones have high quality built-in flashlight integrated with the camera. This light sources can be directly controlled using software installed on a mobile phone.

A. *Mobile application development*

Mobile application development for colorimetric measurements involves capturing, storing and analysis of an image of a sample. To determine a concentration of a substance, color information from an image has to be extracted and matched with the values from a calibration curve. Fig. 1 (a) shows the algorithm used for the colorimetric measurement.

B. *Color processing*

The image of the dipstick is taken using a built-in camera. After that a region of interest is chosen in the middle of a test pad responsible for the needed analyte. The ROI is a square 10x10 pixels. Color information in the ROI of the captured images as shown in Fig 1 (b) was extracted using a built-in function. Red, green and blue (RGB) values of the corresponding pixels inside the ROI were obtained. RGB is a non-absolute color space as the color values depend on external factors like illumination, sensitivity of camera sensor, etc [15-17]. CIE L*a*b* color model provide more accurate and uniform color representation [18]. L* value indicates lightness and it range from 0 to 100 (black to white). a* value indicates red/green color components (positive value represents red region and negative value represents green region). b* value indicates yellow/blue color components (positive value represents yellow region and negative value represents blue region). There is no direct standard formula to convert RGB to L*a*b* values. Mobile app is programmed to convert obtained RGB values to CIE L*a*b* values indirectly, by calculating XYZ tristimulus values. Standard illuminant D65 was considered for the RGB to L*a*b* color space conversion.

C. *Measurement technique*

Color values obtained in the previous step were used to compute the concentration value of the substance. Equations fitting the calibration curves were built into the mobile app. Some substances change color non-linearly with linear change of concentrations, what adds complexity to the computation procedure. In this case, calibration equation of particular color component from L*,a* and b* is used to determine the concentration of the substance in the sample and the values obtained from the calibration equations of other color components are used in further decision making process.

III. RESULTS AND DISCUSSIONS

Clinical utility of the smartphone based colorimeter was demonstrated using Urinalysis Reagent Strips. Twelve samples with different concentrations of glucose and protein were prepared. D-(+)-Glucose solution (45%) and Bovine serum albumin from Sigma-Aldrich were used as a source of glucose and protein. They were added to the artificial urine solution from Flinn scientific inc. Eight samples with 0, 100, 250, 375, 500, 750, 1000 and 2000 mg/dL concentrations of glucose and another eight samples with 0, 15, 30, 100, 300, 750, 1500 and 2000 mg/dL concentrations of protein were prepared.

Test strips were briefly dipped into the artificial urine samples. After ensuring all the reagent pads on the test strip were moistened, excess of the sample were removed by wiping the edge of the test strip. After the needed reaction time the test strips were placed on the cassette and loaded into the holder module. Mobile app programmed with the calibration equations for the respective substances was started. It captured and stored the images of the test strip and extracted the color values from those images. The calibration equations were used to calculate the concentrations of substances present in the samples which were displayed to the user and also saved in the database.

Correlation graph between the standard glucose concentrations in the sample and the measured concentration values by smartphone based colorimeter is shown in the Fig. 2 (a). The graph indicates a good agreement between observed and modeled values. This application that quantifies the glucose value can be used to detect medical conditions related to glucosuria - excretion of glucose in the urine, that may be due to untreated diabetes mellitus or due to renal glucosuria [19].

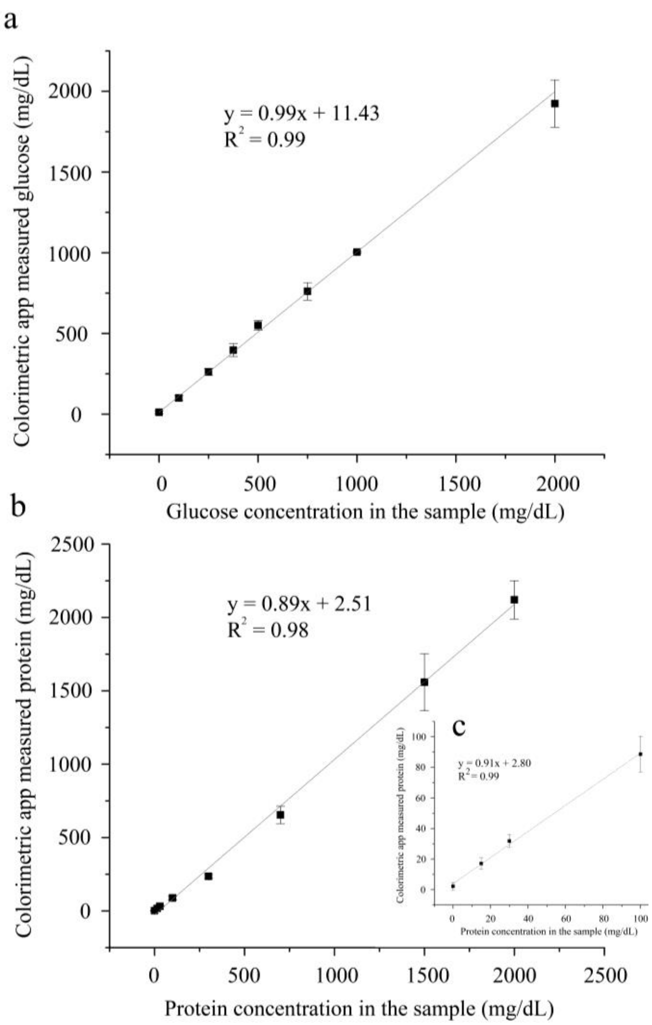

Fig 2. Correlation graphs for (a) the glucose concentrations in the samples and values measured by the app, (b) and (c) the protein concentrations in the samples and values measured by the app.

Correlation graph between the standard protein concentrations in the sample and the measured concentration values by smartphone based colorimeter is shown in the Fig. 2 (b) (c). We can notice that the app measured values are correlated well with the modeled values. The app quantified values can be used to detect medical conditions related to proteinuria - excretion of protein in the urine, that may be due to nephrotic syndrome, pre-eclampsia, sickle cell disease, glomerular disease, diabetes mellitus, dehydrations, toxic lesions of kidneys, HELLP syndrome, etc [20].

IV. CONCLUSIONS

Advancements in smartphone technology paved the way for development of innovative point-of-care diagnostic devices. Here we demonstrated a mobile phone-based low cost portable colorimeter that can determine the concentrations of protein and glucose in a biological sample. Our device does not require regular calibration, as it is independent of external lighting conditions. The same app can be programmed to measure concentration of other urine components, like ketone, bilirubin, hemoglobin, nitrite, leukocytes, urobilinogen, and other, by adding corresponding calibration equations.

The total cost for manufacturing our smartphone based colorimeter was less than 15 USD in addition to the existing mobile phone. This makes our device, a low cost alternative for expensive commercial test strip analyzers that cost several hundred dollars. Our mobile app provides the optional feature of sharing these results to the registered members. In addition, this app can store the concentration values in the phone memory along with the user identity information and optionally the app can use cloud storage which makes it a potential product for telemedicine applications.

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