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Pap Smear Image Analysis Based on Nucleus Segmentation and Deep Learning – A Recent Review

Nur Ain Alias[1], Wan Azani Mustafa[1,2,*], Mohd Aminudin Jamlos[3], Shahrina Ismail[4], Hiam Alquran[5], Mohamad Nur Khairul Hafizi Rohani[1]

[1] Faculty of Electrical Engineering Technology, Universiti Malaysia Perlis, UniCITI Alam Campus, Sungai Chuchuh, 02100 Padang Besar, Perlis, Malaysia
[2] Advanced Computing (AdvCOMP), Centre of Excellence, Universiti Malaysia Perlis (UniMAP), Pauh Putra Campus, 02600 Arau, Perlis, Malaysia
[3] Faculty of Electronic Engineering Technology, Universiti Malaysia Perlis, UniCITI Alam Campus, Sungai Chuchuh, 02100 Padang Besar, Perlis, Malaysia
[4] Faculty of Science and Technology, Universiti Sains Islam Malaysia (USIM), Bandar Baru Nilai, Negeri Sembilan, 71800, Malaysia
[5] Department of Biomedical Engineering, Jordan University of Science and Technology, Irbid 22110, Jordan

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ABSTRACT

Cervical cancer refers to a dangerous and common illness that impacts women worldwide. Moreover, this cancer affects over 300,000 people each year, with one woman diagnosed every minute. It affects over 0.5 million women annually, leading to over 0.3 million deaths. Recently, considerable literature has grown around developing technologies to detect cervical cancer cells in women. Previously, a cervical cancer diagnosis was made manually, which may result in a false positive or negative. Automated detection of cervical cancer and analysis method of the Papanicolaou (Pap) smear images are still debated among researchers. Thus, this paper reviewed several studies related to the detection method of Pap smear images focusing on Nuclei Segmentation and Deep Learning (DL) from the publication year of 2020, 2021, and 2022. Training, validation, and testing stages have all been the subject of study. However, there are still inadequacies in the current methodologies that have caused limitations to the proposed approaches by researchers. This study may inspire other researchers to view the proposed methods' potential and provide a decent foundation for developing and implementing new solutions.

1. Introduction

Cervical cancer denotes a dangerous and common illness that troubles women worldwide [1-3]. This cancer impacts over 300,000 individuals yearly, with one woman diagnosed every minute. It impacts more than 0.5 million women yearly, culminating in more than 0.3 million deaths.

Cervical cancer has the second-highest death rate among women in developing nations, behind breast cancer, and is among the tumors that can be treated if detected soon enough [4,5]. Early detection and Pap smear cell images' classification are crucial in identifying cervical cancer [6-9].

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[*] *Corresponding author.*
E-mail address: wanazani@unimap.edu.my

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Cervical cancer is among the death causes within cancer patients and among the leading causes of gynecologic cancer, despite being treatable if identified earlier. These cancer cells can potentially be transmitted to other critical organs, for instance, the bladder, liver, and lungs, further complicating the situation [10,11]. Early detection and categorization of cervical lesions enhance patients' chances of effective treatment, and automated detection and categorizing of cervical lesions using Pap smear images are becoming quite prevalent [12]. Note that this test could detect pre-cancer in the uterine cervix [11,13]. The most popular screening mechanisms for the cervical lesion are the visual inspection and Pap smear test with acetic acid to categorize the cervical cells as normal, precancerous, or cancerous, as shown in Figure 1 [14,15].

The Pap test refers to the cancer prevention method that involves a specific and labor-intensive analysis of cytological arrangements to trace possibly cancerous cells from the external and internal cervix surface [16]. While looking for abnormal cells, a cytopathologist must examine various microscopic regions [17]. However, due to human error, this manual screening approach has a high rate of false-positive results. Other than distinguishing several restrictions, identifying cervical cells in a Pap smear is challenging.

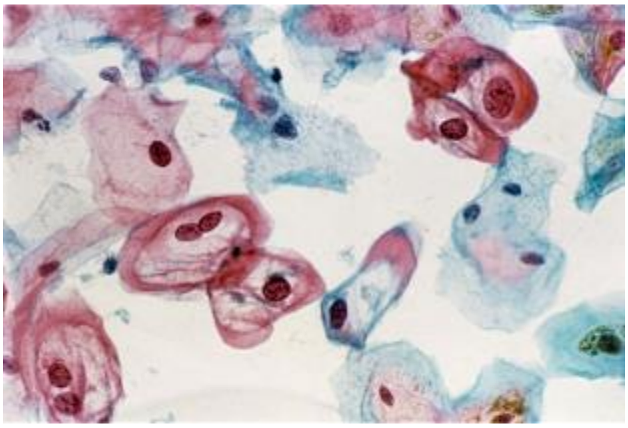

Fig. 1. Pap Smear image of cancer affected [1]

Image analysis is a vital medical topic, especially in cytology. In addition, visual interpretation is utilized in various medical diagnostic procedures. DL approaches have recently overtaken prior state-of-the-art Machine Learning (ML) approaches for various issues involving image classification. For example, it is difficult to categorize cells in Pap smear images, yet cytopathologists are still required to accomplish it [18,19].

An important element in automated cervical cancer screening is nuclei segmentation in cytology Pap smear images. The work is arduous because cervical cells have artifacts, neutrophils, overlapping cells, and spurious edges [20,21]. Precise cell segmentation, especially nuclei, is critical to the diagnostic and analysis procedure. Separating contacting nuclei in microscopy images has been a struggle in medical and biological disciplines [22].

Computer-aided diagnosis (CAD) systems based on DL and ML were widely investigated to describe cervical Pap cells in terms of enhancing manual screening techniques [2,14]. However, to get effective classification results, most research demands pre-segmented images. Cell clustering, on the other hand, makes reliable cervical cell segmentation difficult. In addition, several investigations depend on handmade characteristics that cannot ensure the classification step performs at its best. Furthermore, if there is an inconsistent data distribution, for example, in the cervical cell dataset, DL performs poorly in a multi-class classification task [23]. Therefore, past researchers have studied the detection method of Pap smear images through different approaches.

2. Review of the Study

2.1 Nucleus Segmentation

Zhao *et al.,* [24] have proposed a new Selective-Edge-Enhancement-based Nuclei Segmentation (SEENS) method. Selective search is combined alongside mathematical operators in the suggested technique to segment full-slide cervical images into tiny Regions Of Interest (ROI) while preventing repetitive segmentation and deleting non-nuclei regions. The block diagram of cervical cancer segmentation is depicted in Figure 2. Furthermore, an edge augmentation approach relying on mathematical morphology and the canny operator is provided, which retrieves edge information as a weight to boost the nucleus edge specifically [24].

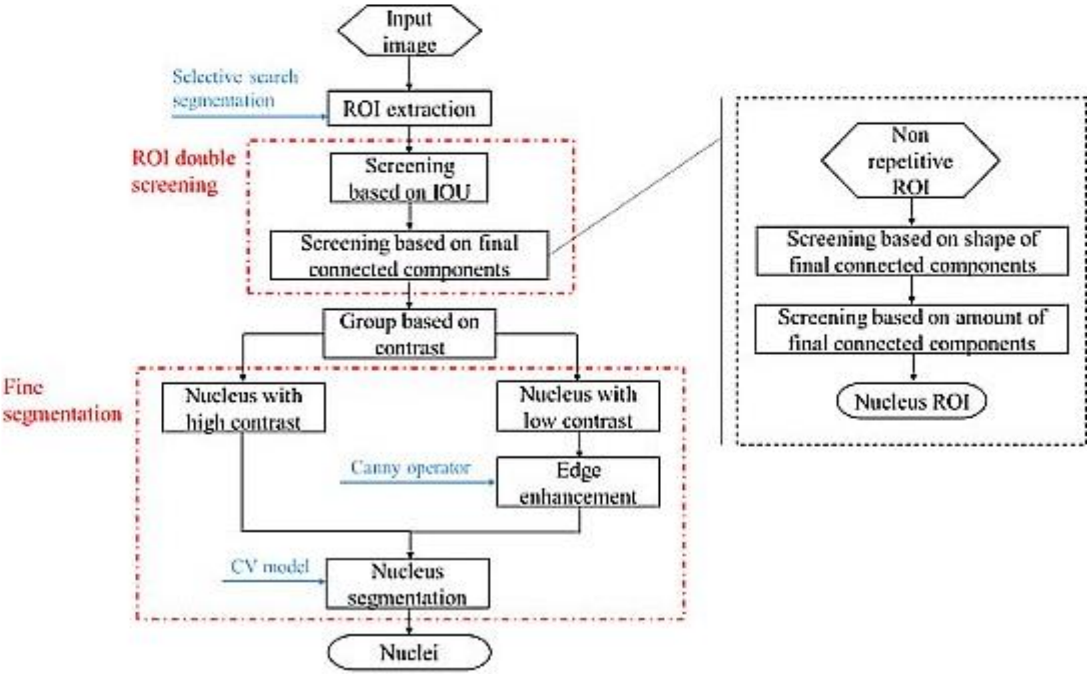

Fig. 2. The block diagram of cervical nuclei segmentation [24]

The Boykov-Kolmogorov Graph Cuts (BKGC) scheme is suggested from a study by Balaji *et al.,* [25]. It presents an efficient BKGC-based image partitioning approach that predicts the image data utilizing a synergy cloud model to form objective functions. Furthermore, in estimating every pixel's deviation on the distinct areas of the cervical Pap smear cells, the suggested BKGC-CMSIS scheme incorporates a data item as a smooth term regarding boundary preservation, as shown in Figure 3 [25].

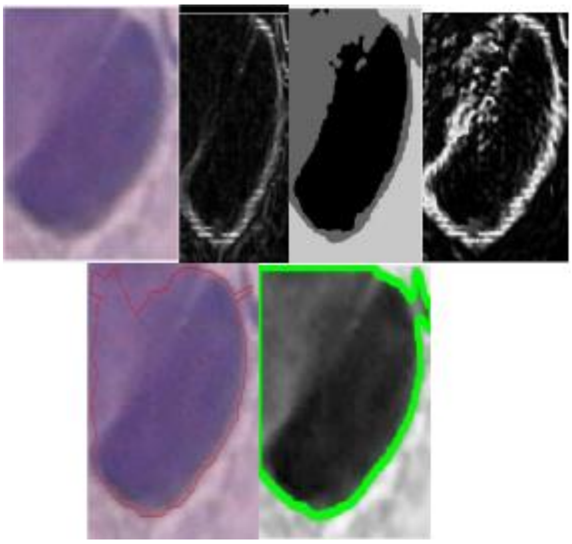

Fig. 3. The generated images following enforcing the suggested BKGC-CMSIS Scheme's sequential phases throughout deployment [25]

This image is provided by Shiney and Rose [26], explaining that three innovative approaches for the automated identification and categorization of cervical cancer in Pap smear images have been created. This framework consists of five stages: data collection, pre-processing, segmentation, extraction of features, and image categorization. The Herlev Pap smear data collection is employed to develop the suggested approach. First, the Pap data's noise was removed by employing an Anisotropic Diffusion Filter with an Unsharp Masking method on the input image from the data set. The suggested Advance Map-Based Superpixel Segmentation (AMBSS) algorithm is then utilized to segment an improved image sequence automatically.

Consequently, Hoque *et al.,* [20] presented a strategy in which the image runs via a convolution filter to filter out certain noise after the initial pre-processing stages of adaptive thresholding. The contours in the resulting image are subsequently filtered, relying on their different contour qualities, and a nucleus size recovery technique relying on the contour average intensity value is performed. The strategy is tested using a general (benchmark) dataset from ISBI and a private real-world dataset.

In addition, Jia *et al.,* [22] presented an article in 2021 aimed toward particular screening scenarios with constrained datasets and labels, proposing a unique multi-layer segmentation framework for effectively and precisely segmenting nuclei. The Watershed, enhanced Gradient Vector Flow (GVF), and Snake model (improved via the corrected gradient) are first merged for rough segmentation. This isolates the nuclei from the background. Hence, the results from the rough segmentation are subsequently utilized to initialize finer segmentation, implementing convex hull detection, concave point detection, and ellipse fitting addressing overlapping nuclei. Note that two ellipse verification requirements are provided to ensure the fitted border's uniqueness. Figure 4 illustrates more on how the multi-layer segmentation works.

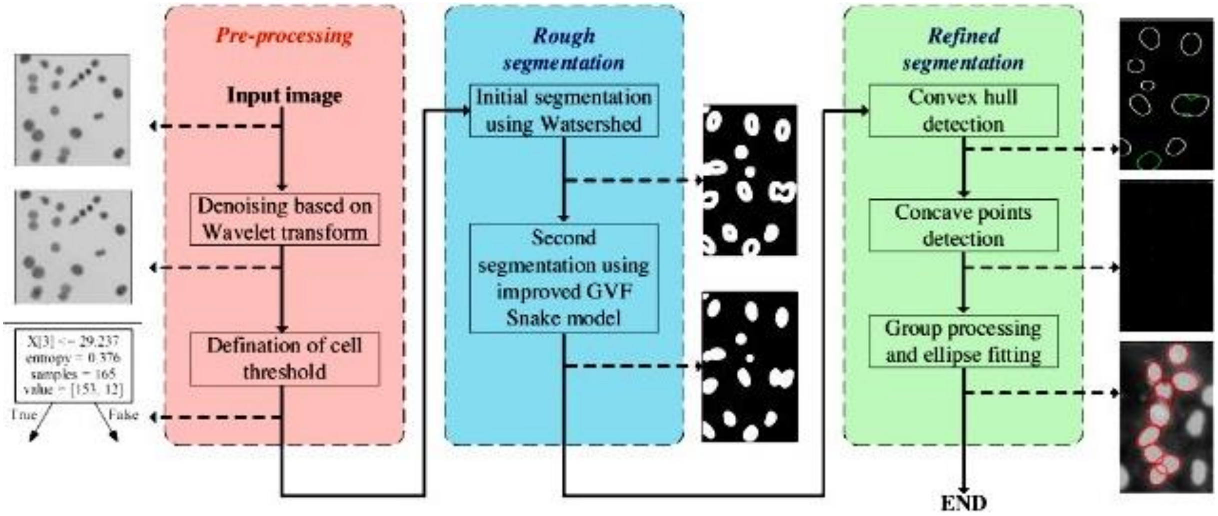

Fig. 4. Proposed multi-layer segmentation framework flow chart [22]

Apart from that, Mustafa *et al.,* [27] suggested a novel nucleus segmentation on Pap smear cell images relying on morphological or structured analysis methods. Morphology is a group of image processing techniques that modify images depending on their structure, size, and shape. This technique utilizes an image's structural feature to generate a similar-sized output image. Dilation and erosion are the greatest basis of these activities.

Furthermore, a unique study utilizes modified fuzzy C-means, extraction of geometrical and textural elements, and Principal Component Analysis (PCA), as well as the classification for the automated identification of cervical cancer. Even though there is ambiguity, modified fuzzy C-means exhibit remarkable outcomes in segmenting the input image into relevant parts. PCA decreases the data set's dimensionality by keeping the uncorrelated elements, reducing the algorithm's processing time. K-Nearest Neighbour (KNN) classification uses k-fold cross-validation to classify Pap smear images into abnormal and normal cells. The results of the suggested technique are contrasted with Linear Discriminant, Ensemble Bagged trees, and Fine Gaussian SVM [4].

Besides, Hussain *et al.,* [28] discovered that the framework allows simultaneous nuclei instance segmentation and estimates the kind of nucleus class corresponding to abnormal and normal classes from smear images in a thorough investigation of cervical cell image categorization. Furthermore, it performs by providing pixel-wise labels to specific nuclei in a full slide image, allowing numerous nuclei from similar or distinct classes to be identified as separate cases. Furthermore, the joint loss function added to the framework overwhelms several minor problems with clustered nuclei separation at the cell level. Finally, a stacked auto-encoder-based shape description learning model is employed before the proposed model to increase the resilience of the overall framework [28].

The standard approach by the researcher related to the Pap smear image analysis and method of detection is presented, and the results will be discussed systematically and in detail. Therefore, the Chan–Vese model can more precisely segment the increased ROI. The approach evaluates 18 complete slide images, totaling 395 cell nuclei. On the other hand, SEENS yields greater precision in cervical nuclei segmentation, according to experimental data. Furthermore, the suggested technique outperforms baselines in low-contrast conditions specifically. The suggested BKGC-CMSIS scheme's experimental findings further demonstrate that it could improve classification accuracy by 14% beyond the benchmarked cervical cancer detection techniques for experiments.

The accuracy of the proposed techniques of nuclei segmentation by Devi and Thirumurugan [4], Hoque *et al.,* [20], and Jia *et al.,* [22] are 97.8%, 91.3%, and 96.31%, respectively. Together, these results provide important insights into the nuclei segmentation technique as one of the developing techniques in Pap smear image analysis. Note that an extensive amount of literature was established regarding nuclei segmentation. The study by Jia *et al.,* [22] presented an effective result with 81.2% of sensitivity. Mustafa *et al.,* [27] reported the sensitivity achieved is about 94.38%, while Lavanya Devi and Thirumurugan [4] achieved 97.96%. The specificity of the nuclei segmentation technique is 82.56% and 83.65% and has been demonstrated in these two reports [25].

When contrasted to the conventional technique, the previously discussed techniques would aid doctors in recognizing patient illness depending on Pap smear analysis, for instance, cervical cancer, enhancing accuracy percentages. In addition, the effective application of nucleus detection techniques to Pap smear images might lead to a new method for identifying microbiological illnesses like Malaria and Tuberculosis.

2.2 Deep Learning

For the initial diagnosis of cervical cancer, Chitra & Kumar presented the Mutation-based Atom Search Optimization (MASO)-optimized DenseNet 121 architecture. The architectural hyperparameters, such as batch sizes, learning rate values, and the neurons' number in the dense layer, are optimized using this approach [13]. When there is an uneven data distribution, Rahaman *et al.,* [23] proposed DeepCervix to enhance the performance of DL for a multi-class classification task. DeepCervix is a DL-based Hybrid Deep Feature Fusion (HDFF) approach for reliably classifying cervical cells. In contrast, the suggested approach uses varied DL models to gather more promising data and improve classification performance. Other researchers have used a similar classification technique but with different approaches. The SIPaKMeD dataset is used to test the HDFD method, while the performance is compared against the base DL models and the Late Fusion (LF) approach. This work proposes that DL classification techniques transfer learning be employed on the SIPAKMED Pap smear image dataset as a baseline for evaluating future categorization methodologies [10].

The narrative review from another existing method was studied, in which Elakkiya *et al.,* [14], Diniz *et al.,* [18], and Khamparia *et al.,* [29] considered deep Convolutional Neural Networks (CNN). This study utilized an efficient DL method utilizing Small-Object Detection-Generative Adversarial Networks (SOD-GAN) alongside Fine-tuned Stacked Autoencoder (F-SAE). It suggests a collection of the three greatest architectures in categorizing cervical cancer upon cell nuclei and minimizing the experts' workload. The dataset utilized in the investigations is obtainable in the Center for Recognition and Inspection of Cells (CRIC) Searchable Image Database. Nevertheless, Khamparia *et al.,* [29] suggested utilizing a variational autoencoder to minimize the data dimensionality for additional processing having the softmax layer's participation for training. Sensitivity, accuracy, F1-score, recall, and precision are all taken into account, and the suggested ensemble outperforms existing two- and three-class classification approaches in the literature. The investigation yielded a novel finding: a six-class categorization system.

According to Wang *et al.,* [12], a DL-based cervical lesions diagnosis system has been depicted to be capable of not only detecting High-grade Squamous Intraepithelial Lesions (HSILs) but a rather high Squamous Cell Carcinoma (SQCC). This implies that patients should generally be declared colposcopy instantly and processed WSIs in seconds for practical clinical use. Prior investigation has mainly focused on two state-of-the-art DL techniques (U-net 19 and SegNet 20) [12]. Scholars contrasted the suggested technique to the benchmark strategies in computing the Jaccard index, F-measure, recall, precision, and speed, prevalently utilized for semantic segmentation to evaluate pixel-level labeling performance. Note that the following four categories are utilized to classify objects: false negative (FN), false positive (FP), true negative (TN), and true positive (TP). Below is the list of evaluation metrics.

$$Precision = \frac{TP}{TP+FP}.$$

$$Recall = \frac{TP}{TP+FN}.$$

$$F\_measure = 2 \times \frac{Precision \times Recall}{Precision+Recall} = \frac{2TP}{2TP+FP+FN}.$$

$$F\_measure = \frac{F\_measure}{(2-F\_measure)} = \frac{TP}{TP+FP+FN}.$$

Previous research has shown that Shanthi *et al.,* [30] have studied to classify the image of the cervical cell by retrieving and choosing the clear-cut characteristics and categorization, as well as the benchmark of Herlev dataset elements. In the classification stage, the Radial Basis Function (RBF) and sigmoid Support Vector Machine (SVM) kernels, including polynomials, are utilized, where the characteristics in the benchmark database are compared [30].

According to current information, the T-test filter approach was performed on the data set once Hosseinabadi *et al.,* [31] extracted the data from the cell images. The investigation utilized a variety of classification algorithms, including ensemble classifiers, KNN, Decision Tree (DT), and SVM) [31-33]. The integration of an ensemble classifier having three of the finest DL models for delivering a great accuracy multi-class classification is highlighted by Hussain, Mahanta, Das, & Talukdar. In addition, the benchmark Herlev dataset and a hospital-based Pap smear dataset obtained utilizing both liquid and conventional-based cytology procedures have been utilized for training and testing all six deep models, including the ensemble classifier [33]. Figure 5 illustrates the types of cell images, consisting of three categories: single-cell, multi-cell, and overlapping cell.

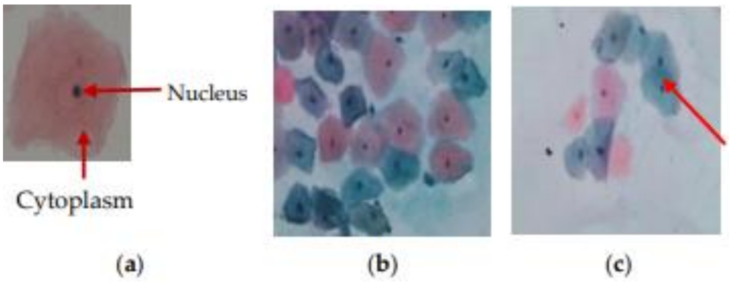

Fig. 5. (a) Single-cell image (nucleus and cytoplasm), (b) Multi-cells image, as well as (c) Overlapping cytoplasm [32]

In 2020, Novitasari *et al.,* [34] conducted a study on the early detection of cervical cancer based on cancer stage utilizing texture information on colposcopy images utilizing the Gray Level Co-occurrence Matrix (GLCM) approach to examine pixel neighbor information. Furthermore, the Kernel Extreme Learning Machine (KELM) approach, an ELM technique's refinement via introducing a kernel to the system, is employed to classify it. With the comparable goal in mind, Palanisamy *et al.,* [6] created a study that includes the CNN module, Dual-Tree Complex Wavelet Transform (DTCWT) module, and data augmentation module for automated Pap smear cell images. Alternatively, the CNN module requires many cell images for a strong classification rate. As a result, the flipping and shearing functions are utilized in the data augmentation process to enhance dataset samples for the CNN classification module [6].

In summary, the previous studies that have been reviewed are demonstrated to detect cervical cancer through Pap smear tests. Furthermore, considering the metrics of accuracy, precision, sensitivity, and specificity proved by the previous studies, these studies provide important insights into the cervical detection method of cervical cancer. Table 1 summarizes all the findings from the prevailing works related to the DL method in assisting the Pap smear images' classification.

Table 1
Summary of the prevailing works

Author /Year	Method	No. of image/ Dataset	Accuracy	Precision	Sensitivity	Specificity
Chitra and Kumar [13]	MASO-optimized 121 architectures	DenseNet	98.38%	99.3%	98.58%	98.83%
Rahaman *et al.,* [23]	DeepCervix, a hybrid deep feature fusion (HDFF)	SIPaKMed	2-Class 99.85% 3-Class 99.38% 5-Class 99.14%	-	-	-
		Herlev	2-Class 98.32% 7-Class 90.32%	-	-	-
Elakkiya *et al.,* [14]	Small-Object Detection Generative Adversarial Networks (SOD-GAN) with Fine-tuned Stacked Autoencoder (F-SAE)	Heterogenous dataset	97.8%	95.62%	-	-
Khamparia *et al.,* [29]	Deep convolutional neural networks and proposes an ensemble of the three best architectures	CRIC Searchable Image Database	2-Class 96% 3-Class 96% 6-Class 95%	2-Class 96% 3-Class 94% 6-Class 85%	-	2-Class 96% 3-Class 97% 6-Class 97%
Tripathi *et al.,* [10]	Deep convolutional and variational autoencoder network	Herlev	2x2 filter size-99.2% 3x3 filter size-99.4%	-	-	-
Wang *et al.,* [12]	Lesions diagnosis system	143 whole slide images	-	93%	-	-
Novitasari *et al.,* [34]	Gray Level Co-occurrence Matrix (GLCM)	Colposcopy data	95%	-	-	-

3. Conclusions

Several approaches and analytical methods centered on Nucleus Segmentation and DL were devised to provide an end-to-end framework for cervical cancer diagnosis and classification. All of the strategies provided were designed to work with multivariate datasets. The recommended methods were further expanded to include determining the kind and phase of cervical cancer and detecting it. Tests were conducted during the training, validation, and testing processes. According to the publications evaluated, present approaches still have flaws, resulting in lower classification accuracy in specific cell types.

However, most available techniques function on multiple or single cervical cancer smear images. Furthermore, there is no evidence that these algorithms will succeed in underdeveloped countries' clinical contexts (in which 85% of cervical cancer cases arise) since competent cytologists are scarce to purchase commercial segmentation software, besides the lack of funding. Therefore, this investigation can motivate similar field academics to recognize the possibilities of certain methodologies investigated, as well as provide a good foundation for developing and implementing new approaches.

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