International Journal of Advanced Information Science and Technology (IJAIST) ISSN: 2319:2682
Vol.4,No.7, July 2015 DOI:10.15693/ijaist/2015.v4i7.50-58

A Review of Image Segmentation and Classification Techniques for Automatic Pap smear Screening

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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. This paper reviews the segmentation and classification methods available in the literature related to cervical cell image analysis. Some segmentation techniques are applied on single cervical cell images. Other techniques are designed to use in single cell or overlapped or multiple cell images. Many classification schemes are proposed for automatic categorization of the cells into two classes: normal versus abnormal. The main aim of all these techniques is to build an automated Pap smear analysis system which analyses Pap smear slides in a short time without fatigue, providing consistent and objective classification results.**

Index terms -Cervical cancer, Pap smear test, Cell images, Segmentation, Classification.

I. 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 degree.

However, 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 reduce human error and to diminish 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 separation of the cells from the background as well as detachment of the nuclei from the cytoplasm within the cell regions. After segmentation, classification mainly focuses on automatic categorization of the cells into two separate classes: normal versus abnormal.

This paper reviews several segmentation techniques as well as classification techniques used for automatic Pap test screening process and is sorted out as follows. Section II presents an overview of cervical cancer and gives an idea about cervical microscopic images and its basic classes. The techniques used to segment and classify Pap smear images as well as the important features are reviewed in section III. Section IV concludes the survey.

II. OVERVIEW OF CERVICAL CANCER

A. Cervical cancer

Cervical cancer is a type of cancer that forms in tissues of the cervix (the organ connecting the uterus and vagina). It is usually a slow-growing cancer that may not have symptoms but rather can be found with consistent Pap tests (a procedure in which cells are collected from the cervix and analyzed using a microscope) [3]. The 2 fundamental types of cells covering the cervix 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. Figure 1 shows the anatomy of a uterus. 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.

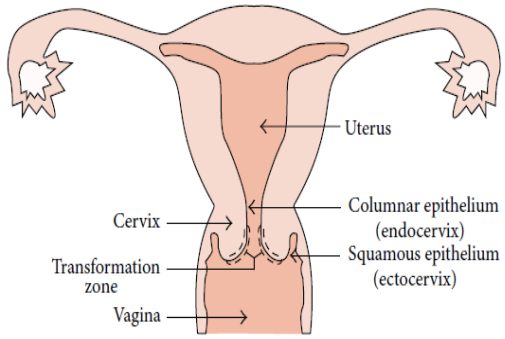


Figure 1.Illustration showing the anatomy of a uterus [3]

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.

B. The cervical cell microscopic image

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 2.

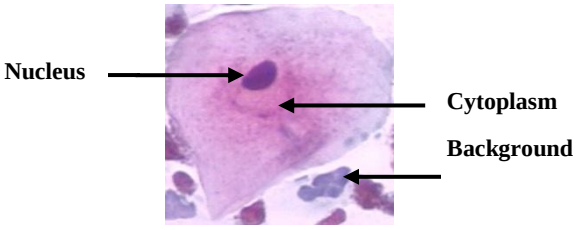
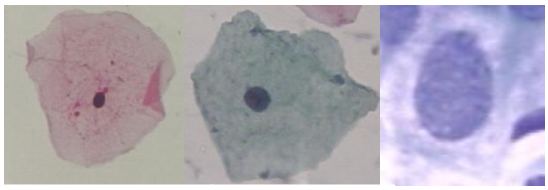


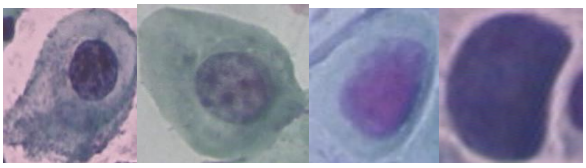
Figure 2.Illustration showing the anatomy of a uterus

C. Classes of Cervical Cell

Herlev dataset [4] consists of 7 cell classes, namely, superficial squamous, intermediate squamous, columnar, mild dysplasia, moderate dysplasia, severe dysplasia, and carcinoma in situ. According to Ref. [5], superficial squamous andinter-mediate squamous classes are considered as a normal class, whereas an abnormal classconsists of cellsfrom 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). Samples cells in the 7 classes are shown in Figure 3.



(a) Normal Cells



(b) Abnormal Cells

Figure 3.The seven classes of cervical cells

III. Techniques Used In Pap Smear Image Analysis

A. Steps of a typical screening system

Any typical computer aided screening system consists of four stages, in particular, preprocessing, segmentation, feature extraction, and classification. Figure 4 summarizes the steps of a typical cancer screening system.

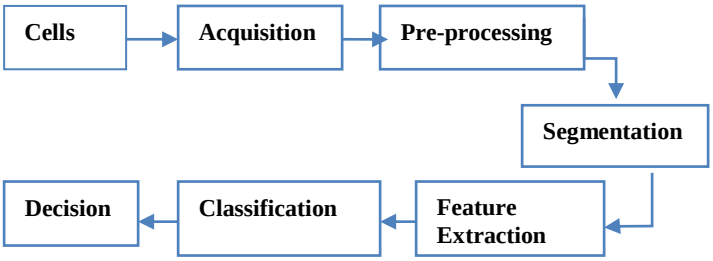


Figure 4. Main steps of computer aided diagnostic system

In the preprocessing stage, the image will be processed in order to eliminate the noise content to increase the visual quality of the image. 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. After features are extracted and selected, classification step is

employed in order to discriminate cancer cells from non-cancerous by training the classifier.

B. Segmentation of cell images

Segmentation is one of the most fundamental problems of quantitative analysis of cells in microscopic images. For cytological images the main focus is generally to isolate the cell nucleus since the malignant or abnormal characteristics are most prominent there. However, the cytoplasm is also a region of interest. Main aim of segmentation is to first extract the whole cell area from background and then to separate the nucleus from corresponding cells cytoplasm. There are several segmentation methods which have been applied to cell microscopic images. Review of the cell and cell nucleus segmentation methods in Pap smear images published in the literature are explained as follows.

a. Thresholding

One of the most simple and frequently used methods for image segmentation is thresholding. Thresholding utilizes the histogram of pixel intensities of the image. It is useful for the segmentation of images where the grey-values of the background pixels lie below or above the grey-values of the object. In other words, the object of interest is brighter or darker than the background. Therefore a threshold value, T, can be applied to the image to convert the grey-scale image to a binary image by replacing all the grey-values greater than T with the value 1 and setting all other grey-levels to 0. Thus by thresholding the original image f(x, y) the segmentation label image g(x, y) is obtained as in equation (1):

$$g(x,y) = \begin{cases} 1 \; if \; f(x,y) > T \\ 0 \; if \; f(x,y) \leq T \end{cases} \qquad (1)$$

Figure 5 depicts thresholding as a plane cutting the 3D image surface.Final location of region boundaries is affected by the choice of T. In the simplest case where the histogram of the image has two dominant peaks, a suitable threshold value lies somewhere between the two peaks (corresponding to foreground and background pixels).

Numerous 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 are known as global thresholding [6]. These algorithms do not make use of any spatial information and lackrobustness to noise and uneven illumination. To overcome these problems several local thresholding algorithms have been proposed. Local thresholding methods [7, 8, and 9] compute separate thresholds for each pixel using additional information derived from the surrounding neighborhood; e.g. Niblack [9] determined a local threshold value on the basis of the local mean and standard deviation of grey-values in the image. The grey-value of each pixel is compared with the average grey-values in some neighborhood. If the grey-value of the pixel is significantly larger than the average it is classified as foreground, otherwise it is classified as background. The major problem with the local thresholding techniques is that they are mostly dependent on many parameters.

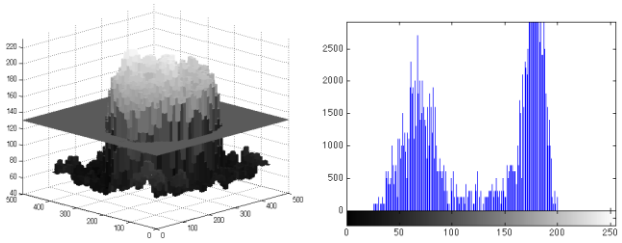


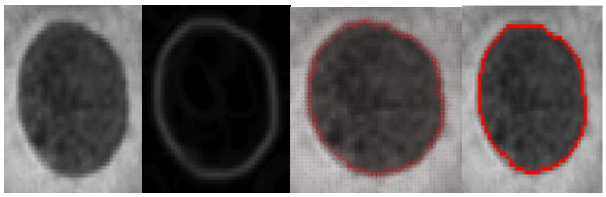
Figure 5.Global thresholding: (a) the grey-level image depicted as a topographic surface is globally thresholded (Topographic image is generated by interpreting the grey values of each pixel as heights). (b) The bi-modal histogram of the image. The threshold value (T = 130) lies somewhere in between the two peaks[6]

b. Active contours and deformable models

Active contours and their associated techniques can be categorized as deformable models. These models have been extensively studied and widely used in medical image segmentation with promising results. An active contour is a planar curve (unbroken border initialized somewhere in the image) with an associated energy function. The position of the initial contour must be localized such that it roughly surrounds the object of interest. The energy function is defined such that it attains its minimum when the contour lies upon the desired object. The snake is an active contour model introduced by Kass [10], and is able to deform elastically.

In order to solve the two major problems of proper initialization of contour and poor convergence to boundary concavities, an external force was introduced by Xu [11]. 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 [11].After introducing the GVF, Xu [12] 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). Figure 6 shows an example of nuclei segmentation by using GVF snake.

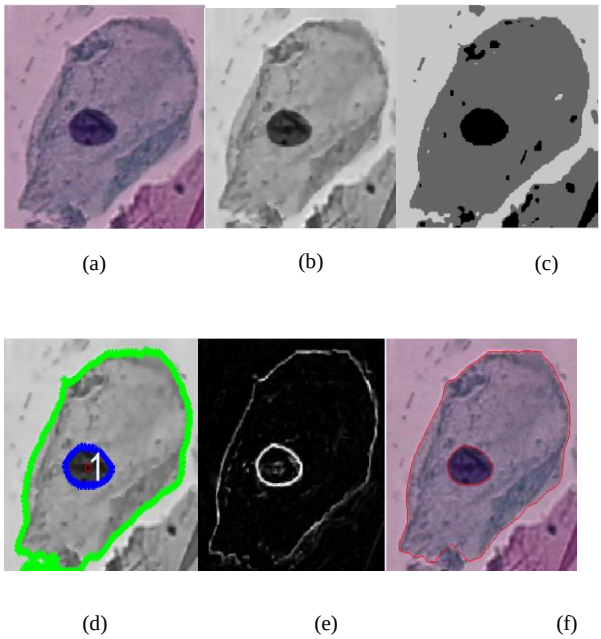
Recently, many new active contour models have been introduced in the literature such as: The high contrast segmentation framework (HCS) based on variational snakes and is efficient for nuclei segmentation, in which a modified internal energy function is introduced [13], Distance mapping active contour, in which distance mapping is used to create a gradient vector flow [14], Multi-direction gradient vector flow using a new anisotropic diffusion filter before applying the multi-direction GVF snake [15] , Active contours using special processing named Selective Binary and Gaussian Filtering Regularized Level Set (SBGFRLS) method [16].



(a) (b) (c) (d)

Figure 6. Cell nuclei segmentation by GVF snake. (a) An example of a cell nucleus (b) Magnitude of gradient (c) The GVF overlaid on the image (d) Segmented nucleus by active contour after 30 iterations. [11]

RGVF Snake [17] is a method proposed to refine the contours. Radiating Gradient Vector Flow shows potential ability to locate the obscure boundaries, and to diminish the contaminations caused by inflammatory cells, blood stains, etc. In addition to the cervical smear images. Figure 7 shows an example of nuclei and cytoplasm segmentation by using RGVF snake.



(a) (b) (c)

(d) (e) (f)

Figure 7. Segmentation by RGVF snake. (a) An example of a cervical cell (b) Denoised image (c) After K- Means clustering (d) Radiating edge map computation (e) RGVF contour refinement (f) Snake deformation.

Major drawbacks of algorithms based on active contours or deformable models are highly dependent on strong prior knowledge about theshape and location of objects in an image to guide the segmentation process. 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.

c. Seeded region growing

The seeded region growing algorithm [18] 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. The seeding algorithm should be able to provide exactly one seed per object. To overcome the problem Adams and Bischof [18] propose that a user (based on personal judgment) manually mark the seeds. Therefore the final segmentation results in the same number of regions as the seeds. However, it is inherently dependent on the order of pixel scanning.

Mehnert and Jackway [19] introduced an improved seeded region growing algorithm that retains the advantages of the Adams and Bischof algorithm whilst being pixel order independent. The feature in common with all seeded region growing algorithms is that the final segmentation result is highly dependent on the chosen similarity criteria and an appropriate seed extraction method.

d. Watershed Transform

The watershed transform has proved to be a powerful and efficient segmentation tool in mathematical morphology [20]. The watershed transform is a special case of seeded region growing. A grey-level image can be regarded as a topographic surface by considering grey levels as altitude information. For example, the gradient of this image has two catchment basins and the boundaries determined by the watershed transform correspond to the transition regions between the two basins. A reliable result is achieved if the catchment basins highly correspond to the regions of interest in the original or gradient image and the watershed lines represent the desired region boundaries. For image segmentation, the watershed transform is typically applied to the gradient magnitude image. However, gradient images are noisy and contain many minima due to local irregularities and intensity variations in the image. Therefore the watershed transform leads to over-segmentation. The marker-controlled watershed devised by Beucher and Meyer [21] offers an efficient solution to the over-segmentation problem. To avoid over segmentation due to numerous sources of flooding, flooding of the topographic surface should only be allowed from a priori defined set of markers (instead of flooding from every minimum in the image).

The most crucial and difficult part of marker controlled watershed-based segmentation is the extraction of object markers. If the marker extraction algorithm fails to mark an object, it will be missed in the final segmentation. In practice, a lot of effort has been made to develop fully automated algorithms for the extraction of appropriate markers. The thresholding method [22] is sensitive to noise and uneven illumination. Utilizing the distance transform [23] for

extracting the markers will lead to multiple markers for a single object particularly when the image objects are irregular in shape. The use of Bayes classier to identify pixel groups as internal markers has good performance in certain applications, but it is complex. The method proposed by Lezoray and Cardot [24] employs pixel classification techniques to extract the object markers. The result in this method is dependent on the number of the classes the pixels belong to. Many of the recent marker extraction techniques are based on mathematical morphology such as h minima [25], top hat transforms and the skeleton of the gradient image. The approaches based on grey-scale morphological reconstruction have achieved remarkable results in the application of cell nuclei segmentation in Pap smear images. However, there is still much scope for improvement.

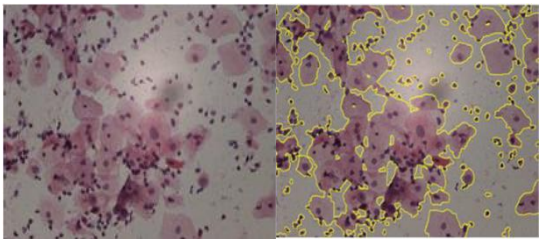
The watershed transform can accurately delineate the object boundaries and is robust to slight optical changes. However, due to the lack of a boundary smoothness constraint, the watershed transform can produce a jagged boundary in some cases. A marker controlled watershed algorithm with a new marking function has been proposed by Kale and Aksoy, [26] to avoid jagged boundaries of segmented regions.

The above described methods do not handle overlapped cells and major methods used for overlapping cell segmentation are described below.

e. Graph cut method

Recently, Zhanget. al. [27] introduced a strategy, based on graph cuts, that is found to be efficient in handling overlapping cervical cells. The method works as follows: cytoplasm segmentation is done using the multi-way graph cut method globally on the a* channel enhanced image, which is effective when the image histogram shows a non-bimodal distribution. Nuclei segmentation, especially when they found to be abnormal, they used graph cut adaptively and locally, which permits the blend of intensity boundary, texture and region information.

Two concave points-based methods are combined to split the touching-nuclei. Prior knowledge like nucleus shape, manual annotation and local image features can be incorporated in the graph cut framework to allow more efficient segmentation. Figure 8 shows segmentation using graph cut methods



(a) (b)

Figure 8. Segmentation using graph cut method (a) original image (b) Segmented cytoplasm boundary [27]

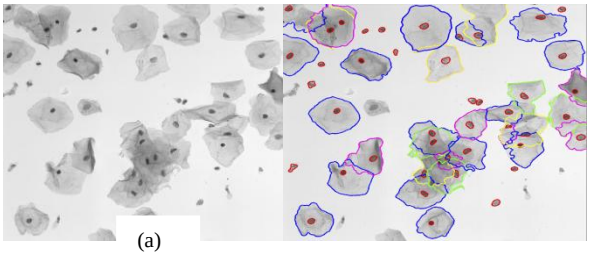
However, their method fails in generating accurate boundaries for each overlapping cell, but generate boundary of for clump of overlapping cells. Issue is that method only segments entire clumps rather individual cells within the clumps which will limit the amount of information available for the classification process.

f. Levelset Method

Level set methods are proven to be effective in various image segmentation tasks. To address the first issue regarding curve parameterization, approaches using the implicit level set method by Osher and Sethian [28] were simultaneously proposed by Malladi et al. [29]. Unlike the Snakes algorithm, which was motivated by energy minimization, the work by Caselles et al. and Malladi et al. was motivated by a geometric curve evolution approach. The basic idea was to generate a speed function which "pulled" the curve towards the boundaries of the target object while the curve was regularized with curvature motion. A typical speed function can be based on image gradients, such that it approaches zero when the norm of the image gradient is large (i.e. there is a distinct edge).

The main advantage of this approach is the level set representation, which allows arbitrary topological changes and robust and stable numerical schemes for the curve propagation. However, the motivation is based on geometrical aspects of the image and the curve, so it is hard to validate the solutions and perform "deeper" mathematical analysis.Recently Zhi Lu, Andrew P. Bradley and Gustavo Carneiro, introduced an improved joint optimization of multiple level set functions for the segmentation of overlapping cervical cells [30]. In their paper, they presented a variational algorithm capable of segmenting individual cytoplasm and nuclei from clumps of overlapping cells. Their methodology make use of joint optimization of multiple level set functions, and each function represents a cell within a clump, having both unary (intracell) and pairwise (intercell) constraints. The unary constraints are mainly on contour length, edge strength, and cell shape, and the pairwise constraint is based on the area of the overlapping regions.

Figure 9 demonstrate complete cell segmentation using joint optimization of level set function.



(a) (b)

Figure 9. Segmentation using level set method (a) Cervical cytological image (b) Complete cell segmentation. [30]

This approach initially performs a scene segmentation to highlight both free-lying cells, cell clumps and their nuclei.

Then cell segmentation is performed using a joint level set optimization on all detected nuclei and cytoplasm pairs. This optimization is constrained by the length and area of each cell, a prior on cell shape, the amount of cell overlap and the expected gray values within the overlapping regions.

C. Feature Extraction

Which features that is extracted from cell images and how they are grouped and/or combined varies. Features can extract either at nucleus level or at cellular level. Basically, extracted features are based on the morphology, texture, shape, and/or intensity of the cellular image.

• Size and shape: This group contains the morphometric features which express the overall size and shape of a cell. To calculate these only things needed are the object mask and border. Morphometric features are perhaps not the most prominent for distinguishing between healthy and abnormal cells but they can be of great use when trying to distinguish between objects of interest and debris. Examples of measurements that fall beneath this group are: position and orientation dependent features (bounding box), geometric features (area, perimeter, and largest indescribable circle), contour features (curvature, bending energy, convex hull, deficiency, elliptic deviation, and Fourier descriptors) and invariant moment features.

• Intensity: A densitometric feature uses the absolute intensity values in the image. Because of this it is important that they are as well controlled and normalized as possible. Furthermore, pure densitometric features use no spatial information which means that all the information can be obtained from the histogram. Some of the densitometric features are: larges/lowest density and different region intensity features (total image, background, object, inside border zone, outside border zone).

• Texture: The main purpose with extracting the textural features is to obtain quantifiable measures of overall local density variability inside an object of interest. Usually the zone of measurement is the entire nucleus. However, it can also be a sub part since splitting the nucleus into different regions can result in better results. Examples of texture measures are: gradient image features, Laplace image features, flat texture image features, topological gradients (watersheds), run-length and co-occurrence features.

• Structure: With structural or contextual features each chromatin particle is considered to be an object. Features are extracted by describing the relationships between these objects. This method requires a way of defining particle followed by a way of generating useful measures from the relationships between the particles. Perhaps the most prominent feature derived this way is the triangulation but some other examples of features are the number of derived particles (varies depending on the definition of a particle), the nearest neighborhood graph, the minimum spanning tree graph and the convex hull derived from different types of particles.

ThanatipChankonga and NiponTheera-Umpon proposed six important nuclei features and 3 important cellular features that are effectively used for pap smear image analysis and classification [31]. These features are:

1. *Area of the nucleus*
2. *Compactness of the nucleus*
3. *Major axis of the nucleus*
4. *Minor axis of the nucleus*
5. *Aspect ratio of the nucleus*
6. *Homogeneity of the nucleus*
7. *Nucleus to cytoplasm ratio*
8. *Compactness of entire cell*
9. *Area of entire cell*

Results of cell classification using these features are promising.

D. Classification of cervical cell images

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) [32, 33, 34, 35], nearest neighborhood (KNN) [36, 37], linear discriminant analysis (LDA) [38, 39, 40], logistic regression [41], and decision trees [42, 43, 44], support vector machine (SVM) [45]. However, it is important to know the advantages and disadvantages of each of the classifier separately. Logistic regression is effective for probability prediction, because it is mathematically constrained to generate probabilities in the range [0, 1] and converges on parameter estimates comparatively easily. 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.

However, 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. In this way, NNs solve classification problems by self-learning and self-organization. The important feature of NN is that we can develop custom neural networks with different number of input hidden and output layers and there are wide varieties of NN available like feed forward neural network, back propagation neural network, perceptron and so on. 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.

Figure 10 shows the major types of classification schemes.

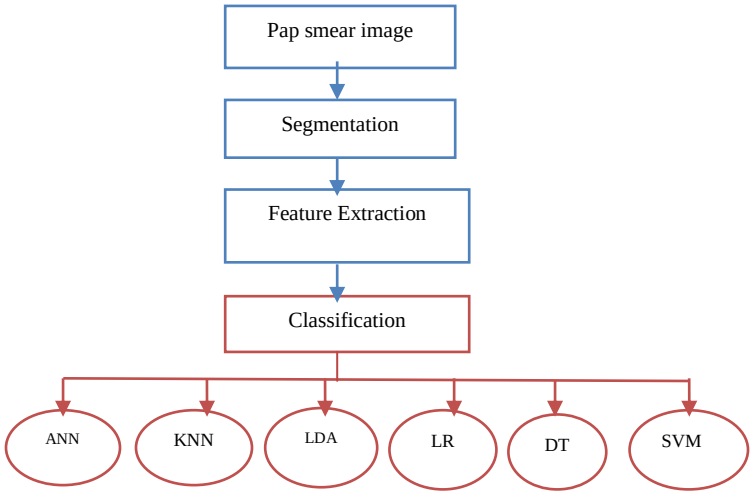


Figure X: General Classification Systems

Decision tree is moderately simple to interpret and to implement. Apart from classification and regression trees, most other methods of decision trees do not provide probabilities of class membership. Results largely rely upon the method used for tree construction and the amount of tree pruning (removal of highly specific nodes).

K-Nearest Neighbor (KNN) and Linear Discriminant Analysis (LDA) are simple and efficient classification tools. Compared to decision trees which detect only local phenomena, both LDA and KNN are able to detect global phenomena. 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 widely used for cancer classification as well as for other classification problems. A distinguishable property of Support vector machine is that it can minimize the empirical classification error and can maximize the geometric margin of a classifier. It is a powerful methodology used for solving problems in non-linear classification, cancer classification, and density estimation, leading to many applications including image interpretation, data mining, biometric authentication, biotechnological investigation, and other wide variety of applications. It has been widely used for automatic classification of cervical cells and additionally be used for the automatic detection of nuclei. It is strikingly intolerant of the sizes of the number of training examples. Since the method is not directly trying to minimize the error rate, but trying to separate the patterns in high dimensional space, the outcome is that Support Vector Machine is comparatively insensitive to the relative numbers and size of each class. The major drawback of SVM is that, if the number of training examples is large, it requires large memory and training time.

VI. 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. Most prominent techniques used for cervical precancerous screening are reviewed in this paper. Review consists of three sets of information: segmentation, feature extraction, and classification. This review will help researchers in bio medical image processing field to understand the state of the art techniques and also have a good start to get off the ground solving it.

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