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Color Space Transformation-Based Smartphone Algorithm for Colorimetric Urinalysis

Renbing Yang,[†] Wenbo Cheng,*[,†,‡,§] Xifeng Chen,[†,∥] Qin Qian,[†] Qiang Zhang,[†] Yujun Pan,[†] Peng Duan,[†] and Peng Miao*[,†]

[†]CAS Key Lab of Bio-Medical Diagnostics, Suzhou Institute of Biomedical Engineering and Technology, Chinese Academy of Sciences, Suzhou 215163, P. R. China

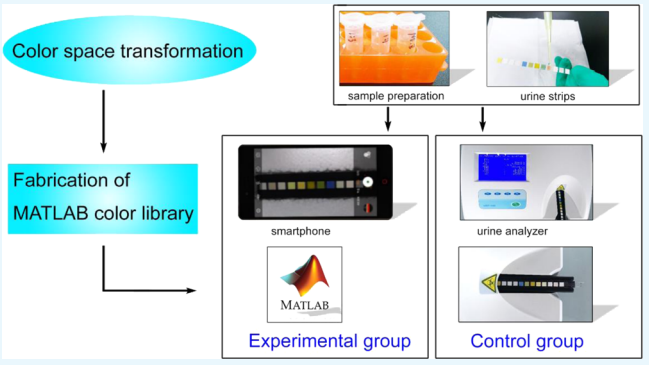
[‡]State Key Lab of Optical Technologies on Nano-Fabrication and Micro-Engineering, Institute of Optics and Electronics, Chinese Academy of Sciences, Chengdu 610209, P. R. China

[§]University of Chinese Academy of Sciences, Beijing 100049, P. R. China

[∥]Tianjin Guoke Jiaye Medical Technology Development Co., LTD, Tianjin 300399, P. R. China

Supporting Information

ABSTRACT: Urine strips are widely applied for rapid analysis of various indexes of urine for clinical examinations. The tests mainly rely on the application of a urine analyzer, which suffers several drawbacks and cannot meet the requirements of point-of-care testing (POCT). The integration of a smartphone with a biosensor has recently attracted great attention. We herein propose a human vision-based smartphone algorithm for colorimetric analysis of various urine indexes. A CIEDE2000 formula in CIELab color space is applied for the evaluation of color difference, which may greatly improve the analytical performances of urine strips. The proposed algorithm also possesses merits such as good accuracy, quantitative analysis, and limited calculation task, which is suitable for the application with smartphone platform. Experimental results demonstrate that the proposed method shows excellent reliability compared with the urine analyzer and some other algorithms. In addition, human real samples are successfully analyzed with excellent accuracy. Therefore, this work provides a convenient colorimetric tool for POCT urine analysis.



INTRODUCTION

The advent of the Internet era brings new life styles for people. In healthcare aspect, the concept of point-of-care testing (POCT) is becoming more and more popular.[1,2] Although instruments in hospital or central laboratory provide extremely high analytical precision, they suffer disadvantages such as high cost, cumbersome registration, long-time consumption, and so on. On the other hand, POCT refers to the point in time when people are served by certain healthcare products.[3] Generally, a series of biochemical, blood, or molecular diagnostic tests are performed rapidly without professional medical personnels and specific places. The attractive features of POCT, including simple operation, ease to carry, and rapid analysis with accurate results, conform to the trend of the times.[4] Smartphone accessories equipped with operating systems have become revolutionary portable diagnostic tools, which can be used to read colorimetric signals directly.[5−7] The smartphone has rich sensors to detect signals, great processing power and memory capacity to analyze and store diagnostic results, high-resolution screen to display calculated results, and multiple data transmission functions such as WiFi, Bluetooth, and USB. In addition, the features of small size, low price, large user community, and high programmability make it much suitable for POCT and mobile diagnostics.[8,9] In the past few years, numerous smartphone-based medical testing techniques emerge, which cover the fields of immunoassay,[10,11] microscopy,[12] flow cytometry,[13] electrochemical,[14] surface plasma resonance,[15] and colorimetric biosensors.[16]

Urine is one type of waste products from the human body, which contains important physiological and pathological information.[17] Urinalysis is a common test for the diagnosis of human diseases and disorders such as diabetes,[18] urinary infection,[19] and nephritis.[20] Commercial urine strips are widely used in urine analysis, and the detection mainly relies on the colorimetric changes of corresponding blocks compared with a reference color chart. Usually, a urine analyzer is used to read and analyze the color changes. Nevertheless, it suffers several drawbacks and cannot meet the requirements of POCT.

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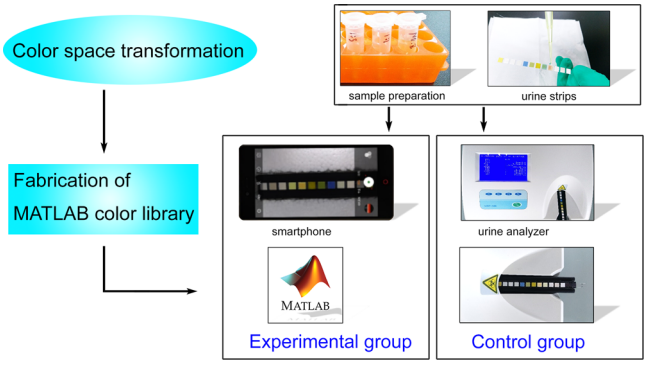
In recent years, certain smartphone algorithms have been designed, trying to replace the urine analyzer. Two strategies are usually exploited to define and describe the color difference of urine strips. One is based on machine learning, in which a lot of images are used as training data and significant color features are then extracted.[21] A model that distinguishes colors of urine strips is finally achieved. However, the calculation task of this strategy is heavy, which is a burden for the processor of a smartphone. In addition, only semiquantitative results can be obtained. The other strategy involves color space transformation. Color space is a set of definitions and rules used to accurately calibrate and generate various colors, which can be reflected as a mathematical model with a set of values. Color difference is usually described by the distance between two points in color space. Images taken by camera are represented in the RGB space. However, it is a nonuniform color space. The distance between two colors cannot represent the color sense of human vision. Therefore, it is necessary to be converted to another uniform color space. In 1931, the International Commission on Illumination (CIE) established the CIE 1931 color space, which is defined by two coordinates that define chromaticity.[22] The degree of color difference can be described according to the distance of each color in the plane.[23] Later, CIE introduced CIE 1976, which is the most suitable color space for human vision so far. However, most of the currently developed algorithms do not conform to human vision; thus, the accuracy is always not satisfactory compared with the urine analyzer.

In this report, we have developed a color space transformation-based smartphone algorithm and fabricated a novel colorimetric method for the analysis of urine (Scheme 1). The

Scheme 1. Illustration of the Process of the Proposed Colorimetric Urinalysis



camera on the smartphone is employed to capture images of reacted urine strips. A colorimetric algorithm with light calculation task is then proposed for quantitative or semiquantitative analysis of various analytes in the urine. Color space transformation from RGB to CIELab is successfully achieved, and the accuracy is promised. This proposed method successfully meets the requirements of low-cost, limited technical support, fast response, and excellent accuracy, which may have great potential utility in the future.

RESULTS AND DISCUSSION

In CIELab spectra, color could be described by the coordinates of L^*, a^*, and b^*, in which L^* stands for the luminance, whereas a^* and b^* represent the changes of color from red to green and yellow to blue, respectively (Figure S2). In CIELab spectra, changes of color and brightness are observed uniformly by human eyes from left to right, which are superior than those of RGB spectra (Figure S3). As a result, we have chosen CIELab to define the degree of color similarity and developed a novel colorimetric urinalysis method. CIEDE2000 is the most accurate color difference formula and is constituent with human vision, compared with previous CIE76 and CIE94.[24,25] Although the complexity of the formula is increased with a number of intermediate parameters, the performance of color difference prediction is not affected with the current processor.

After color space transformation from RGB to CIELab and color difference calculation, URIT 11A strips are employed and tested to evaluate the performance of the proposed algorithm. URIT 11A strips contain a blank block for urine analyzer correction and 11 testing blocks for the analysis of pH value, nitrite, glucose, ascorbate, specific gravity, blood, protein, bilirubin, urobilinogen, ketone, and leukocytes. Each testing block is immobilized with corresponding reagents. After dipping urine samples on them, specific reactions occur and the color changes could be used to represent the level of each index after comparing with the standard color card (Figure S4). MATLAB is then used to calculate the values of corresponding indexes according to the proposed algorithm, which are compared with those measured by the urine analyzer.

For the samples of UQ-11 control solutions, the concentration of a certain analyte with high concentration is defined as C_h, and the concentration of N-fold diluent is C_{test}, which satisfies the following relationship

$$C_{test} = C_h/N$$

Because of the uncertainty of the value of C_h, we analyze the relationship between C_{test} and dilution ratio of N after the following transformation

$$\ln(C_{test}) = \ln(C_h) - \ln(N)$$

The UQ-11 control solutions are diluted with 2, 4, 6, 8, 10, 12, 14, 16, 18, and 20 times, which are analyzed by the proposed method and a urine analyzer. As shown in Figure 1, the histograms represent semiquantitative results by the urine analyzer and the scatter diagrams show the results calculated by the colorimetric algorithm. Taken glucose, ascorbic, blood, and ketone as examples, the excellent agreements demonstrate that the algorithm is highly suitable for the analysis of urine strips. In addition, the insets reflect the relationship between calculated values and the logarithmic diluted times, most of which show linear relationships and meet the expectations. We have also tested the other six indexes (Figure S5). The fine results promise the potential of the method for quantitative analysis.

The accuracy of the semiquantitative analysis by the proposed algorithm is further confirmed. The semiquantitative results for the analysis of 10 indexes (each three times) achieved by the proposed method and urine analyzer are compared (Figure 2). The numbers of coincident results take up about 85% of all detections and the erroneous judgements adjacent to the standard results without significant deviations.

The pH value of the standard positive urine is faintly acid. Therefore, the color of the alkaline reaction cannot be obtained. Because the preparation of gradient acid and alkali solutions and the determination of pH values are quite easy, we have prepared the samples with different pH values to verify

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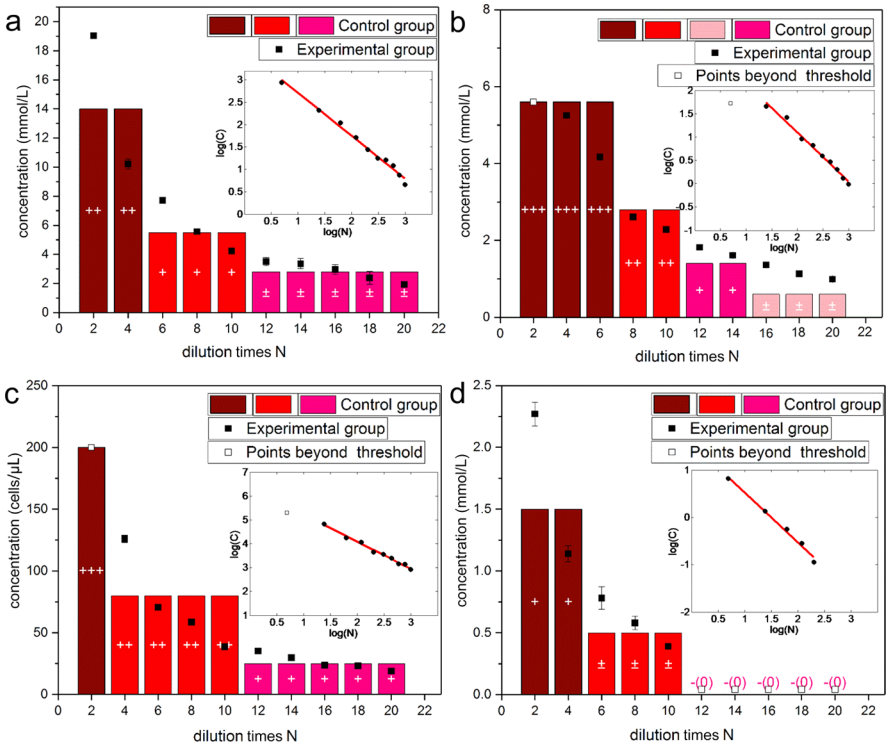

Figure 1. Comparison of the results of proposed colorimetric urinalysis (experimental group) and commercial urine analyzer (control group) for the detection of (a) glucose, (b) ascorbic, (c) blood, and (d) ketone.

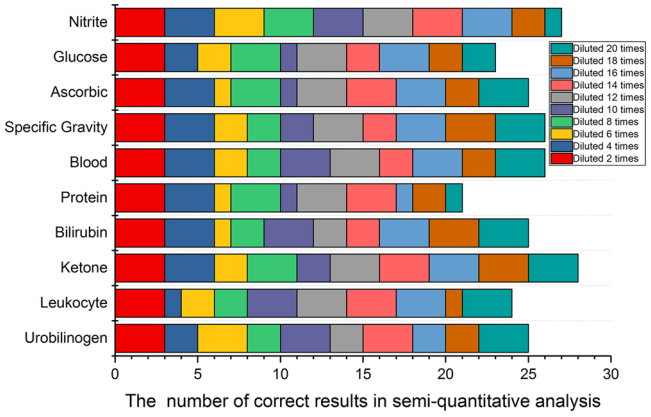

Figure 2. Accuracy evaluation of the proposed method.

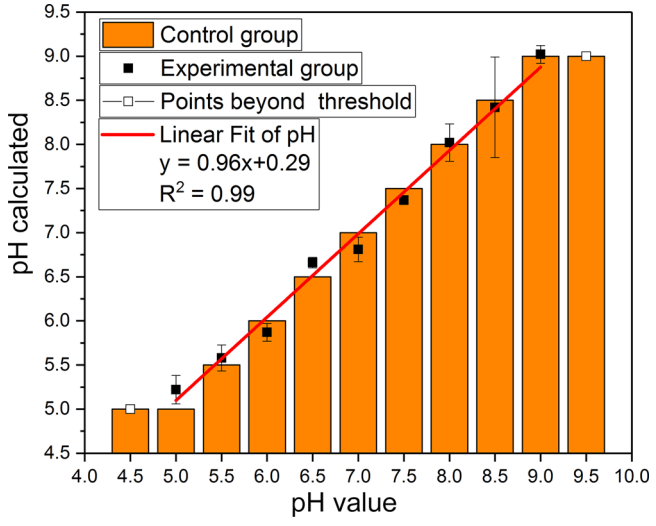

Figure 3. Comparison of the calculated pH values and standard values.

the effectiveness of the algorithm on pH sensing. As shown in Figure 3, the pH values of the reference color card are from 5 to 9. However, the range can be extended from 4.5 to 9.5 based on the novel algorithm. The results are in good accordance with the theoretical expectation. The fitting curve obtained by this algorithm is much close to that of control method, which confirms the high accuracy of the method. All of these results show high stability of the algorithm, which is applicable to the colorimetric analysis of the urine strips.

To verify the practical utility of the proposed method, we have employed 25 real samples (urina sanguinis samples) for analysis, which are collected from local hospitals. The color difference between samples collected from different patients is mainly determined by their contents. The detected results can be used to reflect the information successfully. In addition, the urine sample storage mode, storage time, and test strip conditions may also influence the sample color, which should be uniformedly controlled before measurement. These samples are measured by a Urit 180 type urine analyzer as the gold standard. In addition, the images captured by the smartphone are analyzed by the proposed algorithm and three other algorithms, which are based on RGB, CIE XYZ, and HSV color spaces, respectively. Detailed results and three exemplary images are shown in Tables S1−S5 and Figure S6. The accuracies are listed in Table 1. The numbers reflect the degree of coincidence compared with the gold standard. The first method using RGB angle is relatively inferior, which is due to the fact that the RGB color space is not uniform; meanwhile, the angle parameter is not sensitive to the color difference. The accuracies of the other three methods perform well, and the

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Table 1. Comparison of the Accuracy of Different Algorithms Challenging Real Samples

analyte	RGB (ref 26)	CIE XYZ (ref 23)	HSV (ref 27)	this work
pH	15/25	18/25	20/25	25/25
nitrogen	25/25	25/25	25/25	25/25
glucose	20/25	24/25	22/25	24/25
ascorbate	23/25	23/25	20/25	24/25
specific gravity	20/25	23/25	22/25	23/25
blood	20/25	25/25	20/25	25/25
protein	22/25	22/25	23/25	23/25
bilirubin	25/25	25/25	25/25	25/25
urobilinogen	25/25	25/25	25/25	25/25
ketone	25/25	25/25	25/25	25/25
leukocytes	25/25	25/25	25/25	25/25

proposed algorithm shows the best accuracy. Although both of CIEDE2000 and CIE XYZ are based on CIELab color space, CIEDE2000 formula have many improvements. For example, a hue term (R_T) is added to deal with the problematic blue region for better perceptual uniformity. Compensations are also involved for neutral colors, lightness, chroma, and hue. Therefore, the accuracy of color difference calculation is improved, and CIEDE2000 is much suitable for colorimetric analysis of urine test strips.

CONCLUSIONS

In summary, we have proposed a smartphone algorithm for colorimetric analysis of urine strips. An optimized color space transformation strategy is designed based on human vision. Original RGB color space is converted to CIELab color space, which only requires small computational capacity. The detected results show that the method is highly accurate for quantitative or semiquantitative analysis of each index in the urine strips. Thus, it is suitable for the application of smartphone platform. The developed method has a wide application prospect in urinalysis and facilitates the assessment of personal clinical status, which is expected to replace the traditional urine analyzer. In addition, this algorithm can also be adjusted to detect other samples and analytes, which result in color differences with different concentrations, such as blood hematocrit, vitamin D, chlorine level in water, cholesterol, and so on.

METHODS

Materials and Instruments. URIT 11A strips and UQ-11 control solutions were obtained from URIT Medical Electronic Group Co., Ltd (Guilin, China). Each control solution contained corresponding contents with different concentrations. The lower concentration was called a negative quality control, and the higher was called a positive quality control (Table S6). Human urine samples were from The First Affiliated Hospital of Soochow University with the informed consent of the donors (Suzhou, China). The first urine samples after getting up in the morning were collected with the urine sampling tubes. All experiments using the samples were performed in accordance with institutional and national guidelines and with the approval of the Medical Ethics Committee of The First Affiliated Hospital of Soochow University (no. 2012076). The study was conducted in accordance with the Declaration of Helsinki. A Nubia Z9 mini smartphone with 16 megapixel HD camera and eight-core CPU was employed. In order to ensure illumination uniformity and remove any influence of external environment, an experimental box was designed and used for photographing, in which a white light source composed of six groups of LED was integrated (Figure S1).

Color Space Transformation. Original RGB color space was converted to CIELab color space which was the best matching for human vision. First, RGB was transformed to XYZ, which was then further transformed to CIELab. The original image was assumed as (R, G, B). The nonlinear sRGB was treated by inverse gamma correction:

$$\begin{cases} R_{\text{linear}} = \gamma^{-1}\left(\dfrac{R}{255}\right) \\ G_{\text{linear}} = \gamma^{-1}\left(\dfrac{G}{255}\right) \\ B_{\text{linear}} = \gamma^{-1}\left(\dfrac{B}{255}\right) \end{cases}$$

$$\gamma^{-1}(x) = \begin{cases} \left(\dfrac{x + 0.055}{1.055}\right)^{2.4}, & x > 0.04045 \\ \dfrac{x}{12.92}, & x \le 0.04045 \end{cases}$$

$$\begin{bmatrix} X \\ Y \\ Z \end{bmatrix} = M \times \begin{bmatrix} R_{\text{linear}} \\ G_{\text{linear}} \\ B_{\text{linear}} \end{bmatrix}$$

in which

$$M = \begin{bmatrix} 0.4124 & 0.3576 & 0.1805 \\ 0.2126 & 0.7152 & 0.0722 \\ 0.0193 & 0.1192 & 0.9505 \end{bmatrix}$$

Next, XYZ was converted using the following equations

$$\begin{cases} L^* = 116f\left(\dfrac{Y}{Y_n}\right) - 16 \\ a^* = 500\left[f\left(\dfrac{X}{X_n}\right) - f\left(\dfrac{Y}{Y_n}\right)\right] \\ b^* = 200\left[f\left(\dfrac{Y}{Y_n}\right) - f\left(\dfrac{Z}{Z_n}\right)\right] \end{cases}$$

$$f(t) = \begin{cases} t^{1/3}, & t > \left(\dfrac{3}{29}\right)^3 \\ \dfrac{1}{3}\left(\dfrac{29}{6}\right)^2 t + \dfrac{4}{29}, & t \le \left(\dfrac{3}{29}\right)^3 \end{cases}$$

X_n, Y_n, and Z_n were the three stimulus values, which were 95.047, 100.0, and 108.883, respectively. The RGB values of each blocks could be converted to CIELab values and were then stored in MATLAB color library.

Calculation of Color Difference. The color difference ΔE_{00} between two color blocks, (L_1^*, a_1^*, b_1^*) and (L_2^*, a_2^*, b_2^*), was calculated using the formula of CIEDE2000. The three parameters of k_L, k_C, and k_H equaled to 1. The calculations could be performed as follows.[28]

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$$C_i^* = \sqrt{a_i^{*2} + b_i^{*2}}, \qquad i = 1,\ 2$$

$$\bar{C}^* = (C_1^* + C_2^*)/2$$

$$G = 0.5\left(1 - \sqrt{\bar{C}^{*7}/(\bar{C}^{*7} + 25^7)}\right)$$

$$a_i' = (1 + G)a_i^*, \qquad i = 1,\ 2$$

$$C_i' = \sqrt{a_i'^2 + b_i^{*2}}, \qquad i = 1,\ 2$$

$$h_i' = \begin{cases} 0, & b_i^* = a_i' = 0 \\ \arctan(b_i^*/a_i'), & \text{otherwise} \end{cases}$$

$$\Delta L' = L_2^* - L_1^*$$

$$\Delta C' = C_2' - C_1'$$

$$\Delta h_i' = \begin{cases} 0 & C_1'C_2' = 0 \\ h_2' - h_1' & C_1'C_2' \neq 0,\ |h_2' - h_1'| \leq 180^\circ \\ (h_2' - h_1') - 360^\circ & C_1'C_2' \neq 0,\ (h_2' - h_1') > 180^\circ \\ (h_2' - h_1') + 360^\circ & C_1'C_2' \neq 0,\ (h_2' - h_1') < -180^\circ \end{cases}$$

$$\Delta H' = 2\sqrt{C_1'C_2'}\,\sin(\Delta h_i'/2)$$

$$\bar{L}' = (L_1^* + L_2^*)/2$$

$$\bar{C}' = (C_1' + C_2')/2$$

$$\bar{h}' = \begin{cases} h_2' + h_1' & C_1'C_2' = 0 \\ (h_2' + h_1')/2 & C_1'C_2' \neq 0,\ |h_2' - h_1'| \leq 180^\circ \\ (h_2' + h_1' + 360^\circ)/2 & C_1'C_2' \neq 0,\ |h_2' - h_1'| > 180^\circ,\ (h_2' + h_1') < 360^\circ \\ (h_2' + h_1' - 360^\circ)/2 & C_1'C_2' \neq 0,\ |h_2' - h_1'| > 180^\circ,\ (h_2' + h_1') \geq 360^\circ \end{cases}$$

$$T = 1 - 0.17\cos(\bar{h}' - 30^\circ) + 0.24\cos(2\bar{h}') + 0.32\cos(3\bar{h}' + 6^\circ) - 0.2\cos(4\bar{h}' - 63^\circ)$$

$$\Delta\theta = 30\exp\left\{-\left[\frac{\bar{h}' - 275^\circ}{25}\right]\right\}$$

$$R_C = 2\sqrt{\bar{C}'^7/(\bar{C}'^7 + 25^7)}$$

$$S_L = 1 + \frac{0.015(\bar{L}' - 50)^2}{\sqrt{20 + (\bar{L}' - 50)^2}}$$

$$S_C = 1 + 0.045\bar{C}'$$

$$S_H = 1 + 0.015\bar{C}'T$$

$$R_T = -\sin(2\theta)R_C$$

$$\Delta E_{00}([L_1^*\ \ a_1^*\ \ b_1^*], [L_2^*\ \ a_2^*\ \ b_2^*]) = \sqrt{\left(\frac{\Delta L'}{k_L S_L}\right)^2 + \left(\frac{\Delta C'}{k_C S_C}\right)^2 + \left(\frac{\Delta H'}{k_H S_H}\right)^2 + R_T\left(\frac{\Delta C'}{k_C S_C}\right)\left(\frac{\Delta H'}{k_H S_H}\right)}$$

Quantitative Analysis. The content of a certain analyte in the urine strips contained five reference color blocks from low to high. According to the previous formulas, the closest reference color blocks could be found and the approximations were measured based on the image processing method. The color differences between test block and two closest color blocks were assumed to be ΔE_1 and ΔE_2. The corresponding concentrations of the two color blocks were assumed to be C_1 and C_2. Therefore, the concentration of the test block could be calculated according to the ratio of the two color differences.

$$C_{test} = \begin{cases} C_1 + \dfrac{\Delta E_1}{\Delta E_1 + \Delta E_2}(C_2 - C_1), & C_1 < C_2 \\ C_1 - \dfrac{\Delta E_1}{\Delta E_1 + \Delta E_2}(C_1 - C_2), & C_1 \geq C_2 \end{cases}$$

Considering that the two endpoint color blocks represented the minimum value C_{min} and maximum value C_{max} measured by the urine strips, the final obtained results should be between these two values.

$$C_{test} = \begin{cases} C_1 + \dfrac{\Delta E_1}{\Delta E_1 + \Delta E_2}(C_2 - C_1), & \Delta E_2 < \Delta E_{12},\ C_1 = C_{min} \\ C_1 - \dfrac{\Delta E_1}{\Delta E_1 + \Delta E_2}(C_1 - C_2), & \Delta E_2 < \Delta E_{12},\ C_1 = C_{max} \\ C_1, & \Delta E_2 \geq \Delta E_{12} \end{cases}$$

Comparison of Experimental Groups and Control Groups. Two kinds of testing samples were prepared. One was positive quality control solutions diluted by negative quality controls with a series of ratios. The other solutions with different pH values were adjusted by HCl and NaOH (pH from 4.5 to 9.5). Samples (20 μL) were added to the test block and blank block of the urine strips, which could be absorbed. The strips were placed in the experimental box. After 59 s, the photograph of the strips was taken by the smartphone camera. For control experiments, the strips were loaded on the urine analyzer for measurements.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acsomega.8b01270.

Picture of experimental box, CIELab color space, RGB spectra and CIELab spectra, standard color card of URIT 11A strip, strip images for real sample detection, comparison of the proposed colorimetric urinalysis and commercial urine analyzer, and corresponding values of the UQ-11 control solutions (PDF)

■ AUTHOR INFORMATION

Corresponding Authors

*E-mail: chengwb@sibet.ac.cn (W.C.).

*E-mail: miaopeng@sibet.ac.cn. Phone: +86-512-69588279 (P.M.).

ORCID

Peng Miao: 0000-0003-3993-4778

Notes

The authors declare no competing financial interest.

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