A New Image Calibration Technique for Colposcopic Images

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ABSTRACT

Colposcopy is a primary diagnostic method used to detect cancer and precancerous lesions of the uterine cervix. During the examination, the metaplastic and abnormal tissues exhibit different degrees of whiteness (acetowhitening effect) after applying a 3%-5% acetic acid solution. Colposcopists evaluate the color and density of the acetowhite tissue to assess the severity of lesions for the purpose of diagnosis, telemedicine, and annotation. However, the color and illumination of the colposcopic images vary with the light sources, the instruments and camera settings, as well as the clinical environments. This makes assessment of the color information very challenging even for an expert. In terms of developing a Computer-Aided Diagnosis (CAD) system for colposcopy, these variations affect the performance of the feature extraction algorithm for the acetowhite color. Non-uniform illumination from the light source is also an obstacle for detecting acetowhite regions, lesion margins and anatomic features. Therefore, in digital colposcopy, it is critical to map the color appearance of the images taken with different colposcopes into one standard color space with normalized illumination. This paper presents a novel image calibration technique for colposcopic images. First, a specially designed calibration unit is mounted on the colposcope to acquire daily calibration data prior to performing patient examinations. The calibration routine is fast, automated, accurate and reliable. We then use our illumination correction algorithm and a color calibration algorithm to calibrate the patient data. In this paper we describe these techniques and demonstrate their applications in clinical studies.

Keywords: Cervical Cancer, Calibration, Colposcopy, Computer-Aided Diagnosis

1. INTRODUCTION

Uterine cervical cancer is the second most common cancer in women worldwide, with nearly 500,000 new cases and over 270,000 deaths annually. Because invasive disease is preceded by pre-malignant Cervical Intraepithelial Neoplasia (CIN), if detected early and treated adequately, cervical cancer can be universally prevented[1].

Colposcopy is once of the primary diagnostic methods used to detect CIN and cancer, following an abnormal cytological screen (Papanicolaou smear). The purpose of a colposcopic examination is to identify and rank the severity of lesions, so that biopsies representing the highest-grade abnormality can be taken, if necessary. A colposcopic examination involves a systematic visual evaluation of the lower genital tract (cervix, vulva and vagina), with special emphasis on the subjective appearance of metaplastic epithelium comprising the Transformation Zone (TZ) on the cervix. During the exam, a 3-5% acetic acid solution is applied to the cervix, causing abnormal and metaplastic epithelia to turn white. Cervical cancer precursor lesions and invasive cancer exhibit certain distinctly abnormal morphologic features that can be identified by colposcopic examination. Lesion characteristics such as color or opacity, margin shape, blood vessel caliber, intercapillary spacing and distribution, and contour are considered by physicians (colposcopists) to derive a clinical diagnosis. Lugol's iodine is another contrast solution often used during colposcopy. The color difference of the iodine staining also assists in differentiating the severity of the lesions.

However, the color and illumination of the colposcopic images vary with the light sources, the instruments and camera settings, as well as the clinical environment. Typically, the color of the epithelium may look very different (including normal and abnormal findings) in cervical images acquired with different instruments or at different times. This makes the assessment of the color information very challenging, even for an expert. Using an objective image calibration technique (accompanied by corresponding monitor calibration technique) may help the physician/colposcopists to better assess the information in cervical images in terms of diagnosis and severity, as well as facilitate the annotation and the use of telemedicine.

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Medical Imaging 2006: Image Processing, edited by Joseph M. Reinhardt, Josien P. W. Pluim,
Proc. of SPIE Vol. 6144, 614466, (2006) · 0277-786X/06/$15 · doi: 10.1117/12.650218

Digital imaging is revolutionizing medical imaging and enabling sophisticated computer programs to assist the physicians with Computer-Aided-Diagnosis (CAD). Clinicians and academia have suggested and shown proof of concept to use automated image analysis of cervical imagery for cervical cancer screening and diagnosis[2]. Various image processing algorithms have been developed to detect different colposcopic features, such as acetowhite color[3], lesion margin[4], and blood vessels[5,6]. However, lack of color calibration makes it very difficult to accurately extract the color property of the acetowhite lesions. The non-uniform light distribution also has been a bottleneck for extracting the correct lesion margin and blood vessel structures.

CAD for colposcopy could have a direct impact on improving women's health care and reducing the associated costs. Color calibration has been a crucial factor in developing a CAD system for colposcopy. Several image enhancement techniques, such as histogram stretching and/or equalization, have been used as an attempt to compensate for the illumination problem[6,7]. To our knowledge, the design of a system that both corrects the non-uniform illumination and calibrates the color of the colposcopic images has not yet been reported.

STI® Medical Systems has been developing digital imaging technology for cervical cancer screening and diagnosis. STI®'s digital colposcope has been developed to acquire high-resolution digital imagery for colposcopy. To accompany the digital colposcope, we have designed a calibration unit to acquire calibration data at the clinical sites. The calibration is performed daily before the patient examination. The process is fast, automatic and easily done by a nurse or clinical operator. We use our illumination correction algorithm and a color calibration algorithm to calibrate the patient data. The illumination correction algorithm normalizes the light distribution by dividing the exam image with its corresponding neutral gray target image. The color calibration algorithm estimates the linear mapping between two different color spaces and uses an optimization process to compensate for the nonlinear effect. Morphological operations are also applied for noise removal and color patch detection. Our calibration system has been successfully applied at multiple clinical sites. A calibrated digital colposcopic image database with 149 human subjects is currently under construction.

The following sections are organized as follows: Section 2 introduces the calibration algorithms used in our system, including gray balance and color calibration. Section 3 explains the calibration hardware design. Calibration results with different instrument settings are presented in Section 4, as well as the performance evaluation. Conclusions are given at the end.

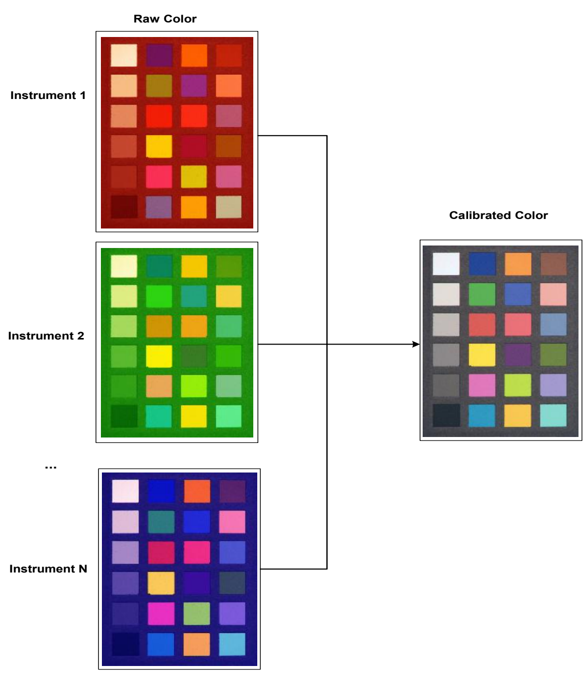


Figure 1. The concept of color calibration: mapping the raw color space of different instruments into a standard color space.

2. METHOD DESCRIPTION

Generally speaking, the colors of an image depend on the camera and light source used in the system. Digital cameras can only "see" a subset of the range of colors visible to the human eye and they also represent colors differently (especially with different light sources). Consequently, depending on lighting condition and camera characteristics, digital color image often appear different from what is perceived by eye. The goal of image calibration is that the colors should appear to be identical, independent of camera/camera settings and light source used. This can be achieved by mapping the color appearance of the images taken with different instruments into a standard color space, as illustrated in Figure 1.

Figure 2 shows the entire calibration procedure proposed for the colposcopic image calibration. Both patient data and calibration data are acquired at the clinical sites using the same instrument. Calibration data includes images of a gray target for gray balance and a color target for color calibration (see Figure 3). (There are also other calibration targets involved in our clinical practice, which are beyond the scope of this paper.) The image of the color target is processed by the gray balance algorithm to normalize the light distribution. This image is then used to compute the color correction matrices for the color calibration algorithm. The patient data are processed using the gray balance algorithm followed by the color correction algorithm. The calibrated patient data are then ready for algorithm development of the CAD system for colposcopy, colposcopic image annotation, and telemedicine. A detailed description of the methods is described in the following subsections.

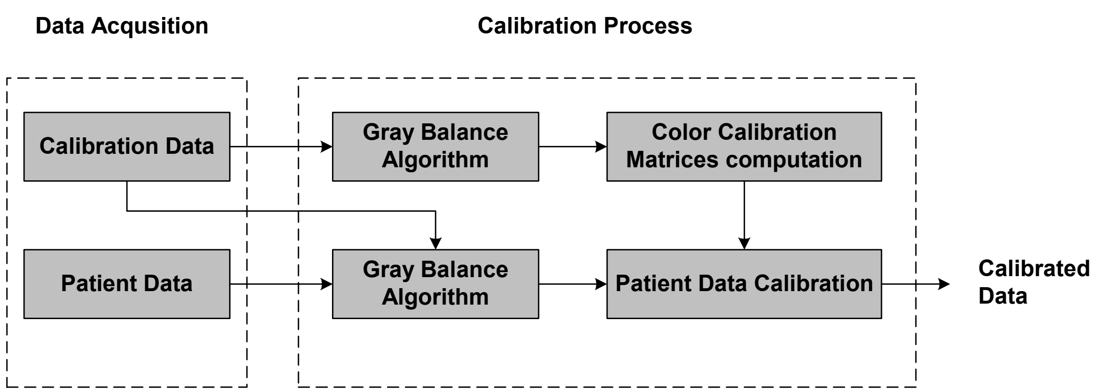
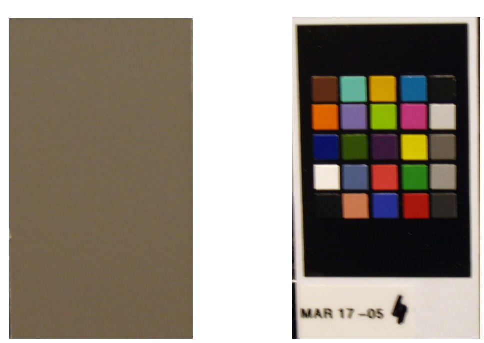


Figure 2. Calibration Procedure

2.1 Gray Balance Algorithm

The gray balance calibration is used to normalize the spatial variations of the light source and the camera responses. We use the gray area corresponding to Neutral 5 color patch in the ColorChecker from GretagMacbeth (www.gretagmacbeth.com) as the calibration target (as shown in Figure 3 (a)). The corresponding 8-bit RGB values are (122, 122, 121) in sRGB color space for illuminate D65.



(a) (b)

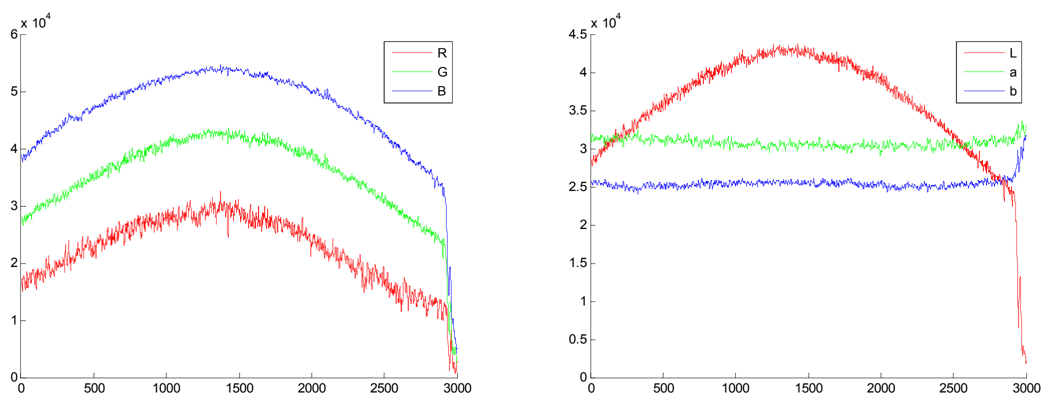
Figure 3. Calibration Targets used (a) Gray target, (b) Color target

The gray balance algorithm is based on the following equation:

$$C_{gb}(x,y) = \frac{C_{raw}(x,y) - C_{background}(x,y)}{C_{grayflat}(x,y) - C_{graydark}(x,y)} \times S_c \tag{1}$$

where $C_{gb}(x,y)$ is the gray balanced image; $C_{raw}(x,y)$ is the raw monochrome channel image; $C_{background}(x,y)$ is the background image that corresponds spatially to the raw image acquired with ambient light on but with the instrument light off. This background image needs to be taken at a very short time before or after the acquisition of the raw image, such that no movement of the scene can happen. It comprises two components, the raw image with the instrument light off and the background illumination. $C_{grayflat}(x,y)$ is the image taken the gray target without ambient light but with the instrument light on, and $C_{graydark}(x,y)$ is the image taken from the gray target with both ambient light and instrument light off. S_c is the gray target ground truth value for a monochrome color channel in the corresponding color space. We currently use the gray dark image $C_{graydark}(x,y)$ as the background image $C_{background}(x,y)$.

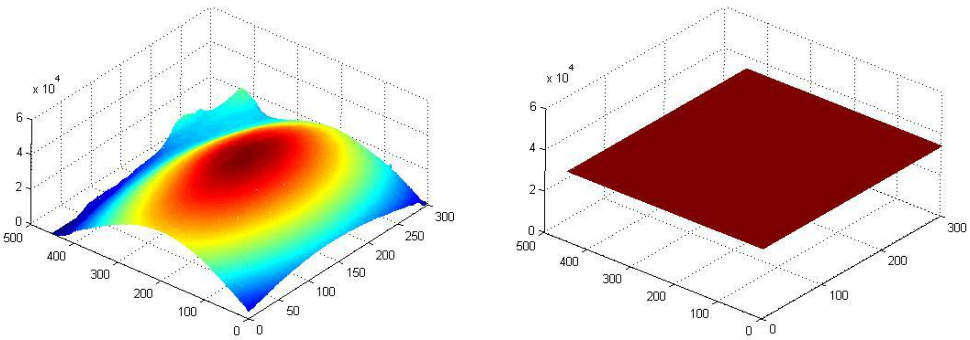
The gray balance algorithm can, in theory, be applied to the image in any color space. The use of RGB space is very common in the digital image processing field, primarily due to the availability of such data sets, as they are produced by most color image-capturing devices and they can be directly displayed on a monitor. However, the use of RGB space in computer vision applications usually has the following drawbacks. First, there is high correlation among RGB channels[8]. Second, the representation of RGB is not very close to the way humans perceive colors, as humans normally determine color by parameters such as brightness, hue and colorfulness, etc. And third, RGB space is not perceptually uniform[9]. CIE-Lab is a perceptually uniform color space that has proven to perform better than RGB for color texture analysis[10]. It has been applied to cervical image segmentation[11]. In our application, if we use RGB color space, we need to apply the algorithm three times on three color channels individually, as shown in Figure 4 (a). If we use CIE-Lab (or any other approximately perceptually uniform space, like HSV or HLS), since the illumination correction only needs the luminosity channel of the image, we need only to apply the gray balance algorithm on the L channel. The two color channels do not need the illumination correction, as shown in Figure 4 (b).



(a) (b)

Figure 4. 16-bit Gray Flat image (a) 1D signal in RGB space, (b) 1D signal in CIE-Lab color Space.

The result of the illumination correction can be visualized in Figure 5. Figure 5 (a) shows the light distribution of the L channel in the gray flat image. Figure 5 (b) is the corresponding light distribution after applying the gray balance algorithm. In practice, we take multiple gray dark and gray flat images and average them to reduce the overall noise level. Low pass filtering has also been applied to compensate for the noise.



(a) (b)

Figure 5. (a) Non-uniform distribution of light, (b) Corrected distribution

2.2 Color Calibration Algorithm

Wolf[12] presented an automated color correction matrix computation approach for correcting inaccurate color output by digital still and video imaging systems. The method uses a known reference image together with a robust least-square algorithm to estimate the optimal color channel matrix that must be applied to the output images in order to correct their color inaccuracies. The color transformation can be represented by the following equation:

$$\begin{pmatrix} A_1 & B_1 & C_1 \\ A_2 & B_2 & C_2 \\ \cdots & \cdots & \cdots \\ A_n & B_n & C_n \end{pmatrix} = \begin{pmatrix} 1 & nativeA_1 & nativeB_1 & nativeC_1 \\ 1 & nativeA_2 & nativeB_2 & nativeC_2 \\ \cdots & \cdots & \cdots & \cdots \\ 1 & nativeA_n & nativeB_n & nativeC_n \end{pmatrix} \begin{pmatrix} a_{11} & a_{12} & a_{13} \\ a_{21} & a_{22} & a_{23} \\ a_{31} & a_{32} & a_{33} \\ a_{41} & a_{42} & a_{43} \end{pmatrix} \quad (2)$$

where n is the number of color patches, (A_i B_i C_i) are the calibrated colors and ($nativeA_i$ $nativeB_i$ $nativeC_i$) are the native colors extracted from the image of the color targets, [a_{jk}] is the 4*3 color transformation matrix.
A third-order polynomial fitting to the individual color components is also applied in order to perform a monotonic non-linear correction:

$$y_j = b_{1j} x_j^{\,3} + b_{2j} x_j^{\,2} + b_{3j} x_j + b_{4j} \quad (3)$$

where j = 1, 2, 3, corresponds to the three channels of the image, x_j denotes the color values of the individual color component before the non-linear correction, y_j denotes the color values after the non-linear correction, and [b_{ij}] composes another 4*3 matrix to be computed.

We adapted Wolf's method into our cervical image calibration system, using the following steps:

a) Automatically extract the color patches from the designed target
b) Compute the color correction matrices between the extracted values and the standard values provided by the manufacturer in CIE-Lab color space using Equation (2) and (3),
c) Apply the calculated color transformation matrix on any raw cervical image.

We have developed an automatic color patch finder to locate the color patches in the calibration images based on morphology operations. The image of the color target is processed by the gray balance algorithm first to normalize the distribution of the intensity image. The ground truth of the color values is provided by GretagMacbeth (D65). The color correction matrices are computed in the CIE-Lab color space. The mean error between the color values of the ground truth and the calibrated color values is less than 6 pixel values. The calibrated result of the color target image is shown in Figure 6. Figure 6 (a) shows the original image, (b) shows the result of the automatic patch finder, and (c) shows the final calibrated color target image.

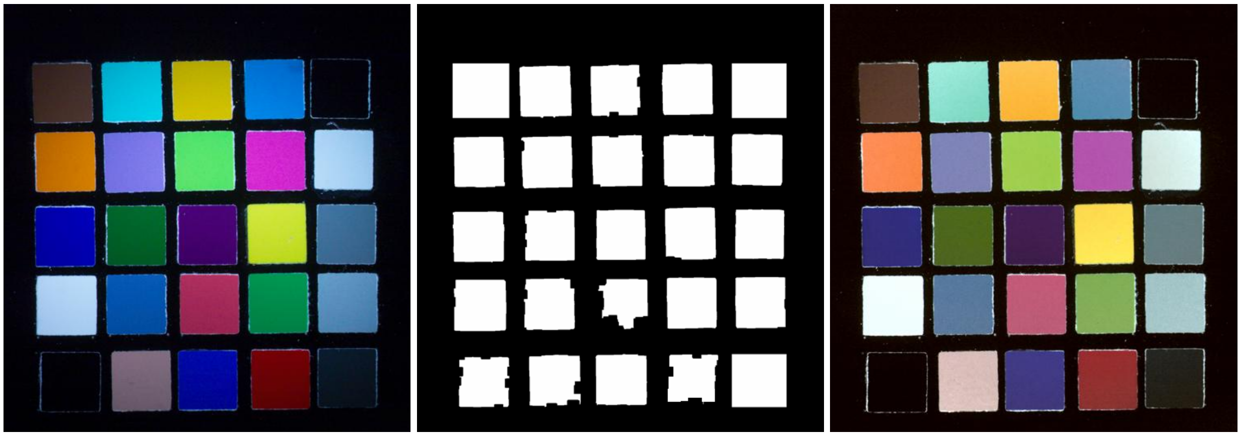

(a) (b) (c)

Figure 6. Images of the color targets, (a) original image, (b) result of patch finder, (c) calibrated image

3. DATA ACQUSITION AND HARDWARE

3.1 Digital Colposcope

Many cervical images have been acquired using a customized 35mm camera, the Cerviscope®, from National Testing Laboratories (NTL). Digital colposcopy is still in its infancy. As a potential source of digital imagery for colposcopy, STI's digital colposcope was developed to acquire images with a resolution sufficient for vessel detection. The digital colposcope utilizes a standard colposcope (Seiler, Series 935), two high-resolution digital cameras (Kodak, DCS Pro 14n or SLR/n), and a fiber guided light source assembly (Seiler, Series 935 original or Perkin Elmer, DiX1765), as seen in Figure 7. In addition to the vessel detection capabilities, the digital colposcope includes stereoscopic (used for three-dimensional image reconstruction) and cross-polarized image acquisition (used to remove specular reflection). The instruments have been used to acquire cervical data at the Tripler Army Medical Center (TAMC), Honolulu, Hawaii, the Eisenhower Army Medical Center (EAMC), Augusta, Georgia, as well as in Instituto Especializado de Enfermedades Neoplásicas, Lima, Peru and Hospital Regional, Cuzco, Peru.

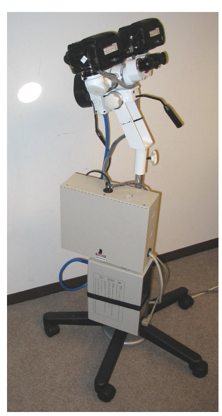
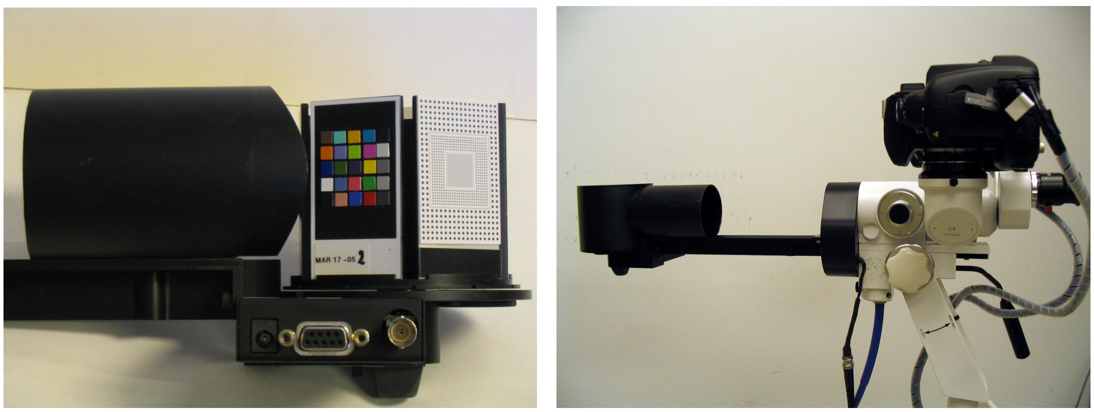


Figure 7. STI's digital colposcope.

3.2 Calibration Unit Design

The calibration unit is designed to fully automate the data acquisition process of the calibration targets at the clinical sites. It consists of three main parts, 1) calibration targets mounted on 2) a motorized filter wheel (customized Thorlabs, FW102), and 3) a light shielding tube (see Figure 8 (a)). Up to six calibration targets including gray target, color target, dot target, and entropy target can be mounted on the filter wheel. (Other targets are used for instrument calibration purposes, which is beyond the scope of the paper). The motorized filter wheel is used to switch the calibration target automatically. The light shielding tube is used to mimic the lighting condition when the patient data is acquired. The calibration images are acquired daily at the clinical site by the operator, who controls the system through a calibration acquisition program. The process is highly automated and requires only three steps to be performed: 1) connect the calibration unit to the colposcope (see Figure 8 (b)), 2) start the calibration program, and 3) remove the calibration unit. The whole process takes less than 12 minutes and requires no supervision by the operator. After this, the digital colposcope is ready for acquiring patient data for the entire day. The acquired calibration data is used to calibrate the patient data taken at the same day. Figure 8 (b) shows the calibration unit mounted on the digital colposcope.



(a) (b)

Figure 8. Calibration unit (a) The major components of the calibration unit: calibration targets, filter wheel, and the tube, (target cover removed) (b) Calibration unit mounted on the digital colposcope to take calibration data.

4. EXPERIMENTAL RESULTS

4.1 Cervical Image Calibration

Our calibration system has been utilized at four clinical sites, using three digital colposcopes. Data for 149 patients are being calibrated, including cervical images before and after application of acetic acid, and Lugol's iodine images.

Examples of calibration results can be seen in Figure 9, Figure 10 , and Figure 11. In the figures, the left column displays the cervical images before calibration, and the right column displays the corresponding calibrated images. In Figure 9 and Figure 10, examples of pre-acetowhite image, acetowhite image, and Lugol's iodine image are shown. The images are taken in Lima, Peru with the same colposcope and different camera settings. Figure 11 shows some examples of acetic acid images taken at TAMC, Honolulu. The colposcope used at TAMC had different cameras and a different light source (Kodak DCS Pro 14n and Seiler, Series 935) compared to the light source and camera (Kodak DCS Pro SLR/n and Perkin Elmer, DiX1765) used in Peru and at EAMC.

Visually, it can be seen that the periphery of the cervix looks darker in the raw image (due to the inherent light source intensity) and thus the periphery is brightened in the calibrated image. In Figure 9 and Figure 10, the raw image looks more bluish than the calibrated image. This is because the Xenon light source (Perkin Elmer DiX1765) has a higher intensity but emits a more bluish light. The reason that the images shown in Figure 11 look redder is because halogen light source was used which has a "redder" emission spectrum. From the calibrated images we can see that the color effect caused by using different light sources has been adequately corrected.

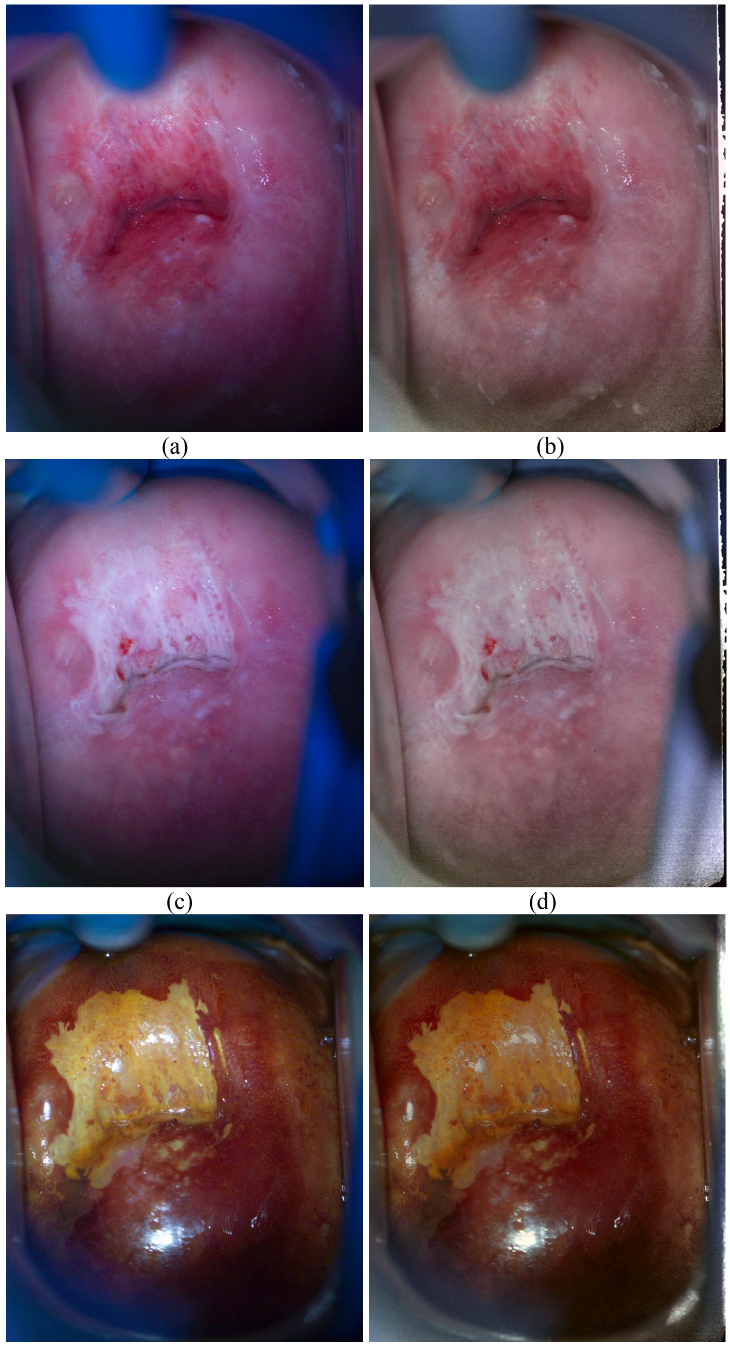


Figure 9. Calibration results I (Xenon lamp), (a), (c), an (e) are colposcopic images before calibration, (b), (d), and (f) are corresponding calibrated images.

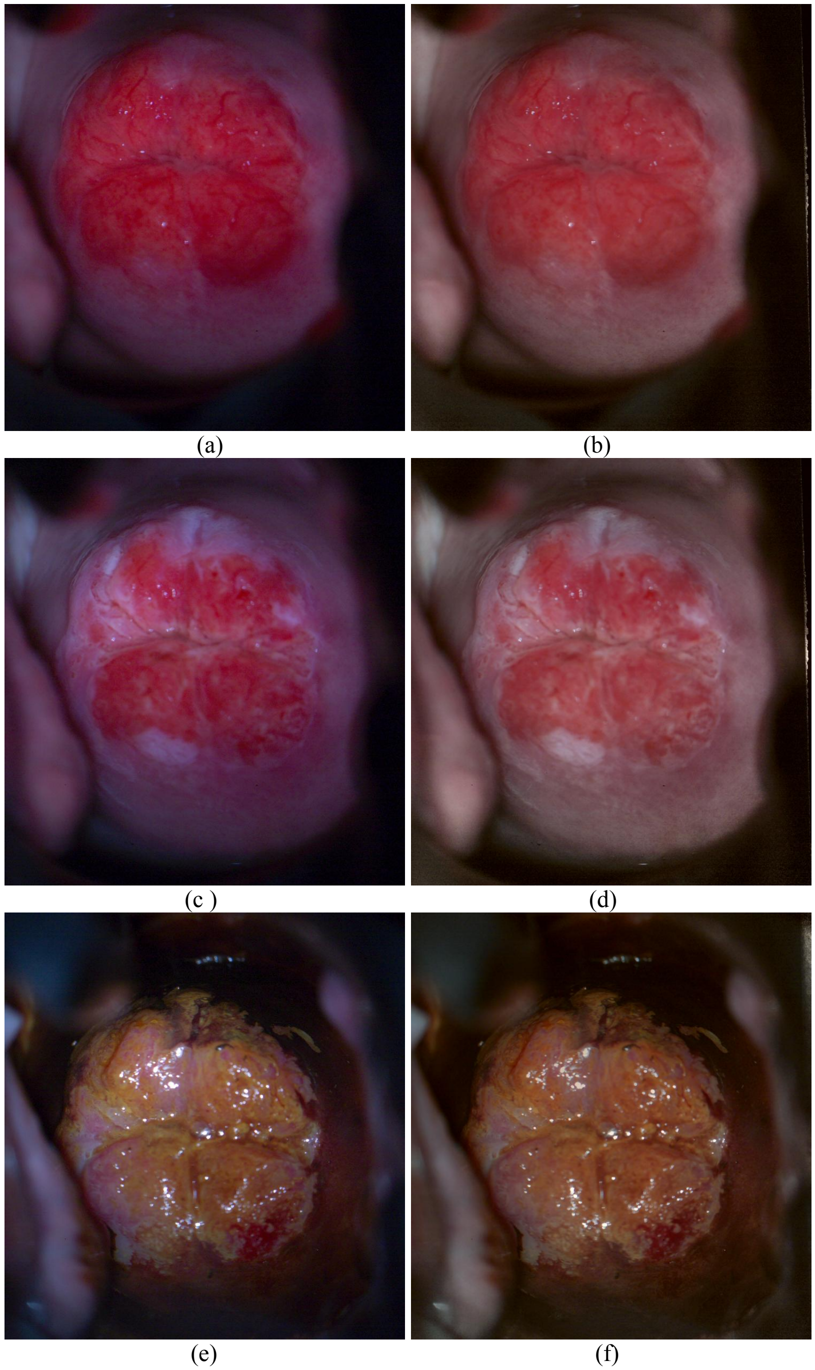


Figure 10. Calibration results II (Xenon lamp), (a), (c), an (e) are colposcopic images before calibration, (b), (d), and (f) are corresponding calibrated images.

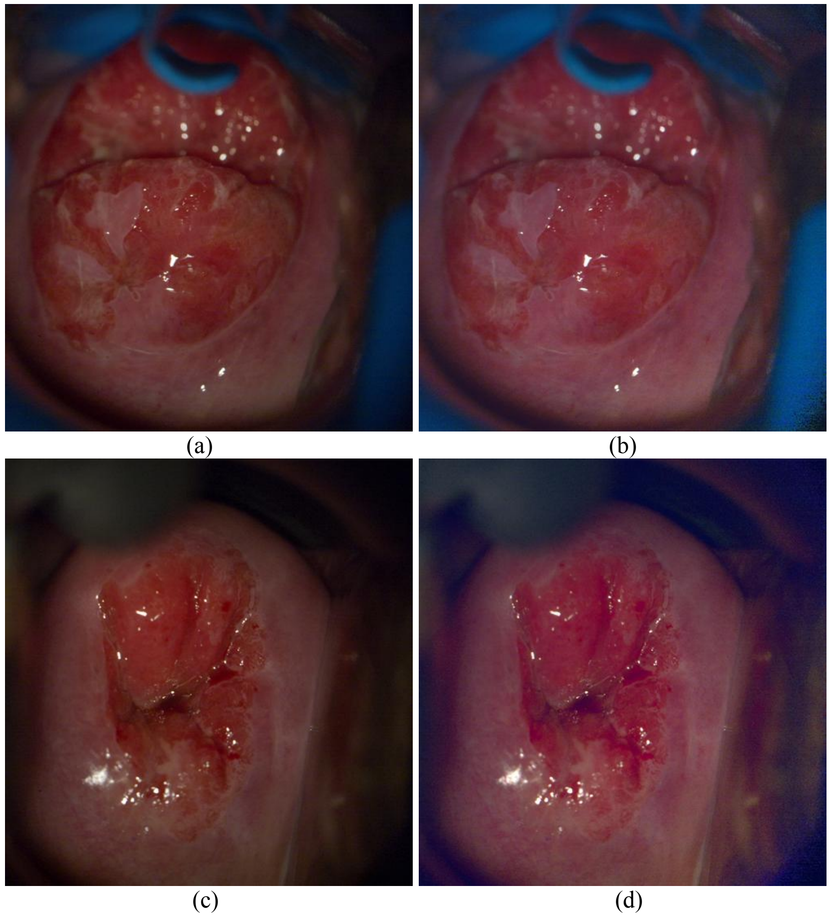


Figure 11. Calibration results III (Halogen lamp), (a), (c) are colposcopic images before calibration, (b), (d) are corresponding calibrated images.

4.2 Performance Evaluation

In colposcopy, epithelium that appears grossly normal but turns white after application of 3% to 5% acetic acid is called acetowhite epithelium. Colposcopists evaluate the color and the density of the acetowhite reaction to assess the severity of the lesion. Abnormal Acetowhite epithelium varies from a faint or a bright white (low-grade changes) to a dense gray-white (high-grade lesions). Acetowhite epithelium is one of the major diagnostic features observed in detecting cancer and pre-cancerous regions. It is the only diagnostic feature used in the cost effective screening method, Visual Inspection with Acetic Acid (VIA). A detailed description of the diagnostic features of acetowhite epithelium can be found in reference[1]. In order to develop a basic CAD system for colposcopy, we have implemented a fully unsupervised acetowhite feature extraction algorithm to analyze the color properties of acetowhite epithelium[13]. The algorithm segments the acetowhite regions based on K-means clustering in joint high dimensional color-texture space, and models different shapes of the colors as Gaussian mixtures. The mean value of the Gaussian represents the color property of the corresponding acetowhite region. In order to access the effectiveness of our calibration approach, we have run this algorithm on both un-calibrated and calibrated images, and compared the detection results with colposcopic annotations.

Figure 12 shows a cervical image taken after the application of acetic acid. The data was acquired in Lima, Peru and has been calibrated accordingly. The subject has been confirmed, by standard histopathologic exam, to have a high grade squamous intraepithelial lesion (HSIL). The acetowhite feature extraction algorithm has been applied to the same region of interest of the images before and after calibration with exact same parameter settings. Since only unsupervised algorithms are involved, no learning and prior knowledge has been used. Figure 12 (a) shows the algorithm result on the un-calibrated image, Figure 12 (b) shows the algorithm result on the calibrated image, and Figure 12 (c) shows the expert colposcopist's annotation. The blue lines indicate the detected acetowhite regions.

(a) (b) (c)

Figure 12. (a) Acetowhite region detection results for un-calibrated image, (b), Acetowhite region detection results on calibrated image, (c) colposcopist's annotation. (Blue curves indicate where the detected regions are.)

Although the current results are preliminary, we can see that the results on calibrated images match much closer to the annotation. The result on the un-calibrated image was significantly affected by the non-uniform distribution of the light intensity. The extracted color values of the corresponding acetowhite regions from both images are represented by the following pseudo images (see Figure 13). The images are composed of the average acetowhite colors extracted from both non-calibrated and calibrated images respectively, such that the visual difference of colors can be easily inspected.

(a) (b)

Figure 13. The average color values of the extracted Acetowhite regions from (a) un-calibrated images and (b) calibrated image.

5. CONCLUSIONS

The color and illumination of cervical images offer important information for cervical cancer screening and diagnosis. The inability to correct the color and illumination in colposcopic images has precluded the development of an effective CAD system for colposcopy. In this paper, a new colposcopic image calibration technique that standardizes the visual appearance of colposcopic images has been presented. Our image calibration technique includes the design of a fully automatic calibration unit for data acquisition at the clinical site, a gray balance algorithm for effective illumination correction, and an adapted color calibration process. The system has been applied in multiple clinical sites with different instruments. The results of acetowhite feature extraction algorithm have shown the effectiveness of the proposed technique. The technique is a vital element for annotation and further algorithm development purpose in CAD system. It is also useful for telemedicine and building standard databases for research and development in industry and academia. The designed calibration system can be easily adapted to other similar medical applications.

ACKNOWLEDGMENTS

Part of the work is supported by the US Army Medical Research and Materiel Command under Contract No. W81XWH-05-C-0005. The views, opinions and/or findings contained in this paper are those of the authors and should not be construed as an official Department of the Army position, policy or decision unless so designated by other

documentation. In the conduct of research where humans are the subjects, the investigators adhered to the polices regarding the protection of human subjects as prescribed by Code of Federal Regulations (CFR) Title 45, Volume 1, Part 46; Title 32, Chapter 1, Part 219; and Title 21, Chapter 1, Part 50 (Protection of Human Subjects).

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