International Journal of Innovative Technology and Exploring Engineering (IJITEE)
ISSN: 2278-3075 (Online), Volume-8 Issue-11, September 2019

Mitotic Cell Classification System Based On Supervised Learning for Histopathological Images of Breast Cancer

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Abstract: ***Breast cancer is a great threat to the women population throughout the world. Due to the technological advancements in medical science and digital imaging technology, histopathological images are widely utilized for better diagnosis. However, the histopathological images involve complicated structure due to the inconsistent staining, lighting conditions and so on. Considering these challenges, this work presents a mitotic cell classification system based on supervised learning for histopathological images of breast cancer. As the classification solely depends on the effectiveness of nuclei extraction, the proposed approach employs twin stage segmentation for better nuclei extraction. The effectiveness of the proposed mitotic cell classification system is matched with the existing approaches and the proposed approach performs better than the existing works with respect to accuracy, sensitivity, specificity and F-measure rates.***

Keywords – Histopathological image, mitotic cell detection, supervised learning.

I. INTRODUCTION

Cancer is a serious hazard to the human well-being and is quintessential to escape from the vindictive disease by proceeding with regular periodical screening tests. The screening examination helps in preventing the occurrence of the disease to some extent and paves way for better recovery. The earlier the disease is detected, the greater is the possibility to treat the disease better. Cancer detection is one of the crucial challenges being faced by the pathologists. Due to the advancement of technology and medical science, automated cancer detection techniques are popular these days. The automated cancer detection techniques are beneficial, as these techniques can assist the healthcare professionals, which in turn increase the accuracy and reduces the time consumption as well. Generally, the healthcare professionals thoroughly inspect the collected samples such that the degree of cell growth can be observed. Due to the increased mortality rates of breast cancer, this article intends to focus on the breast cancer. The severity of breast cancer is usually identified with the help of a universal cancer grading system called Nottingham Scoring (NS) scheme. The NS scheme grades the breast cancer with respect to three important attributes such as nuclear pleomorphism, tubule formation and mitotic cell count [1].

Manuscript published on 30 September 2019.
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Nuclear pleomorphism is a condition in which the nuclei of epithelial cells appear larger, darker and arrangement becomes inconsistent. On the other hand, the normal nuclei of epithelial cells are arranged consistently with unvarying size and shape [2]. Tubule formation indicates the count of cancer cells in the duct structure [3]. The mitotic cell count is the most important attribute that could effectively grade the severity of breast cancer. The mitotic cells have the capability to determine the virulence and the spreading nature of the cancer [4].The mitotic cell division happens and it involves four significant phases that includes prophase, metaphase, anaphase and telophase [5]. The shape of nuclei varies in all the phases and is difficult to detect the nuclei. Additionally, the histopathological images suffer from inconsistent illumination and stains [6], which further toughen the process of nuclei detection. As this is a complex and tedious process, it is indeed tough for the healthcare professional to analyse and assess the image with complete manual effort. It would be better when the healthcare professional is assisted by an algorithm, which in turn improvises the overall functionality and reliability of the system.

Understanding the need and the challenges confronted to the automated mitosis detection, this work aims to present a technique which can differentiate between the mitotic and non-mitotic cells. This objective of the research is attained by segregating the work into four key phases such as histopathological image pre-processing, nuclei extraction, feature extraction and classification.

The histopathological image pre-processing phase removes the unwanted data from the input images and prepares it for further image processing activities. The histopathological image appears inconsistent and the pre-processing phase of this work performs stain normalization, noise removal and image smoothening. The second of the work aims to extract the nuclei from the image such that further analysis is made possible. The nuclei are extracted by means of a twin-stage segmentation process such as rough and fine segmentation processes.

When the nuclei are extracted from the images, the features are extorted from the nuclei which describe the characteristics of nuclei and act as the deciding factor. The features utilized by this work are intensity, shape and Haralick texture features. The extracted features are utilized to train the Extreme Learning Machine (ELM) classifier. The highlights of this work are presented as follows.

- This approach pays more attention towards histopathological image pre-processing, which involves stain normalization, noise removal and image smoothening operations. All these activities together help in better analysis of the images.
- The twin stage segmentation process extracts the nuclei better and paves way for better feature extraction.
- Intensity, shape and haralick texture features are extracted from the nuclei for providing knowledge to the classifier. These features show a promising feature set for better discrimination.
- ELM is employed as a decision maker for distinguishing between the mitotic and non-mitotic cells. ELM is employed for its quicker learning ability.
- The effectiveness of the proposed approach is analysed with respect to accuracy, sensitivity, specificity and time consumption. The effectiveness of the proposed approach proves minimal false positive and negative rates.

The rest of the article is systematized in the following format. The second section reviews the recent literature with respect to mitotic cell classification. The proposed mitotic cell classification scheme is discussed elaborately in section 3. The effectiveness of the proposed approach is explored and evaluated in section 4 and the final section concludes the article.

II. REVIEW OF LITERATURE

In [7], an Expectation-Maximization based geodesic active contour with overlap resolution is presented for lymphocyte partition in breast cancer histopathology. This work detects and segments lymphocytes automatically and the work is carried out on HER2+ BC histopathology images. EMaGACOR employs the EM algorithm for starting a geodesic active contour and a method meant for heuristic division of contours is employed. This is achieved by the detection of high concavity points to resolve overlapping EMaGACOR, which is carried out on a total count of 100 HER2+ breast biopsy histology images.

A breast cancer histopathology image classification based on complete convolutional auto-encoder is presented in [8]. This work mines and compares the models of normal and cancerous images to form a probability plot of irregularities to check the reasoning. Specifically, a complete convolutional auto-encoder is employed for learning the dominant structural patterns in the normal image patches. The image patches that stand different from normal population are identified and analysed by employing one-class Support Vector Machine (SVM) along with one-layer neural network.

In [9], an automated classification of breast cancer stroma maturity from the histopathological images is proposed. The work analyses and automatically classifies between the stromal regions with respect to the maturity. This work is based on multi-scale based image features and Local Binary Patterns (LBP) along with random decision trees classifier for classification of breast cancer stroma regions of interest.

The breast cancer analysis over histopathological images is reviewed in [10]. This work considers the whole slide imaging (WSI) scanners, which supports in attaining cost-efficient and better throughput in histopathology slide digitization. This could support the pathologist to come out of normal optical microscope.

In [11], a Stacked Sparse Auto-Encoder (SSAE) for nuclei detection is presented for breast cancer histopathology images. A Stacked Sparse Auto-encoder (SSAE) based on deep learning strategy is presented for nuclei detection and this technique works for high-resolution breast cancer histopathological images. The nuclei are classified by with the help of high-level features with respect to pixel intensities for differentiating the nuclei. A sliding window operation is carried out on each image for representing image patches with respect to high-level features acquired by the auto-encoder. These features are then passed to a classifier for differentiating between the nuclear and non-nuclear regions.

A global covariance descriptor meant for nuclear atypia achievement in breast histopathology images is presented in [12]. This work presents a image descriptor for nuclear atypia grading in breast cancer histopathology images. This work considers the region covariance descriptor, which cannot handle histopathological images and hence, this work modifies the descriptor with the help of geodesic mean.

In [13], a multiple classifier system is proposed for automated mitosis detection using deep belief networks is presented. This paper presents a technique for detecting mitotic cells in Hematoxyline and Eosin (H & E) colored images and the work relies on nuclei segmentation and classification. The nuclei segmentation is carried out by Krill Herd Algorithm (KHA) algorithm, which relies on localized active contour model with deep belief network is presented for nuclei classification into mitosis and non-mitosis classes.

A multiple instance multiple label learning for multiple class differentiation of entire slide breast histopathology images in [14]. Initially, this work extracts the regions of interest from the screened images of pathologists with different behaviours such as enlarging, panning, fixation and so on. A scheme for every slide is created by means of group of instances indicating the sample ROIs and a group of class labels extorted from the pathology forms. At last, four different multiple instance multiple label learning algorithms are presented concerning the slide and ROI-level predictions of diagnostic classes in the complete slide breast histopathology images.

In [15], an analysis of near-infrared autofluorescent images for the breast cancer prediction is presented. This work considers three important components of breast tissues such as cancerous, fibrous and adipose. Every tissue sample of optical spectroscopic images is compared with the histopathological image slides.

An automated identification and extraction of cell nuclei for histopathological images is presented in [16]. Initially, the histopathological image foreground is extracted with the help of graph-cut algorithm based binarization automatically. The nuclear initial points are then detected by clubbing the multiple scale Laplacian of Gaussian filter being restricted by the distance plot based dynamic scale selection.

The segmentation is carried out with these points and the outcome is again enhanced by a graph-cuts oriented algorithm with alpha expansions and graph coloring for minimizing the computational complexity. In [17], a scheme to detect Ductal Carcinoma In Situ (DCIS) in complete slide H&E coloured breast histopathology images. This work applies a multiple scale superpixel classification technique to identify the epithelial parts in complete-slide images. The spatial clustering approach is then applied to define the regions with significant parts in tissues such as ducts and lobules. A regional classifier is trained with statistical, structural texture features and architectural features for better classification between DCIS and benign/normal structures.

Certain methods to detect, segment and classify nuclei of digital histopathological images are reviewed and discussed in [18]. This work discusses about the automated approaches that could minimize the human interference with clinical data. The pathological studies are carried out for various cancer prediction and grading applications meant for several human body parts. This work presents a general view of different techniques such as nuclei localization, extraction, feature computation and classification techniques meant for histopathology images for H&E images.

In [19], a robust extraction of overlapping cells in histopathological specimen on the basis of parallel seed detection and repulsive level set is presented. This work presents a novel algorithm, which could differentiate between cells in H&E breast TMA specimens being collected with a standard RGB camera. This algorithm employs a single-path voting and mean-shift clustering initially. The outline of every cell is acquired by employing an interactive model based level set algorithm.

An automated learning model for strong nucleus segmentation is presented in [20]. A learning framework is presented to carry out automated nucleus extraction. This work is based on deep Convolutional Neural Network (CNN), which forms a probability plot and a merge operation is carried out. A segmentation algorithm is then employed to extract nuclei with the help of a selection-based sparse shape model and a local repulsive deformable model.

A cancer detection scheme with multiple neural networks is presented in [21]. This work presents a portable desktop prototype device for presenting an accurate neural network classification of malignant and benign tissues. This work is carried out by six varied Back Propagation Neural Networks (BPNN).

An automated feature discovery structure relies on class oriented dictionaries is presented in [22], which makes classification and disease grading made possible for histopathological images. The proposed Discriminative Feature-oriented Dictionary Learning (DFDL) method trains the class-specific dictionaries with respect to sparsity constraints and the learned dictionaries indicates a new image sample through a dictionary with respect to the class identity of a specific sample.

Encouraged by the existing literature, this work presents a mitotic cell classification system with minimized false positive and negative rates. The proposed approach is elaborated in the following section.

III. PROPOSED MITOTIC CELL CLASSIFICATION SYSTEM BASED ON MACHINE LEARNING ALGORITHM

This initial part of the section outlines the proposed approach followed by which the proposed work is elaborated phase-wise. The overall view of the proposed classification system is shown in figure 1.

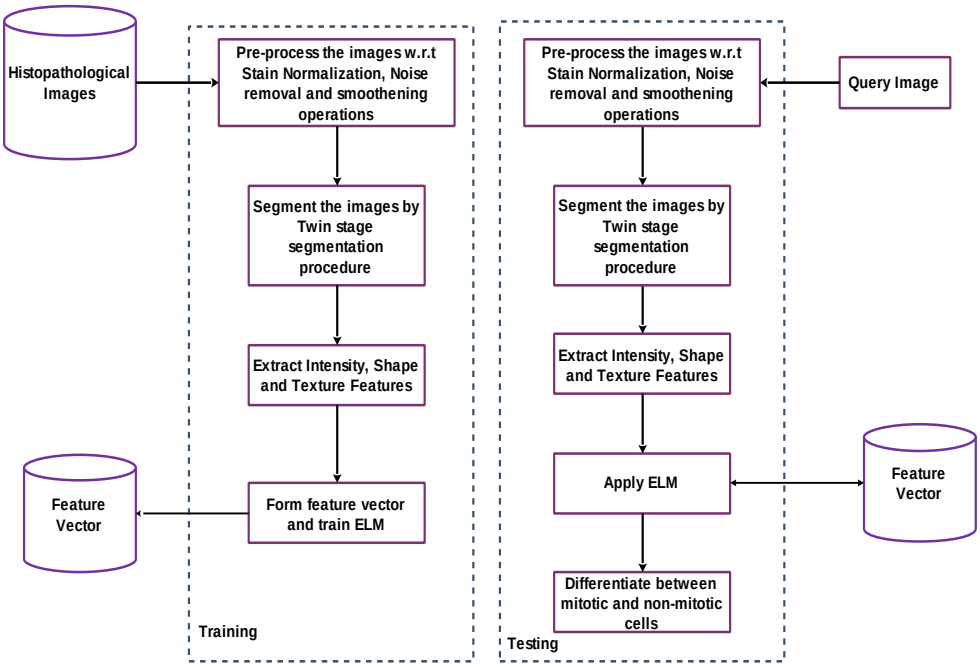

Fig.1. Overview of the proposed work

3.1 Outline of the Proposed Model

The aim of this article is to differentiate between the mitotic and non-mitotic cells from the breast cancer histopathological images. Due to the advancement of medical science and technology, computer aided systems become popular in disease diagnosis. The main advantages of computer aided systems are it demands minimal human intervention and it assists the healthcare professionals better. The accuracy of the system can be improved, as the diagnosis is performed by double checks. The computer aided systems rely on advanced image processing activities such as histopathological image pre-processing, nuclei extraction, feature extraction and classification. The image pre-processing activity intends to normalize stains, eiminate noise and smoothen the image. The nuclei are extracted by employing twin-stage segmentation process in which the final segmentation stage refines the roughly segmented image. The potential features are then extorted from the extracted nuclei and the mitotic cells are differentiated by employing ELM classifier.

3.2 Histopathological Image Pre-processing

The purpose of pre-processing phase is to manipulate the images for the forthcoming image processing activities. The better the pre-processing, the better is the performance of the image processing algorithm. Considering this fact, the proposed approach focuses on stain normalization, noise removal and texture smoothening. All these activities make the image content distinguishable, while preserving the details of an image. The sample pre-processed images are displayed in figure 2.

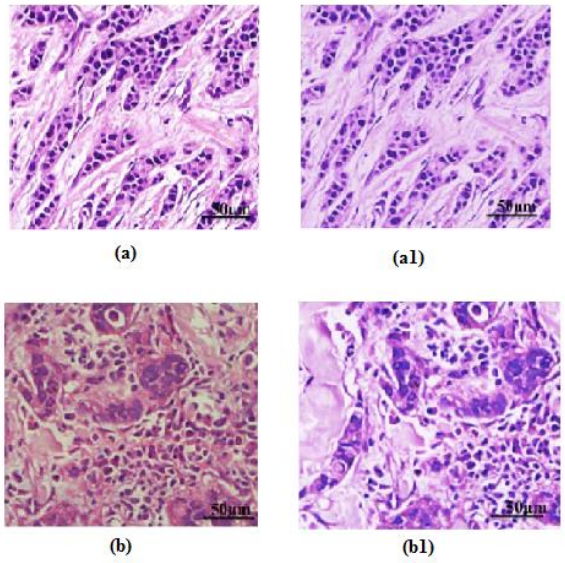

Fig.2. Sample pre-processed images after stain normalization

The histopathological images are observed with inconsistent staining, which hides the minute details of the image. This work normalizes the stains present in the histopathological images by employing the technique in [23]. This work obtains the colour information from every pixel for generating probability maps with respect to each stain. Two stains are involved in this work, which are H and E.

The probability maps helps in assuming the colour involved in every stain image and all the operations are carried out with respect to pixels. By following this way, the stains are normalized and the noise removal is carried out by Gaussian filter [24]. The Gaussian filter is employed, as it denoises the image while preserving the edges. The Gaussian filter is a two dimensional convolutional operator which shows bell shape as given in the following equation.

$$I(x,y) = \frac{1}{\sqrt{2\pi\sigma^2}} exp\left(\frac{\left(x-\frac{wd}{2}\right)^2+\left(y-\frac{wd}{2}\right)^2}{2\sigma^2}\right) \quad (1)$$

In the above equation, x and y are image pixels, wd is the size of the window and σ is the standard deviation of the filter. The image texture is then smoothened with the help of Adaptive Median Filter (AMF). The AMF smoothens the image without disturbing the details of an image, especially the edges. The AMF detects the noisy pixel by matching the processing pixel against the surrounding pixels. Suppose when an unmatched pixel is identified with respect to surrounding pixels then the unmatched pixel is replaced by the median value of the surrounding pixels. As the filter is adaptive by nature, the size of the window is not static, as in the case of standard median filter. Hence, the histopathological images are pre-processed by performing stain normalization, noise removal and texture smoothening of images. When the pre-processing phase is accomplished, the nuclei extraction is performed, which is as described in the following section.

3.3 Nuclei Extraction by Twin-Stage Segmentation Process

The proposed work extracts nuclei from the images by carrying out twin-stage segmentation process, which relies on a rough and fine segmentation processes. The rough segmentation procedure considers both the edges and the details of an image. Initially, the outlines of nuclei are represented by the level set method, which is based on the varying energy function as in equation 2 [24].

$$E(\emptyset) = -W_1 \int_{ID} (Im - GL)HF(\emptyset)did + W_2 \int_{ID} GR|\nabla HF(\emptyset)|did \quad (2)$$

In the above equation, $\emptyset$ is the empty set of embedding function with respect to the contour C. Im is the image passed into the segmentation process, $HF(\emptyset)$ represents the Heaviside function and ID stands for image domain. GR is the image gradient which can be stated by $GR = GR(|\nabla|Im)$, W_1 and W_2 are the balancing attributes. The first part of the equation represents the image region, in which the term GL represents the grey level of the nucleus. Hence, this part allows the edges to include the areas with grey values greater than GL. The sample nuclei detected images are shown in figure 3. The second part of the equation is meant for the boundary and is the geodesic active contour function meant for level set. As this work handles colour images, the RGB gradients are calculated in the place of greyscale gradients. Hence, $E(\emptyset)$ is altered such that the RGB components are considered. With this function, the nuclei are segmented roughly and normally, the shape of nuclei is ellipse as cited in [25]. However, the nuclei cannot be perfectly detected with this function due to the overlap. This issue can be addressed by considering both the global and local information of the area, as given in equation (3).

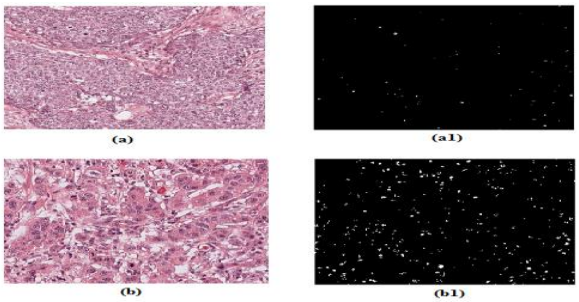

Fig.3. Sample nuclei detected images

$$L_i = \int_{I(CN)} (AF(I) - I - v_1)^2 dCN + \int_{O(CN)} (AF(I) - I - v_2)^2 dCN \quad (3)$$

In the above equation, $AF(I)$ is the average filter and the average intensities with respect to the inner $I(CN)$ and outer areas of contour $O(CN)$ are represented by $AF(I) - I$. Hence, the issue of overlap can be treated by considering both the inner and outer areas of the contour. This idea results in effective extraction of nuclei from the images and now the extracted areas are treated with the feature extraction phase.

3.4 Feature Extraction

When the nuclei are extracted, the classifier must be trained by some effective mean such that the classifier could distinguish between the involved classes. Features of the image are the most important metric for the classifier to learn about the samples of all classes. This work focuses on three sets of features based on intensity, shape and Haralick texture features. The intensity based features being considered are mean, variance, skewness and kurtosis. The shape features of this work are area, perimeter and solidity. The haralick texture features are then considered with the count of 14. The features are extorted in four angles such as $0°, 45°, 90°, 135°$. Finally, all the extracted features are averaged and the total count of features is 21. With the extracted features, the ELM classifier is trained, as presented in the coming section.

3.5 ELM Classification

ELM is utilized to classify between the mitotic and non-mitotic candidates, owing to its faster learning ability [26]. Initially, the ELM is trained with the feature set, which is explained in the previous section. Sample detected mitotic cells are shown in the following figure 4.

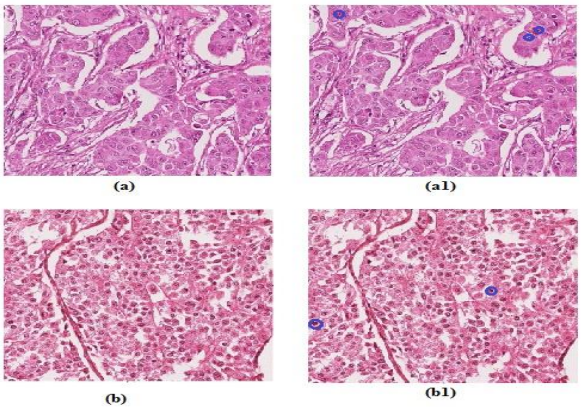

Fig.4. Sample mitotic cell detected images

Consider A as the training samples which are denoted by (x_i, y_i); where $x_i = [x_{i1}, x_{i2}, \dots x_{is}]^q \in Im^s$; where s is the dimension of the training representatives. $b_i = [b_{i1}, b_{i2}, \dots b_{it}]^q \in Im^t$ indicates the i^{th} class label of dimension t. Here t is the number of classes and it is set to two. A Single hidden Layer Feed-Forward Neural Network (SLFN) is constructed by an activation function $act(x)$ and R neurons, which is denoted by

$$\sum_{i=1}^{R} \beta_i act(wt_i . a_j + e_i) = b_i; i = 1,2, \dots, n \quad (4)$$

In equation (4), wt_i is the weight of the feature vector and e_i is the bias of the i^{th} hidden neuron. Let Hd_l be the ELM's hidden layer output matrix, where the i^{th} column of Hd_l denotes the i^{th} hidden neurons output vector by taking the inputs $a_{i1}, a_{i2}, \dots, a_{in}$.

$$Hd_l = \begin{bmatrix} act(wt_1 . a_1 + e_i) & \dots & act(wt_v . a_1 + e_G) \\ \vdots & \vdots & \vdots \\ act(wt_1 . a_n + e_i) & \dots & act(wt_v . a_n + e_G) \end{bmatrix} \quad (5)$$

$$\beta = \begin{bmatrix} \beta_1^q \\ \vdots \\ \beta_G^q \end{bmatrix} \quad (6)$$

$$B = \begin{bmatrix} b_1^T \\ \vdots \\ b_n^T \end{bmatrix} \quad (7)$$

The matrix format is denoted by

$$Hd_l \beta = B \quad (8)$$

The output samples are computed by norm least-square solution, as presented in the following equation.

$$\beta = Hd_l{}^{\dagger} B \quad (9)$$

In the above equation, $Hd_l{}^{\dagger}$ is the HL's Moore-Penrose generalized inverse. The ELM training phase is done by computing equation (9). In the testing phase, the output matrices are computed and added together for finding the greatest value against the row. The output matrix is computed by

$$b_{testing}(z) = Hd_{l_{testing}}(z) \times \beta_z \quad (10)$$

The z value of this work is 14 and this value is chosen by trial and error method. The performance of the proposed approach begins to deteriorate, when the value of z exceeds 14. Hence, the ELM classifier distinguishes between the mitotic and non-mitotic cells. The performance of the proposed approach is presented in the following section.

IV. RESULTS AND DISCUSSION

The performance of the proposed mitotic cell detection and classification approach is simulated in MATLAB 2013a version on a stand alone computer with 8 GB RAM. The performance of the proposed work is tested on a public dataset namely Mitos [27] and the size of the image is $1376 \times 1539 \times 3$. This dataset contains the High Power Field (HPF) images of breast tissues, which are stained with Hematoxylin and Eosin. The classifier is trained in such a way that the mitotic areas with the probability of more than 0.6 are considered as mitosis. Sixty percent of the data are utilized for training and the rest of forty percent is employed for testing. The training set declares the cell as mitotic or non-mitotic by considering the ground truth image. The performance of the work is compared with the existing approaches such as deep belief networks [13], neural networks [21] and Dictionary Learning [22] in terms of accuracy, sensitivity, specificity and time consumption.

Published By:
Blue Eyes Intelligence Engineering
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The formulae for computing the performance metrics are as follows. The accuracy rate is the most significant metric of any classification algorithm, as it decides the correctness of the algorithm. The accuracy is calculated by

$$A = \frac{TP+TN}{TP+TN+FP+FN} \times 100$$

(11)

The sensitivity and the specificity rates of an algorithm should be as great as possible, which makes the classification results accurate as computed by

$$Sen = \frac{TP}{TP+FN} \times 100$$

(12)

The specificity rate should be maximal, as it proves the capability of the classification algorithm that it can distinguish between the mitotic and non-mitotic cells.

$$Spec = \frac{TN}{FP+TN} \times 100$$

(13)

The F-measure rate is computed by eqn.14.

$$F_m = \frac{2 \times Sen \times Spec}{Sen+Spec}$$

(14)

In the above equations, TP, TN, FP, FN stand for true positive, true negative, false positive and false negative rates. Though achieving greater accuracy rate is the main target of several classification algorithms, better accuracy may be attained by involving greater false positives in certain cases. The false positive and false negative rates impact over the sensitivity and specificity rates, which are meant for better reliability. Greater sensitivity and specificity rates indicate the occurrence of minimal FN and FP rates. The experimental results of the proposed work are presented in the following figure 5.

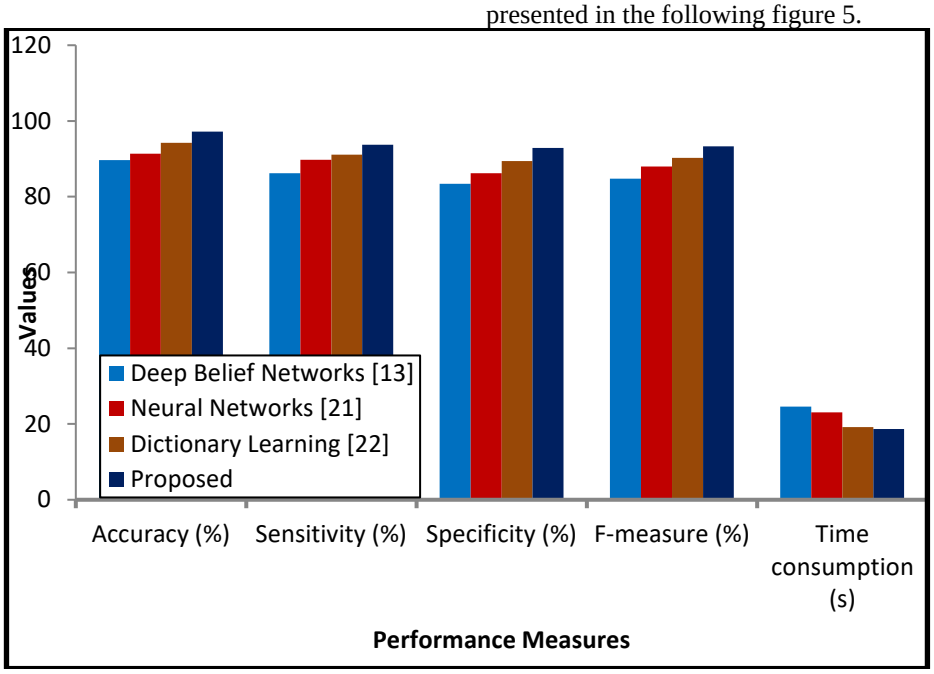

Fig.5. Performance analysis

From the experimental results, it is shown that the proposed work proves better performance, when compared against the existing approaches. The main cause for this performance is the effective pre-processing, better segmentation and strong set of features and better classification. This work pre-processes the histopathological images by considering stain normalization, noise removal and texture smoothening. Twin layered segmentation is employed, such that the refined result is provided by the nuclei extraction process. The crispy set of features is extracted and the ELM is trained, which enables it to differentiate between the mitotic and non-mitotic cells. The following section concludes the paper.

V. CONCLUSION

This article presents a mitotic cell classification system meant for histopathological images of breast cancer. This proposed work relies on four important phases such as histopathological image pre-processing, nuclei extraction, feature extraction and classification. The pre-processing is the most basic activity, which attempts to normalize the stains, denoise and smoothen the texture of an image. The nuclei are extracted by a twin stage segmentation process, which considers both the boundary and the regions of the image. The shape, intensity and Haralick texture features are extracted from the images and the ELM classifier is employed for distinguishing between the mitotic and non-mitotic cells. The performance of the proposed work is evaluated in terms of accuracy, sensitivity, specificity and time consumption rates. In future, this work plans to employ three dimensional images for mitotic cell classification. In addition to this, multispectral images can also be employed, to check the work performance.

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