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Inflammation Detection in Cervical Cytology Images

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Abstract: Cervical cancer is a leading cause of cancer-related deaths in women worldwide. If detected at a precancerous condition it is completely curable. Several screening methods are available and Pap smear test is a preliminary screening method. Hence an automatic detection method for cervical cancer will be preferred. Cervical Screening System is a computer assisted screening solution, where the digitized images of the PAP-Smear are analyzed and classified through advanced image processing and classification algorithms. The LBC slides are analyzed for the detection of normal and abnormal cells. But some slides will be inflammatory, that are neither normal nor abnormal, but existing systems categorize them as abnormal and will go for further review. The inflammatory slides should be identified and categorized as Inflammatory so that they will not go for further review, instead they will go for a repap (preliminary) test after 6-9 months. The identification of Inflammatory slides inturn increases the system accuracy which increases specificity and sensitivity.

Keywords: Cervical Screening System, Feature Extraction, Inflammation, Neutrophils, Segmentation, SVM

I. Introduction

Cervical cancer kills more than 288,000 of women each year. The growing risk of cervical cancer in women in India is 2.4% compared to 1.3% for the world. If detected at a pre-cancerous stage, this cancer is 100 percent preventable. Pap smear or Pap test is a medical screening method used to detect potentially pre-cancerous and cancerous processes in the Endocervical canal. An automated Pap smear [1] analysis system helps reducing time spent for slide examination in Pap screening process.

Screening by PAP smear for the detection of precursors of cervical cancer has been proved to be a successful public health measure which ensures the prevention of this cancer. Cervical cancer usually develops very slowly. It starts as a precancerous condition called dysplasia and it will take almost

5-10 years [2] to develop to cervical cancer. The slides are categorized as normal or abnormal whereas the abnormal slides go for further review. The inflammatory slides need not go for further review and hence they need to be categorized as Inflammatory. The inflammatory slides should go for repap test after 6-9 months; hence the patient should not need a follow up tests which costs more. This also increases the system accuracy which increases sensitivity and specificity.

II. Related Works

Cancer of the uterine cervix is the second most common cancer in women worldwide. If proper screening is done and detected at an early stage it is curable.

Different methods of detecting cervical cancer have been discussed in Jaganathan *et al*. (2011) and Rajesh Kumar *et al*. (2011) [3, 4] focus on the problem of detecting and removing the artifacts in cervical cells attained from the digitized LBC slide images. This paper describes a classification methodology which eliminates artifacts from LBC Slides and hence enhances the classification of normal and abnormal cells. The artifacts present in a massive order which is similar in size and shape to abnormal cells would cause the misclassification of cytology images in the screening process. This increases the false positive rate which can hinder the mass screening. Therefore the elimination of these artifacts plays a key role in designing a proper classification strategy for the malignancy detection from cytology images.

LBC slide preparation techniques remove biological artifacts and clustering to some extent but not completely. Hence cluster detection in automated cervical cancer screening becomes significant. This paper, [5] discusses the cluster detection in cytology images using a graph based method called cell graph method. The proposed approach aims at finding clusters of cell nuclei in cervical cytology specimens so that those cells can be analyzed with special consideration of the fact that they belong to a cluster thus improving the decisions on the specimen level. The nuclei in clusters can't be properly segmented and resulting missing cells is one issue in cytology images. And also features of nuclei in clusters vary because of overlaps and lack of focus problems. Hence the information that a nucleus belongs to a cluster adds value to further analysis by way of compensating or extrapolating data for the missing nuclei.

Early Detection of Cervix Cancer can be done on 2D Cervical Cytological Digital Images [6], an automated recognition system is developed to enable automatic identification of anomaly in the cervix cells. Recognition of patterns inside a cervix cell is based on the cell morphological features, in terms of size, shape, and color.

Detection of cervical precancerous lesions using the Cervical Screening SystemTM system [7], compared with the liquid-based Pap smear and colposcopy directed biopsy exam, this system works better with a high sensitivity and specificity.

Cervical cancer could be largely preventable and curable with regular Pap tests. This test can find nuclei changes in the cervix. Accurate nuclei detection is extremely critical as it is the previous step of analyzing nuclei changes and diagnosis afterwards and this approach is discussed in the paper [8].

The purpose of segmentation is to automatically determine the location for a biopsy to be taken for diagnosis, a process that is currently done manually is discussed in [9]. [10], presents a domain-specific automated image analysis framework for the detection of pre-cancerous and cancerous lesions of the uterine cervix.

III. System study

Cervical cancers start in the cells on the surface of the cervix. Hence cell changes are examined to detect precancerous condition. Cervical cancers are caused by HPV (human papilloma virus).

A. Cervical Cell Types

Normal cells of the cervix consist basically of squamous, glandular, and metaplastic epithelial cells. The squamous cells line the ectocervix (outer portion) and the glandular cells line the endocervix (the inner portion). Squamous metaplastic cells originate from the transformation zone of the cervix where the inner (endocervix) and outer (ectocervix) meet.

Squamous cells of the cervix are stratified (have distinct layers) into four cell layers-the top superficial layer, the intermediate layer just underneath this layer, the parabasal layer, and finally, the basal or reserve cell layer. Under the influence of estrogen and progesterone, the toplayers are continuously being sloughed off and replaced by new cells that mature, starting from beneath at the basal layer. There are generally three types of squamous cells seen on Pap Tests (named after Dr. George Papanicolaou, inventor of the multicolor “Pap” stain and sampling technique) the superficial, intermediate, and parabasal cell types.

The glandular cells of the endocervix, the endocervical cells, are occasionally seen throughout the Pap sample. They are simple columnar epithelial cells that appear singly, in small clusters, in tight honeycomb-like groups, or are dispersed in streaks of mucous with stripped nuclei. Normal appearing endometrial cells may also be seen just prior to or during menstruation. Both endocervical and endometrial glands cells are stimulated to differentiate and divide under the influence of estrogen and progesterone. Too much hormonal stimulation can produce abnormal cell morphology and may lead to precancerous or cancerous change similar to that of squamous cells.

In the background of the cell sample it is common to see white blood cells, particularly histiocytes and PMN’s (polymorphonuclear leukocytes), as well as varying numbers of RBC’s (red blood cells).

B. Screening Methods of Cervical Cancer

Cervical screening is a way of checking women regularly for changes in the cells in the cervix. Invasive cervical cancer is largely preventable if pre-cancerous lesions are detected by effective screening and then adequately treated. Several screening modalities are now available for early detection of cervical cancer and its precursor lesions. For most women, the test is recommended every one to three years, depending upon the woman’s age and history of abnormal results. For women who have a past history of an abnormal screening test or who have risk factors for cervical cancer, testing is recommended. The Papanicolaou (Pap) smear is the most common screening method used to detect precancerous changes for squamous cervical cancer.

The most common form of diagnosis for detecting cervical cancer in its early stages is a procedure called a Papanicolaou test or Pap smear. This test is painless, normally takes less than 5 minutes to complete and can be performed in a doctor s office. Cells from the cervix will be exfoliated after some period and these will be scraped and the cells are then sent to a laboratory where they are studied under a microscope to determine if any precancerous or cancerous cells exist. If the tests show any abnormalities, the patient will be asked to return to the doctor so an additional test can be performed. Pap smear test is mostly still done conventionally. Due to the small number of skilled and experienced cytologists, the screening procedure becomes time consuming and highly prone to human errors which leads to inaccuracy and inconsistency of the diagnosis. So various automatic detection methods are there to detect cervical cancer.

Follow up tests include Colposcopy-directed biopsy, Liquid-Based Cytology (LBC), Visual Inspection of the Cervix with Acetic Acid (VIA).

The effectiveness of any cervical cancer screening program that relies on cervical cytology is the quality control of the cytological review of Pap smears. Cervical Screening System [3] is a computer assisted screening solution, where the digitized images of the PAP-Smear are analyzed and classified through advanced image processing and classification algorithms. Since more than 90% of the smears are normal, this would greatly reduce the time required of the cyto-technologist or cyto-pathologist in manually screening all the slides and instead he can focus on the 10% of slides suspected to be in cancerous or pre-cancerous stages.

In automated screening, Cervical Screening System, the inflammatory slides are not detected. Because they are neither normal nor abnormal but they will be send for further review which is not necessary and will decrease system performance. So this paper concentrates on the detection of such inflammation in cervical cytology images.

Cervical cells can go through many types of changes that are not cancer. These changes can be caused by:

1. Inflammation (redness and swelling),
2. An infection (bacterial, viral, or yeast),
3. Growths, such as benign (noncancerous) polyps or cysts and
4. Changes in hormones that occur during pregnancy or menopause.

Although many cervical cell changes are very common and not related to cancer, they sometimes make cervical cells look like abnormal cells, so health care provider may suggest to repeat the Pap test or to have other follow up tests to be certain that the cell changes are not cancer.

C. Inflammation

Inflammation forms part of the complex biological response of vascular tissues to harmful stimuli such as pathogens, damaged cells, or irritants. Inflammation is a protective attempt by the organism to remove the injurious stimuli and to initiate the healing process. Inflammation can be classified as either acute or chronic. Acute inflammation is the initial response of the body to harmful stimuli and is achieved by the increased movement of plasma and leukocytes from the blood in to the injured tissues. A cascade of biochemical events propagates and matures the inflammatory response, involving the local vascular system, the immune system, and various cells with in the injured tissue. Prolonged inflammation known as chronic inflammation, leads to a progressive shift in the type of cells present at the site of inflammation and is characterized by simultaneous destruction and healing of the tissue from the inflammatory process.

Inflammation can be detected by certain features.

1) Morphological Changes of Cells

- This includes
- Eosinophilic Cytoplasm
- Cytoplasmic Vacuolation
- Cytolazes(bare nuclei)
- Nuclear fragmentation or degeneration
- Nuclear Edema
- Perinuclear halo
- Presence of Bacilli

Eosinophilic refers to the staining of certain tissues, cells, or organelles after they have been washed with eosin, a dye. This is a bright-pink dye that stains the cytoplasm of cells. Vacuolation is the state of having cytoplasm filled with vacuoles. A small cavity in the cytoplasm of a cell, bound by a single membrane and containing water, food, or metabolic waste. Bare nuclei and nuclear degeneration are some other morphological changes.

2) Background Changes

This includes:

- Lymphocyte(chronic)
- Polymorphs(acute)
- Obscuring Lymphocytes

Some of the causes of inflammation are:

- Response to tissue injury
- Parasite Infections
- Nonspecific causes
- Mucus will also attract inflammatory cells

D. Neutrophils

Neutrophils are the key for determining inflammation. Neutrophil granulocytes are the most abundant type of white blood cells in mammals and form an essential part of the innate immune system. In general, they are referred to as either neutrophils or polymorphonuclear neutrophils. Neutrophils are normally found in the blood stream. During the beginning (acute) phase of inflammation, particularly as a result of bacterial infection, environmental exposure and some cancers, neutrophils are one of the first responders of inflammatory cells to migrate towards the site of inflammation. Neutrophils are recruited to the site of injury within minutes following trauma and are the hallmark of acute inflammation.

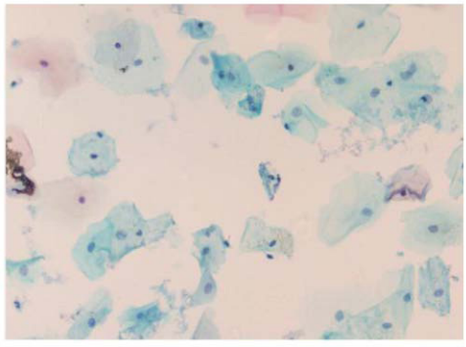

Fig. 1: Normal Slide

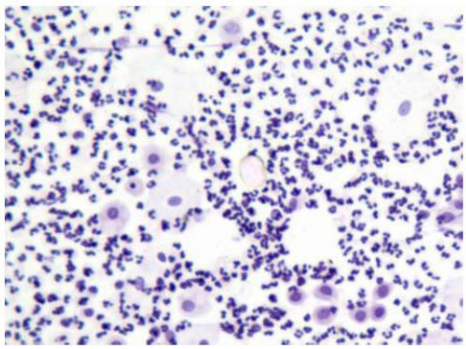

Fig. 2: Inflammatory Slide Which Shows the Abundance of Neutrophils

IV. System Overview

Cervical cancers start in the cells on the surface of the cervix. The detection of inflammatory slides will increase the system accuracy. The inflammation conditions has to be clearly identifed. The main image processing tasks are Segmentation, Feature Extraction and Classification.

The main steps are Preprocessing, Segmentation of objects, Feature Extraction to distinguish cells from artifacts, Classification, Feature Extraction to distinguish neutrophils from debris, miscellaneous objects, classification. Our aim is to identify neutrophils which becomes a key for detecting an inflammatory Slide.

In cytology images there will be normal cells, abnormal cells, and some artifacts. After preprocessing, segmentation has to be applied to distinguish cells from artifacts. Classification has to be done. These artifacts will contain neutrophils as well as other compounds. We will be concentrating on these neutrophils, these are the white blood cells which will be present in the slides due to inflammation. Hence from the segmented results we have to clearly identify these neutrophils. Next task is to extract the features of these neutrophils. By extracting these features we will be identifying them. After this our next aim will be identifying whether the given slide is inflammatory or not.For this we have to consider certain features like count of neutrophils, density etc. The cytology images are given as input and our aim is to identify the inflammatory slides.

A cervical smear contains Squamous cells, glandular cells, endometrial cells, white blood cells like PMN and lymphocytes and RBC. To analyze neutrophils or polymorphonuclear neutrophils (or PMNs) first we need to filter out everything other than neutrophils. To do that we follow a hierarchical approach where we first filter out Squamous cells, glandular cells and endometrial cells.

In first stage an image containing a Field of view will be read, preprocessed and segmented. From the segmented objects we filter out cells using various shape, size and textural features. We make use of support vector machine(SVM) to do this classification. The resulted objects contains objects from cytoplasm parts, debris other than neutrophils.

In next stage a set of size, shape and textural features shall be extracted from the resulted objects in previous stage. A suitable classifier shall be identified and resulted objects contain only neutrophils. This information will be fed into last and final stage where we calculate the abundance/density of neutrophils and classify that image/smear as either inflammatory or not.

The figure below shows the block diagram of the system

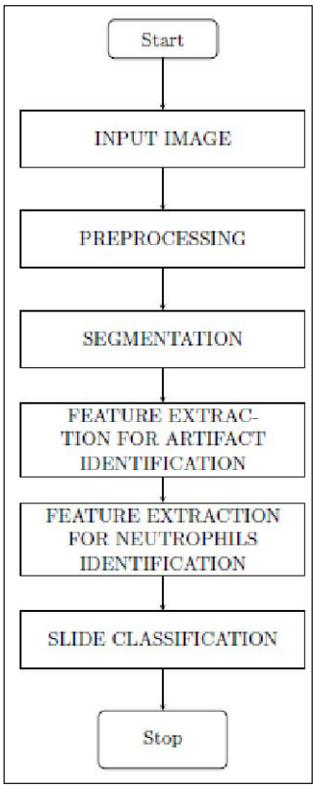

Fig. 3: Block Diagram of the System

A. Preprocessing

Preprocessing methods use a small neighborhood of a pixel in an input image to get a new brightness value in the output image. Such preprocessing operations are also called filtering. One of the method is Smoothing, which suppresses noise or other small fluctuations in the image; equivalent to the

supression of high frequencies in the frequency domain. In this we are using a median filter for preprocessing operations.

B. Segmentation

Segmentation is one of the most important task and it segments the objects in the image. A single slide may contain thousands of cells and artifacts. Each image captured at 40x magnification represents only a small field of the slide containing about 40-50 cellular bodies. The segmentation technique will be edge based

Laplacian of Gaussian(LoG) method.

1. Apply LOG (Laplacian of Gaussian) kernel with the median filtered image.
2. Objects which are detached are tied together. After filling the holes morphological operations like erosion and dilation is used.
3. Nucleus Minimum Area, Medium Area and Maximum Area will be found out. Then objects whose size less than minimum area and size greater than maximum area are removed. The remaining objects are retained.

C. Feature Extraction for Artifact Identification

This module accepts segmented image as the input to it. So, once the cells have been segmented, cell features can be extracted and it gives output in variable form. The features extracted should be able to classify the objects as epithelial cells or artifacts and provided the cells as normal or malignant. These features may describe the overall morphology of the cell and its nucleus as well as the fine chromatin structure of the nucleus.

Features are extracted to distinguish normal cells from artifacts. Feature Extraction is carried out for prominent features which were estimated by histogram analysis and chosen by ranking through a maximization function. This is the stage 1 feature extraction in which artifacts should be extracted. The artifacts will be useful for detecting whether a slide is inflammatory or not. After the segmentation of cells have been performed, cellular features are extracted. Using the features extracted it should be possible to classify the objects as epithelial cells or artifacts and finally as normal or malignant. The features will be extracted for identifying these artifacts.

Detailed Description of Feature Extraction Module

The objects which include cells and artifacts are seperated and the segmented image is the input to this module. The features will be evaluated for each of these objects. The features are listed below

1) Densitometric Normal Features

a. Optical Density: The maximum intensity of the nucleus has to be found out. Optical density is calculated by dividing this maximum intensity by each of the pixel intensity values and then take the logarithm.
b. Optical density = log10(Max Intensity/Each pixel intensity value).
c. OD(optical density) = Log_{10} (Io / I)
d. IOD(Integrated Optical density) = sum(OD)
e. MeOD(Mean Optical Density)is the mean of optical density.
f. SDOD(Standard Optical Density) is the standard deviation of optical density.

2) Gray Co-occurrence Features (Texture based Features)

This includes mainly 4 features and they are Contrast, Correlation, Energy and Homogenity. Here we have to find the gray level co-occurence matrix. Then these features are the properties of the co-occurence matrix.

a. Contrast: Returns a measure of the intensity contrast between a pixel and its neighbour over the whole image. $p(i, j)$ is the gray level co-occurence matrix

$$\text{Contrast} = \sum_{i-j} |i-j|^2 \, p(i, j)$$

b. Correlation: Returns a measure of how correlated a pixel is to itsneighbor over the whole image.
c. Energy :Returns the sum of squared elements in the Gray Level Co-occurence matrix.
d. Homogenity: Returns a value that measures the closeness of the distribution of elements in the GLCM to the GLCM diagonal.

3) Morphometric features

This mainly includes area,eccentricity and perimeter. Here we need to find the connected components in an image. Then for each connected component(object) in an image a set of properties has to be measured.

a. Area: It gives the actual number of pixels in the region
b. Eccentricity: It is the ratio of the distance between the foci of the ellipse and its major axis length.
c. Perimeter: It is the distance around the boundary of the region. The distance between each adjoining pair of pixels around the border of the region.

4) Fourier Analysis Features

This includes Mean Radius, Majortominor and Boundary Variable.

a. Mean Radius: finding the radius for each of the boundary pixels and it is integrated to find mean.
b. MajortoMinor: It is a measure of elongation of the contour. This parameter was especially intended for detection of cylindrical cells. It is by dividing the sum of first coefficients (positive and negative) by Difference of first coefficients (positive and negative) of Discrete Time Fourier Series.

$$\text{Major to Min} = \frac{|a_{-1}| + |a_1|}{|a_{-1}| - |a_1|}$$

c. Boundary Variable :This gives shape variation about an object .It is by integrating all the positive and negative coefficients.

$$\text{BDYVAR} = \sum_n (a_n^2 + a_{-n}^2)$$

5) Wavelet features

The dimensionality of the features have to be reduced. For that we use some aspects.

a. Feature ranking based on Maximisation Formula $[(\mu_1 - \mu_2) / (\sigma_1 + \sigma_2)]$.
b. Histogram plotting.

The features Boundary variable, area, eccentricity and Integrated Optical Density are used to distinguish cells and artifacts. The classification is done using Support Vector Machine where a training set is selected and testing set is trained.

D. Feature Extraction for Neutrophils Identification

The identification of neutrophils is the key for identifying inflammation. Neutrophil granulocytes are the most abundant type of white blood cells in mammals and form an essential part of the innate immune system. For that we need to extract features which can clearly distinguish neutrophils from others. The artifacts includes neutrophils, debris, misclassified cells and other miscellaneous objects. The artifacts have been identified and classified in the previous module. The neutrophils have to be identified and classified. The classification is done using SVM (Support Vector Machine).

Out of the features, the following features where selected since we got promising results to distinguish neutrophils from others.

a. Standard Optical Density
b. Mean Optical Density
c. Area
d. Boundary Variable

E. Slide Classification

The task to be performed next is from these neutrophils how to identify whether a slide is inflammatory or not. For that we need to get the count of these blood cells. The abundance of neutrophils is a major cause of inflammation. The count of these neutrophils where found out and based on this a threshold is set to categorize slide as inflammatory or not.

V. Results

In inflammation detection of cervical cytology images, the identification of neutrophils is the key task. Segmentation and Feature extraction has been done. The features includes

a. Densitometric Normal Features.
b. Gray Co-occurence features (Texture based Features).
c. Morphometric Features.
d. Fourier Analysis features
e. Wavelet features

The handmarking of ground truths has been done with the help of a utility called 'Cellmarker'. Using this utility the neutrophils, misclassified cells, debris has been marked. Marked 15 slides with a total of 250 images. This includes almost 2240 neutrophils,300 debris and misclassified cells. This acts as a training set. We have taken these 37 features and all these features has been plotted for neutrophils, misclassified cells and debris.We need to identify features which could clearly distinguish neutrophils from others. Out of these 37 features, four features has been selected for identifying neutrophils.The features are Standard Optical Density, Mean Optical Density, Area and Boundary Variable.

These four features are selected and we need to classify these neutrophils from others.

The classification has been done through SVM. With these four features, neutrophils has been identified and it is outlined. We have taken the counts of these neutrophils. We have found the percentage of neutrophil count. Neutrophil area has been found out. Percentage of neutrophil area compared with the total image area has been found out. The result is quite satisfactory compared to the neutrophil count. The threshold is set and the slide is classified as inflammatory.

VI. Screen Shots and Graph Plots

The original image is shown below

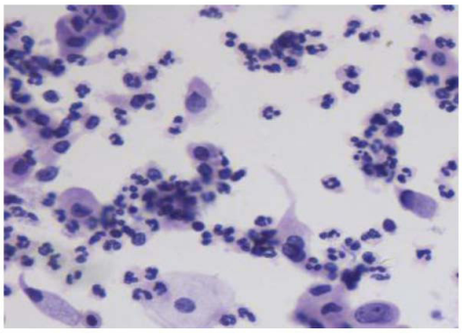

Fig. 4: Normal Slide

Preprocessing has been done on the image and for this a median filter is used.

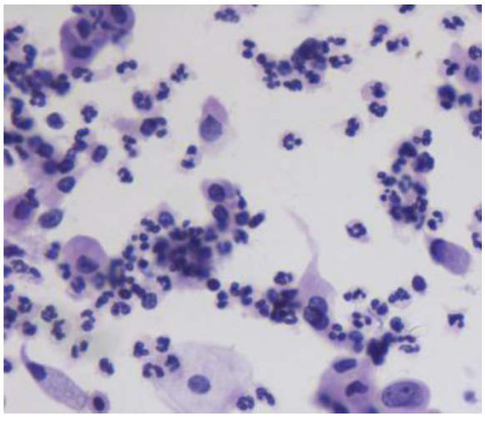

Fig. 5: Preprocessed Image

Segmentation has been done on the preprocessed image and the figure below shows the segmented objects.

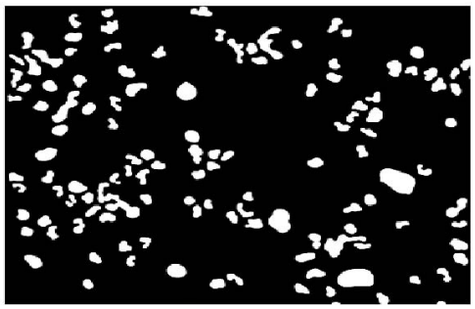

Fig. 6: Segmented Image

After segmentation, the artifacts and cells has to be clearly distinguished. We have used the corresponding features and classification has been done. The cells and artifacts has been outlined. In order to detect inflammation, we need to identify neutrophils. The artifacts which we got from the previous section consists of neutrophils, misclassified cells and debris. Now we need to distinguish between neutrophils and others (misclassified cells and debris). We are using four features for this which includes mean optical density, standard optical density, area and boundary variable. Classification has been done using SVM and the neutrophils and debris has been outlined.

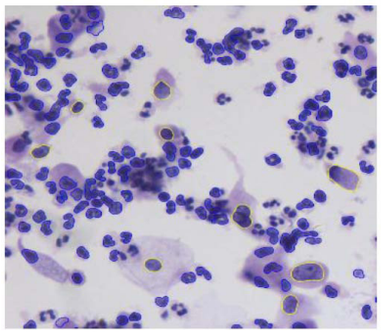

Fig. 7: Artifacts Classification: Artifacts Outlined in Blue and Cells Outlined in Yellow

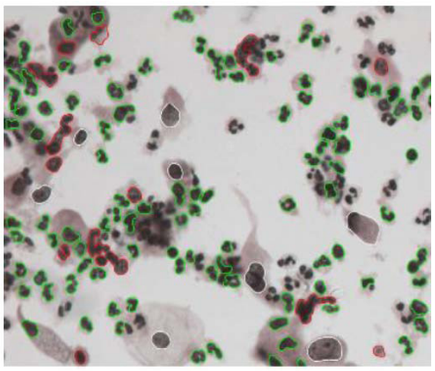

Fig. 8: Neutrophils Classification: Neutrophils outlined in green, debris outlined in red and cells outlined in yellow

The count of neutrophil is computed and percentage of their abundance with respect to total segmented objects is found out. A threshold is set and the images which exceeds that threshold is detected as inflammatory.

The following are the histogram plots which shows the features that distinguishes neutrophils from others (debris and miscellaneous objects).

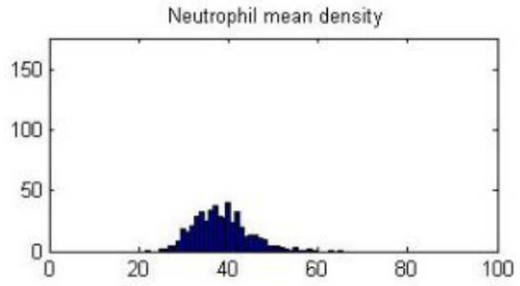

Fig. 9: Histogram Plot of Mean Density

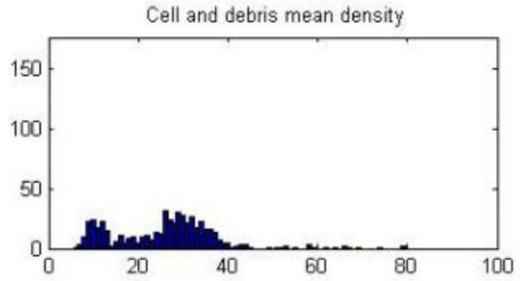

Fig. 10: Histogram Plot of Standard Density

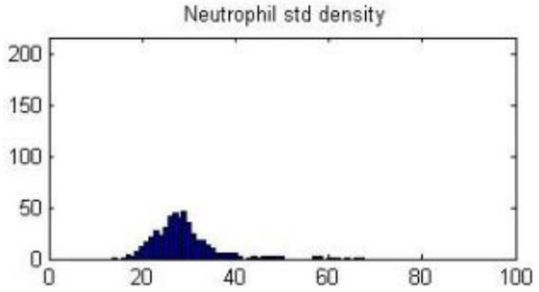

Fig. 11: Histogram Plot of Area

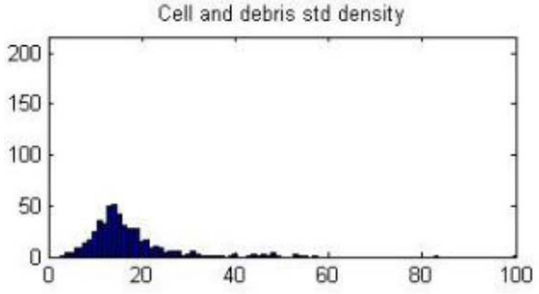

Fig. 12: Histogram Plot of Boundary Variable

VII. Conclusion

Cancer of the uterine cervix is the second most common cancer in women worldwide. If proper screening is done and detected at an early stage it is curable. In the existing system, the inflammatory slides are not detected and they will go for follow up tests. The detection of inflammation is important since the slide which is detected as inflammatory should not go for further review, instead it should go for a preliminary test after 6-9 months. Hence the detection of inflammation in turn increases system accuracy by increasing sensitivity and specificity.

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