Automated Image Analysis of Uterine Cervical Images

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ABSTRACT

Cervical Cancer is the second most common cancer among women worldwide and the leading cause of cancer mortality of women in developing countries. If detected early and treated adequately, cervical cancer can be virtually prevented. Cervical precursor lesions and invasive cancer exhibit certain morphologic features that can be identified during a visual inspection exam. Digital imaging technologies allow us to assist the physician with a Computer-Aided Diagnosis (CAD) system.

In colposcopy, epithelium that turns white after application of acetic acid is called acetowhite epithelium. Acetowhite epithelium is one of the major diagnostic features observed in detecting cancer and pre-cancerous regions. Automatic extraction of acetowhite regions from cervical images has been a challenging task due to specular reflection, various illumination conditions, and most importantly, large intra-patient variation. This paper presents a multi-step acetowhite region detection system to analyze the acetowhite lesions in cervical images automatically. First, the system calibrates the color of the cervical images to be independent of screening devices. Second, the anatomy of the uterine cervix is analyzed in terms of cervix region, external os region, columnar region, and squamous region. Third, the squamous region is further analyzed and subregions based on three levels of acetowhite are identified. The extracted acetowhite regions are accompanied by color scores to indicate the different levels of acetowhite. The system has been evaluated by 40 human subjects' data and demonstrates high correlation with experts' annotations.

Keywords: Cervical Cancer, Colposcopy, Acetowhite, Computer-aided diagnosis (CAD)

1. INTRODUCTION

The advent of medical image digitalization has lead to an increasing important and evolving role for image processing and computer-aided diagnosis (CAD) systems in numerous clinical applications. Cervical cancer is the second most common cancer affecting women worldwide and the leading cause of cancer mortality in developing countries [1]. It can be cured in almost all patients, if detected early and treated adequately. An automated image analysis system of uterine cervical images analyzes and extracts diagnostic features in cervical images and can assist the physician with a suggested clinical diagnosis. Such a system could be integrated with a medical screening device to allow screening for cervical cancer by non-medical personnel. This system has potential applications in the screening of, for example, female soldiers, marines and sailors who are deployed in locations where annual Pap testing is not possible. Further, such a system has tremendous potential benefits for screening underserved women in developing countries.

During a clinical exam, a 3%-5% acetic acid solution is applied onto the cervix. Epithelium that appears grossly normal but turns white after acetic acid application is called acetowhite epithelium. Colposcopists evaluate the color and density of the acetowhite reaction to asses the severity of possible lesions. Abnormal acetowhite epithelium varies from a faint or bright white to a dense gray white color. The amount of whiteness has been shown to be proportional to the severity of Cervical Intra-epithelial Neoplasia (CIN). Furthermore, the opacity or translucency of the acetowhite reaction varies across the spectrum of CIN: Normal metaplasia and low-grade lesions usually appear faintly white or slightly translucent whereas the acetowhite reaction of high-grade lesions appears more opaque. Therefore, acetowhite epithelium is the one of the major diagnostic features in detecting cancer and pre-cancerous regions[2].

Automatic extraction of acetowhite epithelium from digital cervical images is a challenging task. Published acetowhite segmentation results are in preliminary stages. Specular reflection (glare) and various illumination conditions have been bottlenecks in developing automated algorithms to extract acetowhite region of clinical significance. To the authors' knowledge, only a very small number of prototype algorithms have been reported. Yang et al. at Texas Tech University

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developed a sophisticated technique for precise detection of the acetowhite regions using K-means clustering and deterministic annealing technique[3]. Gordon and coworkers at Tel-Aviv University developed an unsupervised segmentation algorithm for three tissue types in cervical imagery using a Gaussian mixture model [4]. In their latest work [5], the acetowhite region was obtained from extracting the highest mean intensity cluster among the smooth regions. They also mention that due to illumination effects and large intra-patient variation, acetowhite lesions are wrongly detected. In addition acetowhite lesions located in shaded areas of the image are not detected at all. The work mentioned above is all based on Cervigram™ images collected by the National Cancer Institute (NCI).

STI® Medical systems has been developing complex imaging technology for diagnosing cervical neoplasia for several years. STI's digital colposcope [6] was designed to acquire high-resolution images with cross-polarization technique and has been used to collect extensive cervical data from a variety of locations, including multiple US locations and in Peru. Part of the Peru data has been annotated by expert colposcopists and pathologists. These annotations serve as ground truth information for our algorithm development.

Using our digital colposcope data, we have developed an automated image analysis system to identify the acetowhite epithelium to match the expert annotation. The acetowhite feature will be combined with other major diagnostic features, such as abnormal vessels [7], lesion margin properties[8] to derive a clinical diagnosis. In order to extract the color information of acetowhite properly, a multi-step procedure has been utilized. First specular reflections are removed by acquiring cross-polarized images and a glare removal algorithm. Second, the images are calibrated to normalize the illumination and color. Third, the anatomy of the cervix is analyzed to identify the cervical os region and columnar region of the cervix. A texture region is also extracted as a perquisite step to detect the acetowhite regions. Next acetowhite regions are extracted by combining color and texture information. Final multi-level acetowhite regions are identified and sorted according their color scores, which indicate the severity of the disease.. The procedure is fully automated and has been evaluated with 40 human subjects. The results demonstrate a substantial correlation with colposcopic and histopathologic annotations.

2. PRE-PROCESSING

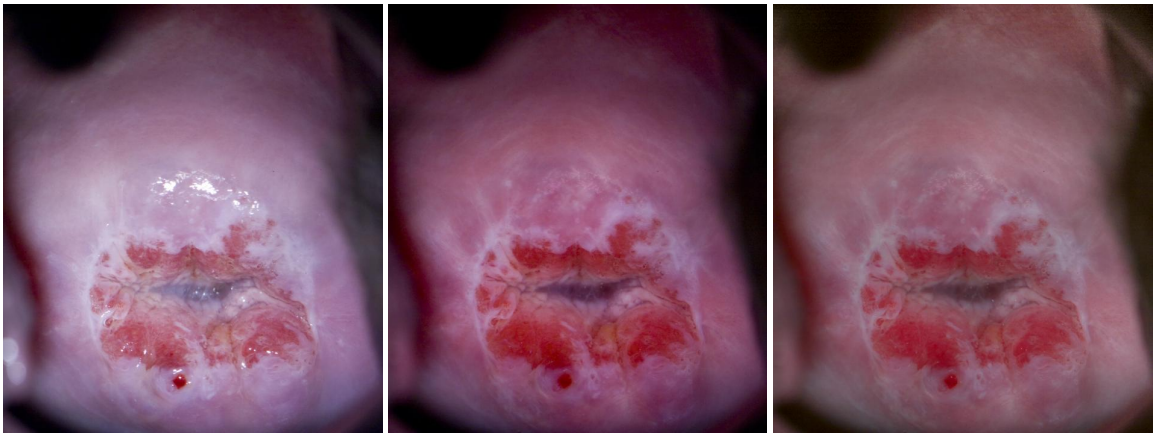
The cervical images taken at 60 seconds after the acetic acid application during the clinical exam are used to detect and characterize the acetowhite epithelium. Both non-polarized and cross-polarized image are acquired at the nearly same time (less than 600ms). First of all, pre-processing are applied to remove glare and calibrate the color and spatial intensity of the images.

2.1 Glare removal

Glare strongly affect the appearance of images, and usually limits the usefulness of applied computer vision algorithms. Algorithms on automatic detection of glare in uterine cervix images have been reported [9,10]. However, using image processing algorithms to remove glare only allows interpolating the saturated image regions, but does not recover the underlying information. Our cross-polarization technique is able to remove most of the glare and, thus, maintains the underlying information. A glare removal algorithm [9] is then applied to remove remaining small regions of glare. Fig. 1 (a) shows the non-polarized image, and Fig. 1(b) shows the corresponding cross-polarized and glare free image.

2.2 Image calibration

In Colposcopy, the color and appearance of the cervical images vary with light sources, instruments and camera settings used, as well as the clinical environment. The color of the epithelium may look very different in images acquired with different instruments or at different times. This makes the assessment of the color information very challenging, even for an expert. Besides, the non-uniform illumination of the light source is also barrier for image processing algorithms. We apply an image calibration procedure based on gray and color target balancing to calibrate the images in terms of illumination and color [6]. An example of a calibrated image is displayed in Fig. 1(c).



(a) (b) (c)

Fig. 1 Preprocessing (a) non-polarized image, (b) cross-polarized, glare removed image, (c) calibrated image

3. ANALYSIS OF ANATOMY OF THE CERVIX

Understanding and finding anatomic features are important steps in the CAD development process. Anatomic features are an indication of the quality of the images and also the adequacy of the exam. Most importantly, they can help us identify where the diagnostic features like acetowhite epithelium are located, which provides crucial information for the final tissue diagnosis.

Only a few attempts to extract one or a few anatomic features from Cervigram™ images have been published [4,5,11,12]. A very popular method for segmenting the cervix region is based on the Gaussian Mixture Model (GMM) in a near perceptual uniform color space. To the authors' knowledge, a complete scheme to extract anatomic features including cervix region, cervical os region, and columnar region has not been reported yet. The following anatomic features are extracted sequentially.

3.1 Cervix region detection

The original colposcopic image usually contains the edge of the speculum, the vaginal wall, and noise from the background. The cervix region needs to be extracted as the Region of Interest (ROI) for further processing. Our cervix region detection algorithm mainly uses an unsupervised two-class clustering technique based on GMM. Unlike previous work [5], we do not assume that the cervix region is preferably located in the center of the image. Our algorithm is fully automated.

First, a Gaussian low-pass filter is applied to the RGB image of the cervix to remove impulse noise. Second, Karhumen-Loeve (*K-L*) transformation is used to transform the image from RGB color space into *K-L* space. The *K-L* space has been proved to be the best space for color-texture characterization for the analysis of skin lesion and colon tumor detection [13]. Practically, it can be produced as a linear transformation of the RGB coordinates [14]. Third, the Expectation Maximization (EM) algorithm is used to cluster the K_1 channel (the eigenvector corresponding to the largest eigenvalue during eigen-decomposition) as foreground and background. The EM algorithm is used for finding maximum likelihood parameter estimates when there is missing or incomplete data. In our case, the incomplete data is the Gaussian cluster to which the points in the feature space belong. We estimate values to fill in for the incomplete data (the "E step"), compute the maximum likelihood parameters estimates using this data (the "M step"), and repeat until a suitable stopping criterion is reached. Finally, a series of morphological operations like hole-closing, opening and dilation are applied as a post processing step. Fig. 2(a) shows the cervix region segmentation result for the cervical image in Fig. 1.

3.2 Cervical os region detection

The cervical os defines the portion of the cervical canal covered by the columnar epithelium. If visible, it is usually a small-area region located in the center of the cervix with low intensity, surrounded by the columnar epithelium and the transformation zone (TZ).

The os region detection algorithm is based on mean shift clustering, given the assumption that the os region is probably located in the center portion of the detected cervical region with the lowest intensity, not the simple image center as in other implementation [5]. Because the cervical canal is approximately 3cm in length [2], the detected reflected light intensity from this area is low. The mean shift algorithm is a nonparametric clustering technique which does not require prior knowledge of the number of clusters, and does not constrain the shape of the clusters. It is based on kernel density gradient estimation theory and is guaranteed to converge to a point where the gradient of density function is zero. More details about the mean shift algorithm can be found in [15].

First, given the detected cervical region as a binary image, a distance transform is computed to create a distance image. The distances are based on Euclidean metrics. The purpose of the distance image is to locate the center portion of the cervical region mask. Second, mean shift clustering is applied on the selected range of the K_1 channel of the image. The cervical os region is then obtained by selecting the cluster with lowest intensity, followed by morphological operations to remove small noisy regions. Fig. 2(b) demonstrates the detection result for the corresponding cervical os region.

3.3 Columnar region detection

The columnar region appears reddish even after application of acetic acid. The color information is crucial in segmenting the columnar region. We apply the mean shift algorithm using the color information in CIE-*Luv* space to segment the columnar region. The result can be seen in Fig. 2(c).

3.4 Texture region segmentation

Texture region is the region that contains rich texture in an image. In a cervical image, texture region could be diseased area such as coarse abnormal vessels or normal findings such as immature metaplasia. Locating the texture region is a necessary step to extract the acetowhite region. We use the technique presented in [16] to extract the texture features in the image. The texture region is obtained by clustering in the texture feature space. The final texture region detected for this case is shown in Fig. 2(d).

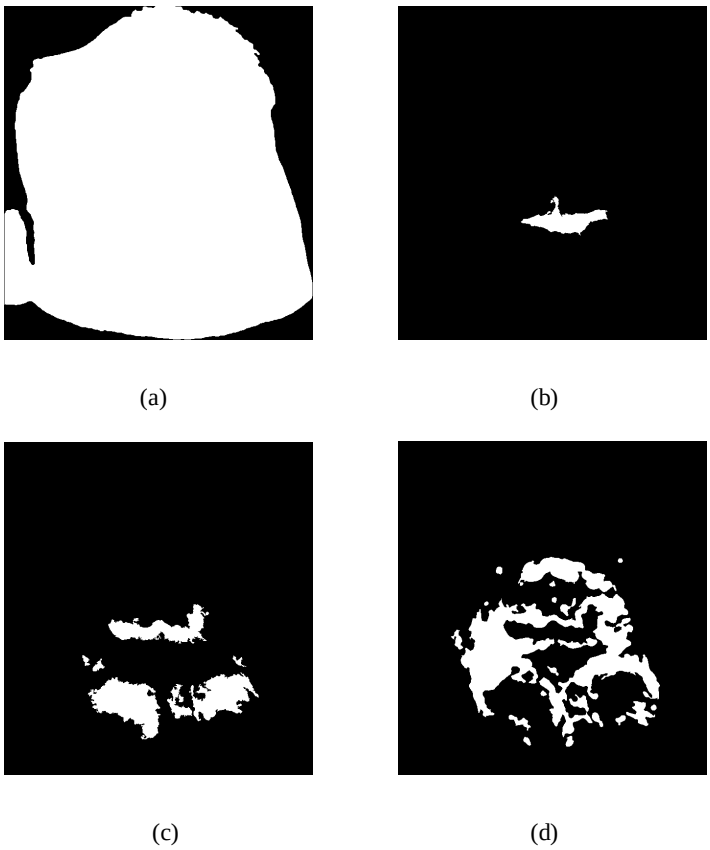


Fig. 2 Anatomic feature extraction (a) cervix region, (b) cervical os region, (c) columnar region, (d) texture region.

4. ACETOWHITE REGION DETECTION AND CHARACTERIZATION

Both color and texture information plays important roles in identifying the acetowhite epithelium. To assess the color property of the acetowhite region, the calibrated image is used as input. Based on the results of anatomic features of the cervix, the flowchart of acetowhite epithelium detection and characterization is shown in Fig. 3.

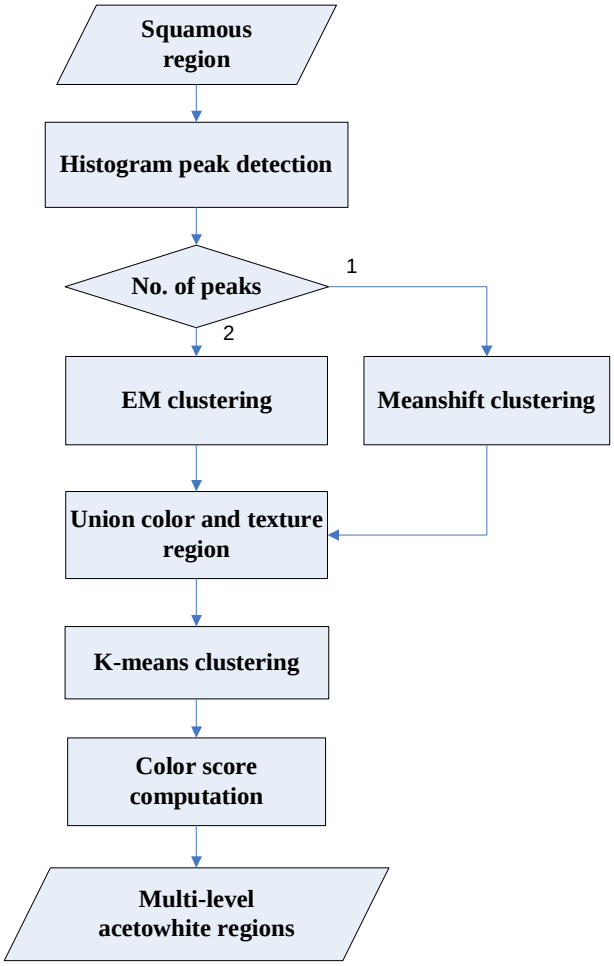


Fig. 3 Flowchart for acetowhite region detection and characterization

4.1 Acetowhite region detection

As stated in Sec. 3.4, the texture region extracted in the anatomic feature extraction contains either disease area or immature metaplasia. However, some dense acetowhite regions appear as homogenous surfaces without texture information. Such regions can be distinguished from the normal mature squamous region (no texture information as well) using color information only. On the other hand, since tissue responds differently to acetic acid, in some subjects, acetowhite region only appears in the texture region. Therefore, acetowhite color region and acetowhite texture region are extracted separately and combined later to formulize one acetowhite candidate region.

By excluding the cervical os region, columnar region and the high texture regions within the cervix region, a region with near homogenous surface is obtained. This region usually consists of the normal mature squamous region and/or dense acetowhite regions. We need to segment the dense acetowhite region from this homogenous region if any. First, we compute the histogram of this homogenous region. The histogram is then smoothed to remove noise. Next, the peaks of the smoothed histogram are detected using a watershed algorithm. An iterative procedure locates the dominant peaks in

the histogram. Two different clustering algorithms are chosen based on the number of peaks detected. If the homogenous region has a one-peak histogram, it indicates that the subject has a minor homogenous acetowhite region and the texture region is dominant in this case. If the homogenous region has a two-peak histogram, the subject has large homogenous acetowhite region.

A one peak histogram (see Fig. 4(a)) means that the area of the acetowhite region with homogenous surface is relatively small. In this case, the mean shift clustering algorithm is used to segment the small area of whitish color region. A two peak histogram (see Fig. 4(b)) means that there is a relatively large acetowhite region (most likely with a dense acetowhite color). The EM algorithm is then used to segment this acetowhite area.

The detected acetowhite area with homogenous surface is combined with the high texture region as the overall acetowhite "candidate" region. This candidate area is further classified using color information to differentiate levels of acetowhite regions, as seen in Fig. 4(b) and (d). Fig. 4(b) shows the three clusters corresponding to three level of whiteness for a texture dominant acetowhite region whereas Fig. 4(d) shows the corresponding three levels of acetowhite regions for a color dominant region.

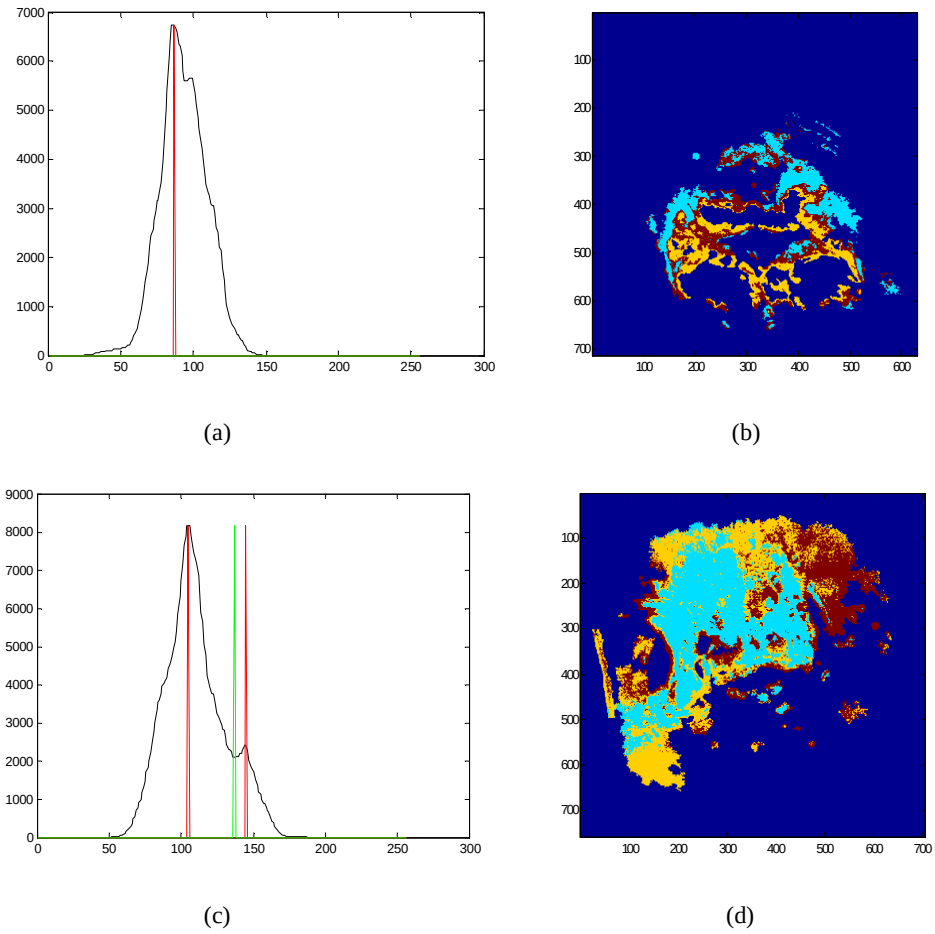


Fig. 4 Acetowhite region detection (a) One-peak histogram (b) texture dominant acetowhite region, (c) Two-peak histogram, (d) color dominant acetowhite region

The use of two different clustering algorithms solves the problem with strong back-reflected light. Due to the "donut" shape of surface of the cervix, some normal mature squamous epithelia also appear as a white color due to the high intensity value caused by strong back-reflected light. The white color of these normal squamous regions resembles translucently acetowhite regions. In these situations, due to the similar color property over the entire squamous epithelium, a one-peak histogram will be detected. Small or no acetowhite color region from the homogenous region is thus detected and only the highly textured region is used for further analysis.

4.2 Acetowhite region characterization

Immature metaplasia also turns white after acetic acid application. Both the acetowhite regions and immature metaplasia may contain textured regions. In order to distinguish the acetowhite region and immature metaplasia, a color score corresponding to each cluster is computed.

Different subjects have different tissue color and properties, and the color score must accommodate a large intra-patient variability. Here we define the color score as the distance of the color channels *(a, b)* in *CIE-Lab* space between the corresponding acetowhite/immature metaplasia region and the average value of the normal squamous region. The rationale is to quantify how "whiter" the possible acetowhite region is comparing to normal squamous tissue. The color score of each level of acetowhite region can be expressed using the following equation:

$$score(i) = \begin{cases} (a_i - a_{sq})^2 + (b_i - b_{sq})^2, & if\ a_i \le a_{sq} \\ -[(a_i - a_{sq})^2 + (b_i - b_{sq})^2], & if\ a_i > a_{sq} \end{cases} \quad (1)$$

where a_i indicates the average value of the a channel in *CIE-Lab* color space for the corresponding region i and b_i indicates the average value in the b color channel. a_{sq} is the mean a channel value of the mature squamous epithelium region in the image.

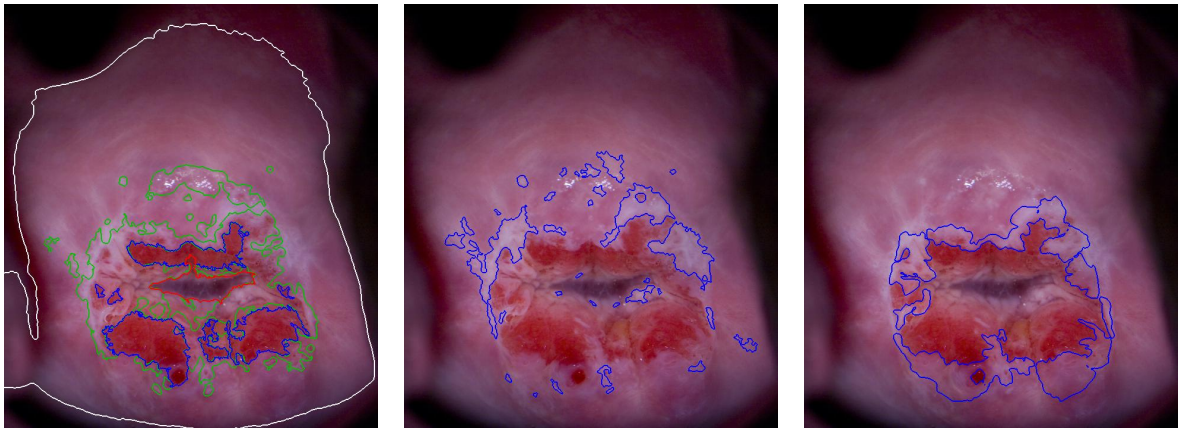
5. EXPERIMENTAL RESULTS

5.1 Experimental results

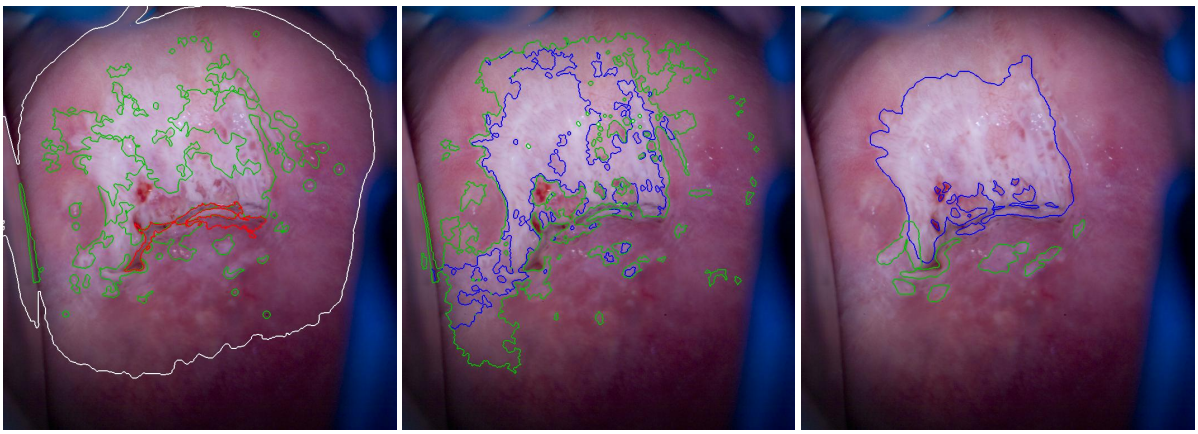
An analysis of 40 human subject data has so far been used to evaluate the capabilities and performance of our image analysis system. Fig. 5 shows some visualization results in comparison with expert annotations.

Fig. 5(a) and (d) are the extracted anatomic features. In these figures, the white contour outlines the extracted cervix region. The red-outlined regions indicate the cervical os region. The blue contours indicate the columnar region, and the green outlines are the texture region. Fig. 5(b) and (e) show the different levels of acetowhite epithelium extracted by the proposed algorithm scheme.

Fig. 5(c) and (f) show the corresponding expert annotation. The blue contour in these images is the first level acetowhite region and the green outline is the second level acetowhite region. Since a lower or negative color score indicates immature metaplasia region, the corresponding clusters are not displayed in the figures. Visually, we can see that the algorithm results show a very good correlation with the expert annotations



(a) (b) (c)



(d) (e) (f)

Fig. 5. Algorithm results vs. expert annotation, (a),(d) anatomic feature detection results, (b), (e) acetowhite epithelium detection results, (c), (f) expert annotations

5.2 Performance evaluation

Quantitative performance analysis has also been performed to analyze the effectiveness of the system. An overall 60.77% of sensitivity and 93.41% of specificity have been achieved for the 40 human subjects in our Peru data set. The details can be seen in Fig. 6. The sensitivity and specificity shown here is the hit or miss rate comparing to the expert annotation of the acetowhite epithelium. The sensitivity and specificity of our diagnosis system against histopathology will be detailed in a future publication. As the acetowhite epithelium is one of the major diagnostic features in Colposcopy and the only diagnostic feature in a VIA (Visual Inspection with Acetic acid) diagnosis system, such an automatic and efficient acetowhite epithelium detection and analysis system is a prerequisite step.

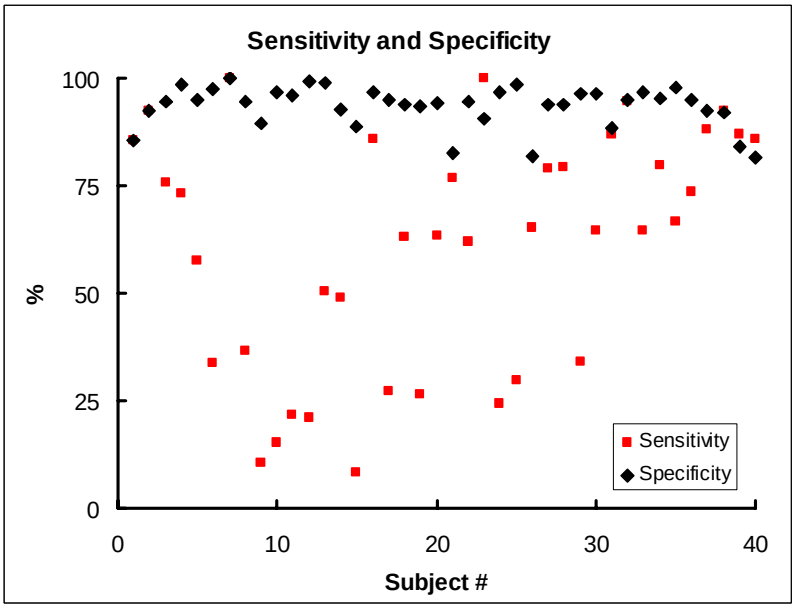


Fig. 6 The sensitivity of specificity of acetowhite extraction results against expert annotation with an average of 60.77% sensitivity and 93.41% specificity.

6. CONCLUSIONS AND FUTURE WORK

We have presented an automated cervical image analysis system to extract acetowhite epithelium in cervical images. The system includes three major processing steps. A pre-processing step includes specular reflection removal and image

calibration. An anatomic feature extraction step analyzes the anatomy of the cervix and extracts the cervix region, os region, columnar region, and texture regions. The last step, acetowhite region detection and characterization outputs multiple levels of acetowhite epithelium regions. Each region is accompanied by a color score that indicates the disease severity. The system has been evaluated by 40 human subject data and demonstrates good correlations with expert annotation.

Future work includes improving the cervix region detection algorithm to remove the vaginal wall along the periphery of the cervix. A more accurate cervix region will also remove false positives of the acetowhite region detection results. Mucus on the cervix has similar color and texture appearance with acetowhite epithelium and the current system sometime miss-interprets dense mucus region as acetowhite region. Leukoplakia also appears similarly as acetowhite epithelium, except that it is already white before acetic acid application. The current system is limited to one input image per subject. Future analysis will also include cervical images taken at different time intervals of the exam (e.g. images acquired before the acetic acid application). The decay sequence of the acetic application is another future improvement step of our system. The system will also be combined with other diagnostic feature extraction algorithms to provide a suggested diagnostic decision to the clinicians.

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