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A Review of Applications of Image Analysis and Machine Learning Techniques in Automated Diagnosis and Classification of Cervical Cancer from Pap-smear Images

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Abstract: Cervical cancer ranks as the fourth most prevalent form of cancer affecting women worldwide and its early detection provides the opportunity to help save life. Automated diagnosis and classification of cervical cancer has become a necessity as it enables accurate, reliable and timely analysis of the condition's progress. This survey paper presents an overview of the state of the art as articulated in a number of prominent recent publications focusing on automated diagnosis and classification of cervical cancer from pap-smear images. It reviews thirty journal papers obtained electronically through four scientific databases searched using three sets of keywords: (1) Segmentation, Classification, Cervical Cancer; (2) Medical Imaging, Machine Learning, pap-smear Images; (3) Automated, Segmentation, Pap-smear Images. The review found that some techniques are used more frequently than others are: for example, filtering, thresholding and KNN are the most used techniques for preprocessing, segmentation and classification of pap-smear images. It has also been observed that the superiority of the results of a classification algorithm over the other greatly depends on a number of factors which include: the set of features selected, the accuracy of the segmentation, the type of pre-processing techniques used and the type of datasets used. Most of the existing algorithms result in an accuracy of nearly 93.78% on open pap-smear data set segmented using commercial digital image segmentation softwares. K-Nearest-Neighbours (has been reported to be an excellent classifier for cervical images giving an accuracy of over 99.27% for a 2-class classification problem. The reviewed papers indicate that there are still weaknessess in the available techniques that result in low accuracy of classification in some classes of cells. This accuracy can be improved by extracting more features, improvement in noise removal, and using hybrid segmentation and classification techniques. Moreover, most of the developed classifiers are developed and tested on accurately segmented images using commercially available softwares. There is thus a deficit of evidence that these algorithms will work in clinical settings found in developing countries where 85% of cervical cancer incidences occur.

Keywords: *Cervical cancer, Pap-smear, Medical Imaging, Machine learning*

1. Introduction

Globally, cervical cancer ranks as the fourth most prevalent cancer affecting women worldwide after breast, colorectal, and lung cancers [1], with 527,624 women diagnosed with cervical cancer and 265,672 dying from the disease every year worldwide [2]. In sub-Saharan Africa, 34.8 new cases of cervical cancer are diagnosed per 100,000 women annually, and 22.5 per 100,000 women die from the disease [1], with over 80% of cervical cancer detected in its late stages. Over 85 per cent of cervical cancer cases occur in less developed countries of which the highest incidences are in Africa, with Uganda being ranked 14th among the countries with the highest incidences of cervical cancer [3]. Over 65% of those diagnosed with the disease in Uganda die from it [4]. This is attributed to lack of awareness of the disease and limited access to health services. In contrast, developed countries have strategies to enable reliable and effective screening methods and thus pre-cancerous lesions are detected and treated at an earlier stage [5]. As a strategy for reducing the occurrences of cervical cancer in Sub-Saharan Africa, the World Health Organization recommends screening and vaccination throughout the sub-Saharan African region so as to help achieve the UN Sustainable Development Goal 3 of ensuring healthy lives and promoting well-being for all [6,7].

Cervical cancer can be prevented if effective screening programmes are in place and this can lead to reduced morbidity and mortality [8]. The success of screening has been reported to depend on a number of factors including: access to facilities, quality of screening tests, adequacy of follow-up, and diagnosis and treatment of lesions detected [9]. Cervical cancer screening services are very low in low and middle income countries due to the presence of only a few trained and skilled health workers, and lack of healthcare resources to sustain screening programmes [10]. It is estimated that only a small percentage (5%-27%) of women in sub-Saharan Africa report having received cervical cancer screening [11]. This is even lower in the East African region where cervical cancer age-standardized incidence rates are highest due to inadequate screening programs [12].

This paper presents a review of several image analysis and machine learning techniques proposed by different researchers for automated cervical cancer screening from pap-smear images. The paper is organized as follows: section 1 gives information about pap-smear images. Section 2 presents a detailed review of medical imaging and machine learning techniques proposed by several researchers, general observations are highlighted in section 3. Section 4 presents discussion of the observations and, finally, conclusions and future research are presented in Section 5.

1.1 The Papanicolaou test (pap-smear)

The pap-test is a manual screening procedure which is used to detect pre-cancerous changes in cervical cells on the basis of color and shape properties of cell nuclei and cytoplasm regions [13]. The test is the commonest technique used for early screening and diagnosis of cervical cancer. Pap-smears have helped to reduce the mortality rate of cervical cancer by between 50% and 70% in developing countries [14]. Samples are observed under a microscope in order to detect any unusual developments indicating any precancerous and potentially precancerous changes. Examining the cell images for abnormalities in the cervix provides grounds for provision of prompt action and thus reducing incidence and deaths from cervical cancer. Pap-smear tests, if done with a regular screening programs and proper follow-up, can reduce cervical cancer mortality by up to 80% [14].

During the screening of a patient, hundreds of sub-images (as shown in Figure 1) have to be examined by a trained cytologist using a microscope. This makes the screening process very tedious, labour intensive, time consuming, subjective and error prone due to inter-and intra-observer variations and monotony [15].

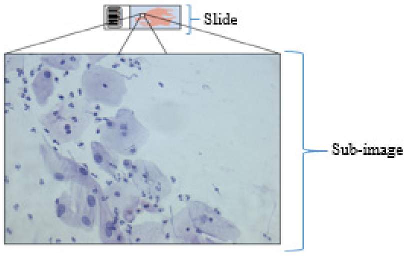

Figure 1: A typical pap-smear image (slide) and a high-resolution field of view (sub-image). During the Manual pap-smear analysis, approximately 10,000 sub-images are needed to cover the whole slide.

1.2 Cervical cancer classification from pap-smear image analysis

The cervical cells are divided into seven classes of which 3 are normal and 4 are abnormal (Normal superficial squamous epithelial, Normal intermediate squamous epithelial, Normal columnar epithelial, Abnormal mild dysplasia, Abnormal moderate dysplasia, Abnormal severe dysplasia and Abnormal carcinoma-in-situ) depending on the cell nucleus [16].

The cell nucleus is usually used for cervical cancer screening and classification as it contributes to the cell changes when a cell has been affected and its properties like size, shape and intensity are usually compared during cell classification as normal or abnormal[17-18].

1.2.1 Feature Extraction

A number of important specific cell features (Table 1) are used for cervical cell image analysis. These features are categorized as: Size (cell area, nucleus area, cytoplasm area etc.); Shape (nucleus roundness, cytoplasm roundness etc.); Ratio (nucleus/cytoplasm ratio, Percentage of empty cells etc.); Topology (Distribution of nucleus, nucleus position etc.); Color intensity (cell, nucleus, cytoplasm brightness etc.); and Texture (Multi-nucleus cells etc.) [19].

Table 1: Some of the Cell Features used for cervical cancer classification [19]

Feature	**Cervical Cancer Class**			
	Normal	**Degree of Dysplasia**		
		Mid	**Moderate**	**Severe**
Nucleus Area(µm^2)	20-50	50+	50+	50+
Nucleus Intensity	dark	light	dark	Dark
Cytoplasm Intensity	light	light	dark	Dark
Nucleus/Cytoplasm Ratio	1-2%	10-20%	20-50%	50% +

1.3 Automated pap-smear analysis.

The aim of automated pap-smear analysis is to segment and then classify cervical cells in the pap-smear images as normal or abnormal [19]. This can help cytologists reduce the time spent performing slide examination in the pap screening process. Timely and reliable cervical cancer screening programs lead to early detection of cervical cancer and this saves lives [12].

Automated pap-smear analysis involves the techniques and processes to obtain detailed information from pap-smears using computers for clinical analysis and medical interventions [19]. These techniques include, but are not limited to, medical imaging and machine learning techniques. Machine learning employs a variety of statistical, probabilistic and optimization techniques that allow computers to "learn" from past examples and to detect hard-to-discern patterns from large, noisy or complex data sets [20]. Machine learning and medical imaging techniques make it possible to automatically analyze pap-smear images and make the screening process faster and more reliable, as proposed by various papers presented in the literature review.

2. Literature Review

This section documents the findings of a literature review of publications spanning a fifteen-year period, relating to the applications of image analysis and machine learning in automated diagnosis and classification of cervical cancer from pap-smear images. The survey reviews 30 journal papers obtained electronically through four scientific databases: Google Scholar, Scopus, IEEE and Science Direct searched using three sets of keywords: Segmentation, Classification, Cervical Cancer; Medical Imaging, Machine Learning, Pap-smear Images; Automated, Segmentation, Pap-smear Images.

2.1 Detailed Review of considered publications in automated pap-smear analysis

Y. Song et al. (2017) [21] proposed a learning-based method with shape models to segment individual cell in pap-smear images. The splitting of the cells was defined as a discrete labeling task with a suitable cost function. The labeling results were then fed into a dynamic multi-template deformation model for further boundary refinement. An evaluation carried out using two different datasets demonstrated the superiority of the proposed method over the state-of-the-art methods in terms of segmentation accuracy.

B. Ashok et al. (2016) [22] compared feature selection methods for diagnosis of cervical cancer using a Support Vector Machine (SVM) classifier. Image segmentation was performed using thresholding. Feature selection was achieved using mutual information, sequential forward search, sequential floating forward search, and random subset feature selection methods. Accuracy of 98.5%, sensitivity of 98% and specificity of 97.5% were obtained using the sequential floating forward selection method, which was higher than the other methods.

H. Lee et al. (2016) [23] proposed an automatic segmentation method for multiple overlapping cervical cells in microscopic images using superpixel partitioning and cell-wise contour refinement. The cells are detected using superpixel generation and triangle thresholding. The nuclei are extracted using local thresholding and cytoplasm by superpixel partitioning. The method showed competitive performances compared to other methods.

J. Su et al. (2016) [24] proposed a method for automatic detection of cervical cancer from pap-smear images using a two-level cascade integration system of two classifiers. The results showed that the recognition rates for abnormal cervical cells were 92.7% and 93.2%, respectively, when C4.5 classifier or LR (logical regression) classifier were used individually; while the recognition rate was significantly higher (95.6%) when the two-level cascade integrated classifier system was used.

M. Sharma et al. (2016) [25] used K-Nearest-Neighbors (KNN) method to classify the stage of cervical cancer from pap-smear images. The classification accuracy of 82.9% with 5-Fold cross validation was achieved.

R. Kumar et al. (2015) [26] proposed a framework for automated detection and classification of cervical cancer from microscopic biopsy images using biologically interpretable features. K-means is used for image segmentation and K-nearest neighborhood is used for cervical cancer classification. The performance measures for accuracy, specificity and sensitivity of 92%, 94% and 81% were obtained.

Y. Song et al. (2015) [27] proposed a multiscale convolutional network (MSCN) and graph-partitioning-based method for segmentation of cervical cytoplasm and nuclei. Deep learning via the MSCN was used to extract scale invariant features, and then segment regions centered at each pixel. Experimental results demonstrate that the proposed approach delivers promising results.

T. Chankong et al. (2014) [28] presented a method for automatic cervical cancer cell segmentation and classification using fuzzy C-means (FCM) clustering technique. Validation with Artificial Neural Networks (ANN) yielded accuracies of 93.78% and 99.27% for the 7-class and 2-class problems, respectively.

Y. Song et al. (2014) [29] applied a super pixel and convolution neural network (CNN) based segmentation method to cervical cancer cells. They also explored the use of Deep learning based on CNN for region of interest detection. Experimental results of 94.50% were achieved for nucleus region detection and a precision of 0.91±0.02 and a recall of 0.87±0.001 were achieved for nucleus cell segmentation.

J. Talukdar et al. (2013) [30] presented a fuzzy clustering based image segmentation of pap-smear images of cervical cancer cells using Fuzzy C-Means (FCM) Algorithm. Two random numbers were used to form the membership matrix for each pixel to guide clustering. Promising results were obtained using the pixel level segmentation.

Z. Lu et al. (2013) [31] presented an algorithm for the segmentation of cytoplasm and nuclei from clumps of overlapping cervical cells. Their approach addresses challenges involved in delineating cells with severe overlap by utilizing a joint optimization of multiple level set functions. Their quantitative assessment demonstrates that the methodology can successfully segment clumps of up to 10 cells, provided the overlap between pairs of cells is < 0.2 mm.

Z. Lu et al. (2013) [32] presented a joint level set optimization method for automated nucleus and cytoplasm segmentation of cervical cells using scene segmentation and unsupervised classification. The method obtained a Jaccard index of > 0.8 with a near zero false negative rate.

A. Genctav et al. (2012) [33] proposed an unsupervised approach for the segmentation and classification of cervical cells. The approach involves automatic thresholding to separate the cell regions from the background. A multi-scale hierarchical segmentation algorithm was used to partition the regions of interest based on homogeneity and circularity. Finally, a binary classifier was used to separate the nuclei from cytoplasm. Performance evaluation using two data sets showed the effectiveness of the proposed approach with an accuracy of 96.71%.

A.Kale et al. (2012) [34] presented a nucleus segmentation technique which determines a segmentation threshold based on the stability of the perimeter of the cell. Cytoplasm and nucleus are separated by clustering. A minimum Mahalanobis distance classifier was used to compare results. The technique achieved an accuracy of 90.0% for two class problems classification.

C. Bergmeir et al. (2012) [35] implemented an algorithm for segmenting the nuclei from pap-smear images. The algorithm localizes cell nuclei using a voting scheme and prior shape knowledge by means of an elastic segmentation algorithm. Edges are extracted with a Canny edge detection algorithm and a randomized Hough transform to find candidate nuclei, which are then processed by a level set algorithm. Experiments showed promising results.

P.Pai et al. (2012) [36] presented a nucleus and cytoplast contour detector (NCC) for cytoplast and nucleus segmentation in pap-smear images using maximal gray-level-gradient-difference (MGLGD) method. Adaptable threshold decision (ATD) method was utilized to separate the cells in the pap-smear images. Results showed that the proposed method is superior to the gradient vector flow-active contour model (GVF-ACM) and the edge enhancement nucleus and cytoplast contour (ENNCC) detector, in segmenting the cytoplast and nucleus of a cell.

I. Muhimmah et al. (2012) [37] presented a novel method for nuclei segmentation using morphological operation and watershed transformation. The method produced promising results when evaluated with respect to its nuclei area and its shape-similarity in comparison to the pathologist truth.

K. Li et al. (2012) [38] proposed a Radiating Gradient Vector Flow (RGVF) snake algorithm to extract nucleus and cytoplasm from single cervical cell image. Special k-means algorithm was used to cluster the image into areas of nucleus, cytoplasm and background. Experiments performed on the Herlev dataset showed that the proposed algorithm is effective.

M. Sreedevi et al. (2012) [39] presented an algorithm based on iterative thresholding method for segmentation of pap-smear images and classification of cervical cells as normal or abnormal based on the area parameter of the nucleus. The features of the nucleus were extracted using region properties, and cells were classified as normal if nucleus area was less than 1635mm and classified as abnormal otherwise. A sensitivity of 100% and specificity of 90% was achieved.

H. Kong et al. (2011) [40] proposed an integrated framework consisting of a novel supervised cell-image segmentation algorithm and a touching-cell splitting method. For the segmentation, the color-texture was extracted at the local neighborhood of each pixel using a local Fourier transform (LFT). The boundaries of touching-cell clumps were smoothed out by Fourier shape descriptor. The pipeline was validated against pathological images giving an error rate of 5.25% per image in terms of under-splitting, over-splitting, and encroachment errors.

L. Zhang et al. (2011) [41] presented a nuclei segmentation algorithm consisting of three main components: preprocessing, binarization and segmentation. In preprocessing, HSV color space was used for enhancing the contrast between nuclei and cytoplast. An adaptive threshold method was used during binarization to separate the nuclei pixels from background pixels. For segmentation, a concave point based overlapped nuclei segmentation algorithm was utilized.

M. Plissiti et al. (2011) [42] presented an automated method for the detection and boundary determination of cells nuclei in pap-smear images. The detection of the candidate nuclei was based on a morphological image reconstruction process and the segmentation of the nuclei boundaries was accomplished with the application of the watershed transform. The method was evaluated on a data set of 90 pap-smear images. Comparisons with the segmentation results of a gradient vector flow deformable (GVF) model and a region based active contour model (ACM) indicate that the method produces more accurate nuclei boundaries that are closer to the ground truth.

S.Sulaiman et al. (2010) [43] proposed a segmentation method for delineating the overlapping cells in pap-smear images. A seed based region growing algorithm was utilized to detect and segment overlapping cells. A pseudo coloring technique was used to delineate the cytoplasm and nucleus.

C. Lin et al. (2009) [44] proposed a method for detection and segmentation of cytoplasm and nucleus from pap-smear images. The approach used a Gaussian filter for noise elimination and a two-group object enhancement technique to enhance the gradients of the edges of the cytoplasm and nucleus while suppressing the noise gradients. Performance was compared with seed region growing feature extraction and level set method and showed promising results.

Y. Marinakis et al. (2009) [45] proposed a meta-heuristic algorithm to classify cervical cells from pap-smear images using a genetic algorithm scheme combined with a number of nearest neighbor based classifiers. Results showed that classification accuracy generally outperforms other previously applied intelligent approaches with accuracy of about 89%.

M. Plissiti et al. (2008) [46] presented an automated method for cell nuclei detection. Fuzzy C-means algorithm was used for segmentation and clustering. The proposed method was evaluated on a data set consisting of 3,085 cells of pap-smear images and showed promising results.

S. Yang et al. (2008) [47] presented an edge enhancement nucleus and cytoplast contour (EENCC) detector to enable cutting the nucleus and cytoplast from a cervical smear cell image for automated cervical cancer diagnosis. A trim-meaning filter was used to effectively remove impulse and Gaussian noise.

N. Ampazis et al. (2004) [16] proposed an algorithm for cervical cancer screening using efficient second order neural network. The classification algorithms used were the LMAM (Levenberg Marquardt with Adaptive Momentum) and OLMAM (Optimized Levenberg-Marquardt with Adaptive Momentum) which resulted into an overall accuracy of 80.7%.

J. Zhang et al. (2004) [49] presented a novel feature screening method by deriving relevance measures from the decision boundary of Support Vector Machine using pixel-level classification for feature selection. Comparative experiments with other algorithms showed significant improvements on pixel-level classification accuracy using the new set of derived features.

3. Observations

The overall aim of the cervical cells preprocessing, segmentation and classification algorithms/methods summarized in this paper is automated diagnosis and classification of cervical cancer from pap-smear images [16, 21-49]. To that end, the reviewed papers document adaptations to the various stages of the medical image analysis pipeline which include: image acquisition, pre-processing, segmentation, classification and validation [50].

The review of relevant literature has highlighted that some techniques are more frequently used than others; with filtering, thresholding and KNN being the most frequently used techniques for preprocessing, segmentation and classification of pap-smear images respectively. It has also been observed that the superiority of the results of a classification algorithm over the other greatly depends on a number of factors that include: the accuracy of the segmentation, pre-processing and the type of datasets used. Table 2 shows a summary of the techniques used in the papers reviewed.

Table 2: A summary of the techniques documented in the papers reviewed.

Image Acquisition	**Pre-processing**	**Segmentation**	**Classification**	**Validation**
-Most of the papers reviewed use open *datasets*. The commonly being: - LCH - ERUDIT and - Herlev datasets -A few authors report to have obtained pap-smear from hospitals with support of skilled cytotechnicians	*Filters*: The commonly used being the Median and the Gaussian Filter	- Adaptive histogram equalization - Thresholding - Hough Transformation - Superpixel based Markov Random Field - Seed Based Region Growing - Watershed segmentation - Shape Prior - Edge detection	- K-means - Artificial Neural Networks - K-Nearest Neighbor - Fuzzy C-Mean - Support Vector Machines - Bayesian Networks - Decision Trees	- Cross validation - Benchmarking with results obtained by other researchers on the same dataset

4. Discussion

The paper reviews a number of prominent recent publications relating to the automated diagnosis and classification of cervical cancer from pap-smear images. This review should help researchers in the field to see the challenges associated with some of the techniques documented, and provided a good basis for designing and developing new algorithms or improve existing ones.

The review has identified that there are still some weak points with regard to the techniques reviewed; these weaknesses include low accuracy of classification in some classes of cells. Furthermore, the algorithms documented work either on single cervical cell images or multiple cervical smear images; hence algorithms that can be used on both single and multiple cell images at the same time should be explored as cells in pap-smear images usually appear as overlapping cells.

Most of the existing algorithms result in accuracy of nearly 93.78% (which is still low) on an open pre-processed pap-smear data set (Herlev dataset images) located at http://mde-lab.aegean.gr/downloads. The reported accuracy can be improved up to the higher level by varying various parameters of the algorithms such as the features to be extracted, improvement in noise removal methods, using hybrid segmentation and classification techniques.

As reported earlier, some segmentation and classification algorithms are more frequently used than others; a situation that might have arisen due to the various advantages of one technique over the other (Table 3).

Table 3: Comparison of different segmentation and classification techniques

	Technique	Advantages	Limitations
1	**Segmentation**		
	Water immersion algorithms	Closed boundaries can be detected	Not good for overlapping cells
	Active contours	Boundaries can easily be detected	Energy minimization is time consuming
	Hough transform	Easily detects similarity in shapes	Detects only round single shapes
	Fuzzy logic	Robust and handles uncertainty in data	Rigid rules and not flexible
	Seed based region growing algorithms	Detects edges	Edge detection is subject to user's defined parameters
	Genetic algorithms	Efficiently searches for a good solution	Slow
	K-means clustering	Threshold values detected automatically	Cannot separate overall aping cells.
2	**Classification**		
	Artificial Neural Networks	Tolerant to noise, Can use more than one instance to classify instances	Over fitting in case of many attributes and complex algorithm
	Bayesian Networks	Easy to understand, based on statistical inference	Assumes normal distribution on numeric attributes, assumes attributes are statistically independent
	Support Vector Machines	Easy to control decision tree and over fitting is unlikely to occur.	Difficult to obtain optimal parameters for nonlinear data and training is slow.
	Decision Tree	Easy to understand	Error in training set can lead to wrong final decisions.
	Genetic algorithms	Finds a good solution and good for optimization	Usually finds local optima that makes it not the most efficient
	k-Nearest Neighbour	Robust, fast and tolerant to noise	Complex as attributes increase in number and assumes that instances of same attributes are similar. This may not be true all the times.

5. Conclusions

KNN algorithm has been reported to be an excellent classifier for cervical images, however combining KNN algorithm with other algorithm (s) like Support Vector Machines (SVMs), pixel level classifications and including statistical shape models can improve performance. Furthermore application of multi-level segmentation can improve performance of a classifier (s).

Most of the algorithms have been cross validated with the training and test datasets provided from the online cervical image datasets like Herlev (http://mde-lab.aegean.gr/downloads). Other new images from hospitals should be used for testing the developed classifiers by a trained cytologist and results reported. Finally most of the developed classifies are developed and tested on accurately pre-processed images segmented using commercially available segmentation software like CHAMP digital image software. There is thus a deficit of evidence that these algorithms will work in clinical settings found in developing countries (where 85% of cervical cancer incidences occur) that lack sufficient trained cytologists and the funds to buy the commercial segmentation software.

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