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Cervical Cancer Detection through Automatic Segmentation and Classification of Pap smear Cells

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Abstract
Pap smear test has been widely used for detection of cervical cancer. However, the conventional Pap smear test has several shortcomings including: subjective nature (dependent on individual interpretation), low sensitivity (i.e. ability to detect abnormal changes) and the need for frequent retesting. There has a great effort to automate Pap smear test and it is one of the important fields of medical image processing. So this paper proposes a method for automatic cervical cell segmentation and classification. A single cervical cell image is segmented into cytoplasm, nucleus and background using Radiating Gradient Vector Flow (RGVF) Snake. Herlev dataset consists of 7 cervical cell classes, i.e., superficial squamous, intermediate squamous, columnar, mild dysplasia, moderate dysplasia, severe dysplasia, and carcinoma in situ is considered. Different cellular and nuclei features are extracted for training the system. Dataset is tested on artificial neural networks (ANN) to classify seven different types of cells and to discriminate abnormal from normal cells.

Keywords: Cervical cancer, Pap smear test, Cell images, Segmentation, Classification.

Introduction

According to World Health Organization report [1], cervical cancer is one of the world's deadliest but most easily preventable forms of cancer for women, responsible for more than 270, 000 deaths annually, 85% of which occur in developing countries. The disproportionate burden of cervical cancer in developing countries and elsewhere in medically underserved populations is mainly due to lack of screening. The precancerous changes in cervical cells are known as dysplasia and these dysplastic changes in precancerous cells potentially could develop into cancer. Unfortunately, cervical cancer is mostly unresponsive to treatments at the late stages. However, it is preventable by the treatment of precancerous lesions when the early dysplastic changes occur in the cervix cells. At this point screening plays an important role in detecting these precancerous cells.

Among many screening test, the most common screening procedure is Pap smear also known as the Pap smear test which is introduced by Papanicolaou in 1940 [2]. The Pap smear is a test which is used to detect the changes in the cervix cells that are cancer or potentially lead to cancer. This technique aims to detect precancerous and cancerous cells by analyzing colored and stained Pap smear slides. In order to detect abnormal changes in the cervix cells, cytotechnicians analyses these Pap smear slides in laboratories using a microscope under the supervision of a pathologist. They examine the cells according to their shape, color, size, nucleus proportion to cytoplasm and categorize the cells according to their abnormality degreeHowever, the Pap smear test has several shortcomings including: subjective nature (dependent on individual interpretation), low sensitivity (i.e. ability to detect abnormal changes) and the need for frequent retesting. Thus, it was a great challenge to automate Pap-test to lessen human error and to reduce the time utilization. An automated Pap smear screening framework should be able to correctly classify normal cells from abnormal.

Any Computer aided screening system involves two fundamental tasks: segmentation and classification. Segmentation mainly concentrates on separating cell region from the background region as well as detachment of the nuclei from the cytoplasm within the cell. After segmentation, classification mainly focuses on automatic categorization of the cells into two separate classes: normal versus abnormal.

Background

A. Cervical Cancer

Cervical cancer is a type of cancer that develops in cervical tissues (the organ connecting the uterus and vagina). It is typically a slow-growing cancer that may not show symptoms but can be found with regular Pap tests (method in which cells are collected from the cervix and analyzed using a microscope) [3]. The 2 major types of cervical cells are squamous cells (on the exocervix) and glandular cells (on the endocervix). The place these two cell types meet is called the transformation zone. Most cervical cancers start from the cells in the transformation zone. To detect the pre-cancerous cells, Pap smear test is conducted and for specimen acquisition it is important that cells are collected from both the endocervical and ectocervical areas, that is, both above and underneath the transformation zone.

Even though cervical cancers start from cells with pre-cancerous changes, only in some women, these pre-cancerous cells turn into true cancer. The transformation usually takes several years − but it may happen in under a year. For most cases, precancerous cells will stay unchanged or even go away without the need of treatment. Still, in some women pre-

cancers transform into true (invasive) cancers. Treating all pre-cancers can anticipate almost all true cancers.

The Pap smear slides usually contain both of single cells and group of cells. Most of Pap smear is found with high degree of overlapping. An example cell from a Pap smear slide with its background, cytoplasm and nucleus after the staining procedure is as shown in Figure 1.

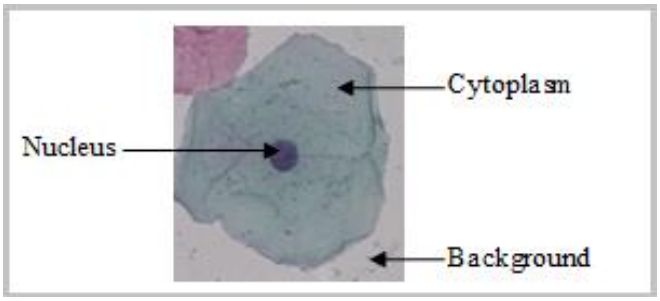

Fig.1. Example cell from a pap smear slide

B. Steps of a typical cancer screening system

Any typical computer aided screening system consists of four stages, in particular, preprocessing, segmentation, feature extraction, and classification.Figure 2 summarizes the steps of a typical cancer screening system.

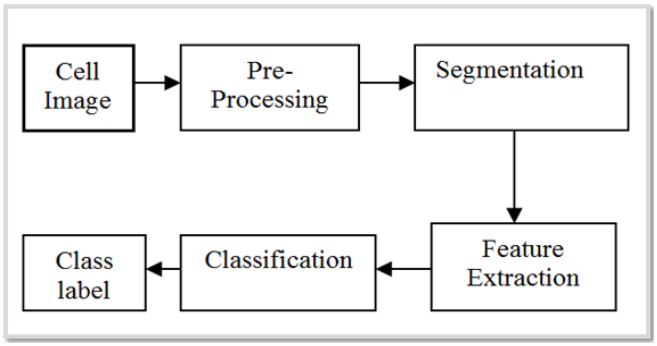

Fig.2. Main steps of computer assisted screening system

In the preprocessing stage, the image is processed to eliminate the noise content to increase the visual quality of the image. Several denoising methods are available to eliminate noise content from image. Preprocessed image is segmented then. Segmentation essentially applied for separation of the cells from background area as well as detachment of the nuclei from the cytoplasm region within the cell. Segmentation is the crucial step in any computer aided screening procedure, because accurate images segmentation could help to lessen the processing time and increase the classification performance. After segmentation, important nuclei and cellular features are extracted. Major features are extracted based on size and shape, intensity, morphology etc. After features are extracted and selected, classification step is employed in order to discriminate cancer cells from non-cancerous by training the classifier.

Literature Review

A. Segmentation Techniques

In general, automated segmentation is one of the most difficult tasks in image processing. Numerous algorithms have been published in the literature for segmenting cells and cell nuclei in microscopy images. One of the most simple and frequently used methods for image segmentation is thresholding. Basic idea behind thresholding is that a Threshold value, T, is determined to separate the background from region of interest. Various parametric and non-parametric algorithms have been proposed to determine the optimal threshold value by locating the valley in the grey-scale histogram. The methods that determine this single threshold value for the entire image i. e, global thresholding is proposed by Otsu [4]. But global thresholding do not make use of any spatial information and sensitive to noise and uneven illumination. To overcome these problems several local thresholding algorithms have been proposed. Local thresholding methods [5, 6, and 7] compute separate thresholds for each pixel using additional information derived from the surrounding neighborhood; e.g. Niblack [7] determined a local threshold value on the basis of the local mean and standard deviation of grey-values in the image. But the major drawback of local thresholding techniques is that they are mostly dependent on many parameters.

Active contours and their associated techniques are widely used to solve typical medical image segmentation tasks. An active contour is a planar curve (unbroken border initialized somewhere in the image) with an associated energy function. The snake is an active contour model introduced by Kass [8], and is able to deform elastically. Two major problems associated with snake model was proper initialization of contour and poor convergence to boundary concavities. In order to tackle those problems, an external force was introduced by Xu [9]. This external force is called gradient vector Flow (GVF), and is computed based on the diffusion or gradual change of the gradient vectors of a grey-level or binary edge map derived from the image [9]. After introducing the GVF, Xu [10] also proposed a generalized form of GVF which is called generalized gradient vector Flow (GGVF) to improve active contour convergence to long, thin boundary indentations, but at the same time keep the desired properties of GVF (e.g. extended capture range).

Recently, many new active contour models have been introduced in the literature such as: The high contrast segmentation framework (HCS) based on variational snakes and is efficient for nuclei segmentation, in which a modified internal energy function is introduced [11], Distance mapping active contour, in which distance mapping is used to create a gradient vector flow [12], Multi-direction gradient vector flow using a new anisotropic diffusion filter before applying the multi-direction GVF snake [13], Active contours using special processing named Selective Binary and Gaussian Filtering Regularized Level Set (SBGFRLS) method [14].

RGVF Snake [15] is a method proposed to refine the contours. Radiating Gradient Vector Flow shows potential ability to locate the obscure boundaries, and to diminish the taint caused by abnormal cells, stains, etc. Major drawbacks of algorithms based on active contours or deformable models are, they highly depend on the shape and location prior information of

object leading to segmentation. Moreover they require the initial contour to be reasonably close to the true object boundaries. As a consequence they can fail in images containing clustered and overlapping cells. These methods can also become trapped in local minima yielding the incorrect segmentation.

The seeded region growing algorithm [16] are another model used for image segmentation which was introduced by Adams and Bischof. It starts from a set of seed regions representing the desired image regions and uses a predefined similarity criterion to append neighboring pixels. This is continued until the entire image has been partitioned. Unfortunately, construction of a seeding method is not straightforward; in fact it is the most difficult part of the segmentation. Mehnert and Jackway [17] introduced an improved seeded region growing algorithm that retains the advantages of the Adams and Bischof algorithm whilst being pixel order independent. The watershed transform has proved to be a powerful and efficient segmentation tool in mathematical morphology [18]. The watershed transform is a special case of seeded region growing. But the problem of watershed transform is that it may lead to over segmentation sometimes. The marker-controlled watershed devised by Beucher and Meyer [19] offers an efficient solution to the over-segmentation problem. The watershed transform can accurately delineate the object boundaries and is robust to slight optical changes. However, due to the lack of a boundary smoothness constraint, the watershed transform can produce a jagged boundary in some cases. A marker controlled watershed algorithm with a new marking function has been proposed by Kale and Aksoy, [20] to avoid jagged boundaries of segmented regions. Fuzzy c means clustering (FCM) is another method proposed used by Thanatip Chankong in [21].

Most of the above methods do not handle overlapping cells. Recently, Zhang et. al. [22] introduced a strategy, based on graph cuts, that is found to be efficient in handling overlapping cervical cells. However, their method fails in generating accurate boundaries for each overlapping cell, but generate boundary of for clump of overlapping cells. Zhi Lu, Andrew P. Bradley and Gustavo Carneiro, [23] introduced an improved joint optimization of multiple level set functions for the segmentation of overlapping cervical cells. But their method requires large computational time.

B. Classification Techniques

After segmentation, classification mainly focuses on automatic categorization of the cells into two important classes: normal versus abnormal. Important classifiers used for cervical cancer problem in detail are artificial neural networks or neural network (NN) [24, 25, 26], nearest neighborhood (KNN) [27, 28], linear discriminant analysis (LDA) [29, 30], logistic regression [31], and decision trees [32, 33], support vector machine (SVM) [34]. The drawback of the logistic regression is that it is not designed to deal with high dimensional data and fail to approximate any smooth polynomial function. Decision tree is moderately simple to interpret and to implement but do not provide probabilities of class membership. K-Nearest Neighbor (KNN) and Linear Discriminant Analysis (LDA) are simple and efficient classification tools. Since they are defined simply, when the data is insufficient to define sample mean and covariance matrices, they can only detect linear phenomena. Support vector machine (SVM) is an effective supervised learning method. The major drawback of SVM is that, if the number of training examples is large, it requires large memory and training time. The NN architecture is at first, not organized and the learning algorithm is in charge for the extraction of the regularities present in the provided data, by discovering a suitable set of synapses during the process of analysis of the examples.. But the drawback of the neural network is that it requires long training time, the results rely up on the initialization parameters and it do not provide probabilities of class membership. To produce better results, different combinations of number of hidden neurons, learning rate, activation function, momentum rate, initial weights, and epoch size have to be tried out.

Materials and Method

A. Dataset

Herlev dataset [35] consist of 7 cell classes, namely, superficial squamous, intermediate squamous, columnar, mild dysplasia, moderate dysplasia, severe dysplasia, and carcinoma in situ is considered. According to Ref. [5], superficial squamous and inter-mediate squamous classes are considered as a normal class, whereas an abnormal class consists of cells from mild dysplasia, moderate dysplasia, severe dysplasia, and carcinoma in situ classes. Columnar cells are classified as neither normal nor abnormal. Database consists of 917 cell images and the number of each image in each class is as follows: superficial squamous (74 cells), intermediate squamous (70 cells), columnar (98 cells), mild dysplasia (182 cells), moderate dysplasia (146 cells), severe dysplasia (197 cells), and carcinoma in situ (150 cells). Sample cells are as shown in Figure 3.

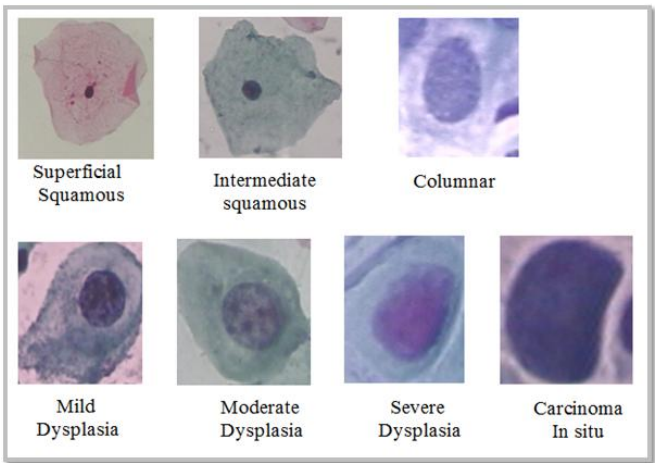

Fig.3. Seven classes of cervical cells in Herlev dataset

B. Proposed Method

The automated screening system uses advanced image acquisition, processing and classification techniques to differentiate normal cells from abnormal cells. The proposed cervical cancer detection framework is designed to work with

single cervical cell images. The total workflow of the proposed system is described in figure 4.The major phases are segmentation, feature extraction and classification. The main of segmentation is to separate nucleus from cytoplasm, and to detach cytoplasm from background. Segmentation is done on a denoised image. Segmentation is the crucial step in computer assisted cancer detection system since further classification result depends on segmentation accuracy. Selected features used to train the classifier are of higher importance.

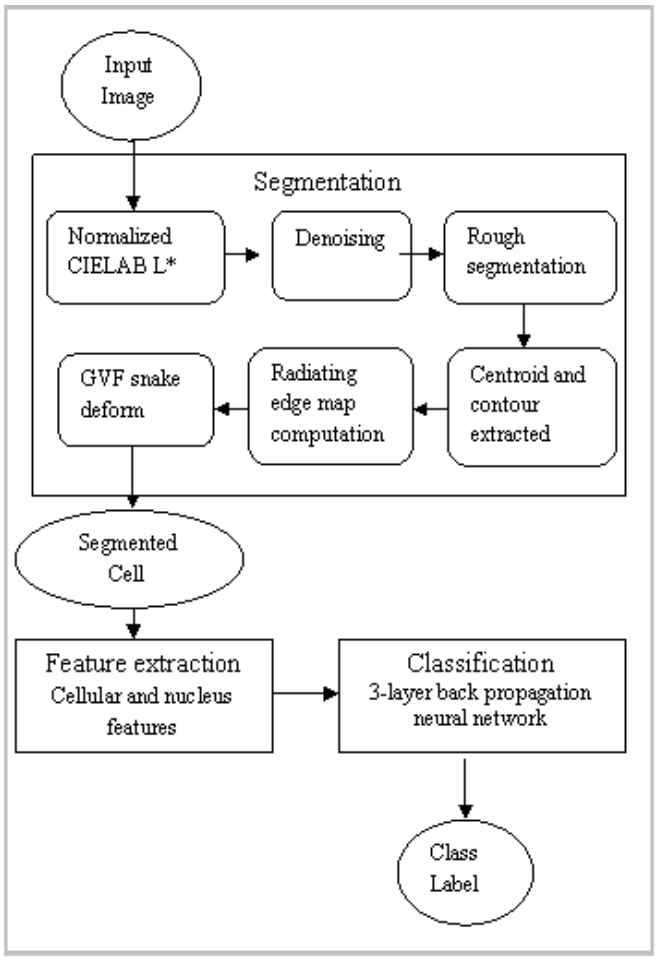

Fig.4. Proposed system

i. Segmentation

Segmentation is performed by adapting Radiating Gradient Vector Flow (RGVF) snake. First input cell image is converted from RGB colour space to CIELAB space. L* (Luminance) dimension of the converted image is extracted, in order to produce grey scale image. Then denoising by using non local means filter is performed. Denoising will removeunwanted noise from the image and improve the visual quality of the image. A spatial K-means based clustering method is applied for roughly divide the cell into cytoplasm, nucleus and background. Rough division produce initial contours of cytoplasm and nucleus. Radiating edge map computation will produce the accurate boundaries of cytoplasm and nucleus. GVF snake based deformation is performed then. This segmentation method is adapted from ref [17]. Segmentation results in contours of nucleus and cytoplasm.

ii. Feature extraction

A set of features are extracted from image obtained by the automatic segmentation using RGVF Snake. Six nuclei based and three cytoplasm based features are extracted. Major nuclei based and cellular features and the mathematical computation of these features are as in equation 1 to 9:

1. Area of the nucleus

A_n= Total number of nucleus pixels (1)

2. Nucleus compactness

C_n : Ratio of Perimeter square and area of nucleus

$$C_n = \frac{{p_n}^2}{A_n} \quad (2)$$

Where p_n is the perimeter of nucleus.

3. major axis of nucleus

L_n= length of major axis of an ellipse that fully cover the nucleus region (3)

4. Minor axis of nucleus

D_n= length of minor axis of an ellipse that fully cover the nucleus region (4)

5. Nucleus aspect ratio

R_n : Ratio of width and height of nucleus region

$$R_n = \frac{W_n}{H_n} \quad (5)$$

Where W_n is the width and H_n is the height of nucleus.

6. Nucleus homogeneity

$$H_n = \sum_{i=1}^{K}\sum_{j=1}^{K}\frac{P(i,j)}{1+|i-j|} \quad (6)$$

Where $p(i,j)$ is the probability of occurrence of a pair of pixel values (i,j) in the nucleus region computed from gray-level co-occurrence matrix. *K* is the number of gray levels in the image.

7. (N/C) Nucleus to cytoplasm ratio

$$NC = \frac{A_n}{A_c} \quad (7)$$

Where A_n is nucleus area and A_c is cytoplasm area.

8. Entire cell area

A_e= Total number of pixels in whole cell(8)

9. Cell compactness

C_n : Ratio of Perimeter square and area of whole cell

$$C_n = \frac{{p_e}^2}{A_e} \quad (9)$$

Where p_e is the perimeter of entire cell.

Nucleus to cytoplasm ratio, entire cell area, cell compactness is computed based on cytoplasm pixel values, all other features are computed based on nucleus alone. Each of the extracted feature value is normalized in the range 0-1 for training process.

iii. Classification

For classifying the cell into normal or abnormal, Artificial Neural Network (ANN) based classifier is used. ANN is designed with multiple layers having different number of neurons. Main 3 layers of ANN are input layer, hidden layer and output layer. 3 Layer back propagation neural network with 9 neurons in input layer and 1 hidden layer with 15 neurons and 7 neurons in the output layer is been used for the classification purpose.

Results and Discussion

A. Segmentation results

Segmentation performance is evaluated using an index called the Zijdenbos similarityindex (ZSI). ZSI is defined as the ratio of twice the common area between tworegions to the sum of the individual areas. A good segmentation is considered to beone with a ZSI >0.7. Table 1 compares the segmentation performance of RGVF with Fuzzy C Means segmentation (FCM) [21]

TABLE.1. Segmentation results (Mean±STD)

Class name	$\mu_{ZSI} \pm \sigma_{ZSI}$	
	FCM	*RGVF*
Superficial squamous	0.90±0.08	**0.9524± 0.0013**
Intermediate squomous	0.91±0.13	**0.9578± 0.0009**
Coloumnar	0.81±0.10	**0.9197± 0.0029**
Mild dysplasia	0.85±0.07	**0.9359± 0.0045**
Moderate dysplasia	0.85±0.08	**0.9334± 0.0038**
Severe dysplasia	0.85±0.07	**0.9333± 0.0030**
Carcinoma in situ	0.86±0.06	**0.9277± 0.0039**
Average	0.86 ± 0.08	**0.9371±0.0029**

From the table it is clear that RGVF segmentation having greater performance comparedto FCM segmentation method. Figure 5 is the corresponding graphical analysisof segmentation performance.

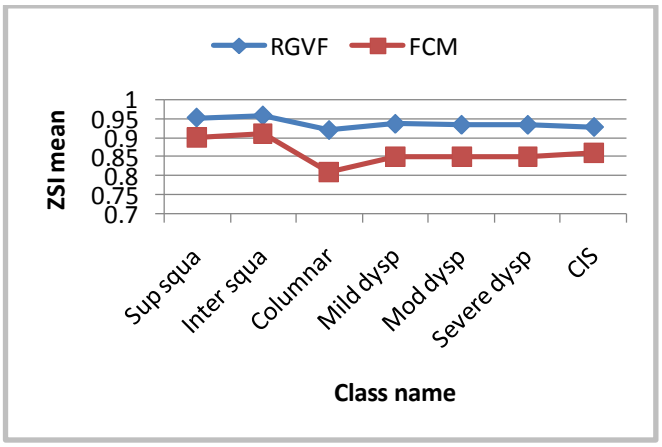

Fig.5. Segmentation Performance

B.Classification results

To evaluate the classification performance three measures were computed including accuracy, sensitivity, specificity.

Accuracy of an N class problem can be computed as in equation 11:

$$Accuracy = \frac{\sum_{i=1}^{N} No.of\ correctly\ classified\ cells\ in\ class\ i}{\sum_{i=1}^{N} Total\ no.of\ cells\ in\ class\ i} \quad (11)$$

Sensitivity can be calculated as in equation 12:

$$sensitivity = \frac{TP}{TP+FN} \quad (12)$$

Where TP stands for True Positive and FN for False Negative.

Specificity is the percentage of the normal data that are correctly classified as normal (true negative) and is computed as in equation 13.

$$specificity = \frac{TN}{TN+FP} \quad (13)$$

Where TN stands for True Negative and FP for False Positive. Table 2 demonstrates accuracy, sensitivity and specificity values obtained for ANN classifier for 7 class classification problem.

TABLE.2. Classification results

Performance measure	*ANN*
Accuracy	85.39
Sensitivity	94.22
Specificity	92.56

Conclusion

Segmentation and classification of cervical cells can be considered to be one of the important tasks for a robust automatic analysis of Pap smear slides. There are several segmentation and classification methods which have been applied to cervical cell microscopic images. But there is no fully efficient automatic analysis system for Pap smear screening. This paper proposed a framework for automatic analysis of single cellular Pap smear slides. Segmentation phase uses RGVF snake method to segment the cell into 3 regions. RGVF segmentation yields high ZSI value compared to that of FCM method for single cervical cell image segmentation. For the classification purpose, 3 Layer back propagation neural network with 9 neurons in input layer and 1 hidden layer with 15 neurons and 7 neurons in the output layer is been used. ANN based model yielded an accuracy of 85.39% and sensitivity of 94.22% and specificity of 92.56%.

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