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Histopathological Image Classification Scheme for Breast Tissues to Detect Mitosis

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Abstract : ***Histopathological images are widely utilized by the pathologists to determine the severity of the cancer. Usually, the pathologists analyse histopathological images manually, which demands more time and effort. The quality of image interpretation can be improvised with the help of a computerized assisting system for image analysis. This idea enhances the accuracy of the system as the computerized system helps in making decisions, which the pathologist may recheck. Understanding the benefits, this article presents a histopathological image classification scheme meant for breast tissues in detecting the mitotic cells. The goal is achieved by pre-processing the image by performing top and bottom hat transformation followed by stain normalization. The nuclei are then located with the help of Localized Active Contour Model (LACM) combined with Lion Optimization (LO) algorithm. The shape, statistical and texture features are extorted from the areas of interest and the differentiation of mitotic cells from the non-mitotic ones is performed by Support Vector Machine (SVM) classifier. The work efficiency is tested with respect to the standard performance measures such as accuracy, sensitivity, specificity and time consumption.***

Keywords : ***Histopathological image, breast tissue, mitotic cell detection, classification.***

I. INTRODUCTION

Breast cancer is the commonest kind of cancer in women population, which affects about 2.1 million cases every year [1]. The World Health Organization (WHO) has reported that about 2.1 women is caught by breast cancer every year and the mortality rates caused by breast cancer is estimated as 15%, out of all cancer types [2]. It is terrible to have greatest mortality rates, in spite of the technological improvements in medical science. The technology advancements in medical science pave way for the digital analysis of medical records. For instance, medical diagnostic imaging techniques such as Magnetic Resonant Imaging (MRI), Computed Tomography (CT), X-rays are so popular and these imaging techniques are enhanced day-by-day for clear-cut analysis. Mammography is so popular with respect to breast cancer screen examination; however the severity of the disease can be ranked only with the help of biopsy. Biopsy is a medical procedure, which intends to extract the sample cells or tissues of the suspected part for better diagnosis. Basically, the so collected breast tissues are analysed with the help of microscope by the pathologists. However, manual analysis consumes more time for carrying out analysis and it is beneficial for the pathologists when the computerized system could assist for making final decisions. This idea conserves time and the quality of results can also be improved, as the final decision is made upon the prior assistance of the computerized system. The computerized decision making system utilizes histopathological images for deep analysis.

Histopathological images are so popular now-a-days, owing to its clarity and presentation of intricate structure of the tissues. However, analysing the histopathological images is so complex, as the images are completely filled up with cell components. In order to rank the severity of cancer, the mitotic cells are needed to be detected initially and it is possible only when the nucleus is identified. Usually, the tumour cells are graded by the Nottingham International Grading System (NIGS) [3-5] and to grade the cancer the mitotic cells are needed to be detected first. Hence, automated mitotic cell detection system is confronted by several challenges such as complex structure, clumsy packing of cell components, irregular staining effects and so on.

Recognizing the benefits of mitotic cell detection and the challenges placed in front of it, this work presents an automated mitotic cell detection system, which is made possible by four noteworthy processes namely histopathological image pre-processing, nuclei segmentation, feature extraction and classification. The initial process is the most fundamental step, which intends to prepare the images for effective analysis. The nuclei segmentation is very important, such that the mitotic cells can be detected. The features are then extracted and the classifier is trained with the collected features. Finally, the classifier distinguishes the mitotic from the non-mitotic cells.

The histopathological image pre-processing step normalizes the unevenly distributed stains and prepares the images for further analysis. The nuclei are then extracted from the images and the potential features are extracted from the image. Finally, the SVM is imparted knowledge by the computed feature vector, which equips the SVM to differentiate between the mitotic and non mitotic cells. The highlighting points are presented below.

- The LACM is employed for segmenting the cells, as it can deal with varying shapes. However LACM struggles to detect the initial curve and this issue is solved by LO algorithm.
- The SVM classifier is trained with the potential features and the mitotic and non-mitotic cells are classified.
- The False Positive (FP) rates of the proposed mitotic cell classification system are quite minimal, due to the attainment of better segmentation and classification processes.

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The rest of this article is prepared in the following way. The recent review of literature is discussed in section 2 and the proposed mitotic cell classification system is explained in section 3. The performance of the proposed work is evaluated in section 4 and the final section concludes the article.

II. REVIEW OF LITERATURE

This section of the article studies and discusses about the recent related literature with respect to mitosis detection in histopathological images of breast tissues.

In [6], a mitosis identification scheme meant for invasive breast cancer grading over histopathological images is proposed. The count of mitosis in histological images is quite important in the breast cancer grading system and this work employs the area morphological scale space for segmenting the cells. The scale space is formed by controlling the scales by maximizing the relative entropy among the cells and background for better segmentation.

A self-regulating mitotic cell detection and segmentation technique for multi-spectral histopathological images is proposed in [7]. This work is based on three important modules such as discriminative image generation, mitotic cell candidate detection with segmentation and classification. The first module obtains the image with the help of Linear Discriminant Analysis (LDA) and the second module detects the mitotic cells by means of Bayesian modelling. The third module extracts the features from the mitotic cells and the classification is done to differentiate between the mitotic and non-mitotic cells.

In [8], a deep learning approach meant for detecting mitosis in breast cancer histology images is presented. This work utilizes Convolutional Neural Networks (CNN) with additional crowdsourcing layer namely AggNet. A multiple classifier system for automated mitosis detection in breast histopathology images is presented by means of deep belief networks in [9]. This work segments the cell nuclei by employing Krill Herd (KH) algorithm and the deep belief network based multiple classifier system is presented to discriminate between the mitotic and non-mitotic cells.

A mitosis detection scheme for Hematoxylin (H) and Eosin (E) based on convolutional networks is presented in [10]. This work trains the CNN by following three tasks. Initially, the images are analysed by means of mitotic activity with respect to phosphohistone-H3 restained slides and registration for building a base model for mitosis detection. The data augmentation strategy then creates a practical stain variation by altering the color channels, with which the training is accomplished. Finally, the knowledge is applied to minimize the computational requirements of the mitosis detection.

An automated detection of breast cancer mitotic cells by combining the features based on texture, statistics and innovative mathematics is presented in [11]. This work employs Complete Local Binary Pattern (CLBP) for extracting the texture features and the mathematical features are extracted by Statistical Moment Entropy (SME) and Stiffness Matrix (SM). All these features are extracted and fused to distinguish between mitotic and non-mitotic cells.

The emerging strategies in targeting mitosis are discussed in [12]. This work discusses about the past cell cycle targeted therapeutics and agent refinement for improving the anti-mitotic strategies. Additionally, the pre-clinical results about anti-mitotic approaches and the therapeutic hang-up of mitotic checkpoints are presented. In [13], a technique to detect and classify breast cancer with the help of whole slide histopathology images based on deep convolutional networks is presented. This work performs classification over breast biopsies in five different classes. A saliency detector with four convolutional neural networks is trained with the samples and the image patches are classified into five categories such as non-proliferative or proliferative changes, atypical ductal hyperplasia, ductal carcinoma in situ and invasive carcinoma.

A general overview and future trends of mammography and breast histology based on deep learning approach are discussed in [14]. This work summarizes the recent CAD systems on the basis of deep learning meant for mammography and breast histopathology images. This work explains the relationship between mammography and histopathology phenotypes by considering the biological aspects. Additionally, the challenges faced by the medical diagnostic systems are reviewed. In [15], a weakly supervised mitosis detection scheme for breast histopathology image is proposed. This work detects the mitosis on breast histopathology images by constructing a deep segmentation network for generating segmentation map. A filtering approach is then employed for producing the detection results. The segmentation framework is trained by the concentric loss function. A mitosis detection scheme based on deep detection, segmentation and verification namely DeepMitosis is proposed in [16]. This work proposes a method to identify the mitotic cells in the histopathological slides by employing a novel multi-stage deep learning framework. This work utilizes a deep segmentation network for producing a mitotic portion, when a weak label is provided and the mitosis is detected by deep network. Finally, the detection accuracy is enhanced by a deep verification network

A cell mitosis detection scheme based on deep neural networks is presented in [17]. The proposed is named as F3D-CNN and is directly trained from the data without depending on any domain dependent features. The F3D-CNN filters the mitosis events by considering the static information in every image and discriminate the candidates by means of spatiotemporal information from image sequences. In [18], an automatic mitosis detection scheme for breast histopathology images based on CNN and deep transfer learning. This work trains the CNN that is altered by combining the random forest classifier with the initial fully connected layers. The features are extracted from the patches of nucleus and the class labels of the nuclei are defined. The altered CNN classifies all the identified cell nuclei with minimal training requirement. An effective deep learning scheme is presented for mitosis detection in [19]. The architecture of this work is based on 5 layers of convolution, 4 layers of max-pooling, 4 rectified linear units (ReLU) and 2 fully connected layers. ReLU is utilized after every convolution layer as an activation function. Dropout layer is utilized followed by the first fully connected layer to eliminate overfitting. Handcrafted features are formed by the morphological, textural and intensity features.

In [20], a self-regulating mitosis detection in histopathology images based on complex wavelet coefficients with non-gaussian modelling is presented. This work decomposes the strong mitotic candidates into multi-scale forms by employing an undecimated dual-tree complex wavelet transform. Two non-Gaussian models (the generalized Gaussian distribution (GGD) and the symmetric alpha-stable (SαS) distributions) are utilized for designing the model of the tailed nature of wavelet marginal distributions.

In [21], the algorithms meant for mitosis in breast cancer histopathology images are assessed. This work considers a dataset with 23 different cases with more than 1000 annotated mitoses. This work compares and contrasts about 11 different existing algorithms. A semantic driven mitosis detection scheme in digital histopathology is presented in [22]. This work is based on knowledge representation and reasoning. The concept of ontology is utilized in this work.

Encouraged by the existing approaches, this work attempts to present a mitotic cell detection and classification scheme for histopathological images of breast cancer. The proposed approach is explained in the following section.

III.PROPOSED MITOTIC CELL CLASSIFICATION SYSTEM FOR HISTOPATHOLOGICAL IMAGES

This section elaborates the proposed approach meant for classifying the mitotic cells of breast cancer in histopathological images. The overview of the work is presented in the following section.

3.1 General Idea of the Work

Breast cancer is one of the serious mortal diseases and the mortality rates due to breast cancer increases year by year. Though the medical science has attained reasonable advancements, the medical facilities fail to reach many patients all through the world. Periodical screening alone can help in reducing the mortality rates due to cancer. With respect to breast cancer, the process of screening is usually carried out by digital mammography. Numerous image processing based applications analyse the mammograms for detecting the presence of any abnormality. However, abnormalities can only be detected through mammograms and the severity of the cancer cannot be predicted.

To determine the severity of the cancer, biopsy is performed and the tissues are examined under microscope. The histopathological images serve best in determining the severity of cancer, however it is difficult to make obvious decisions owing to the intricate details of the image. Recognizing the potential of histopathogical images, this work intends to classify between the mitotic and non-mitotic cells. Though the objective is to classify between the mitotic and non-mitotic cells, it cannot be achieved in a single stretch. This is because, classification can be performed only when the nuclei are detected from the complex histopathological image. The overall flow of the work is depicted in figure 1.

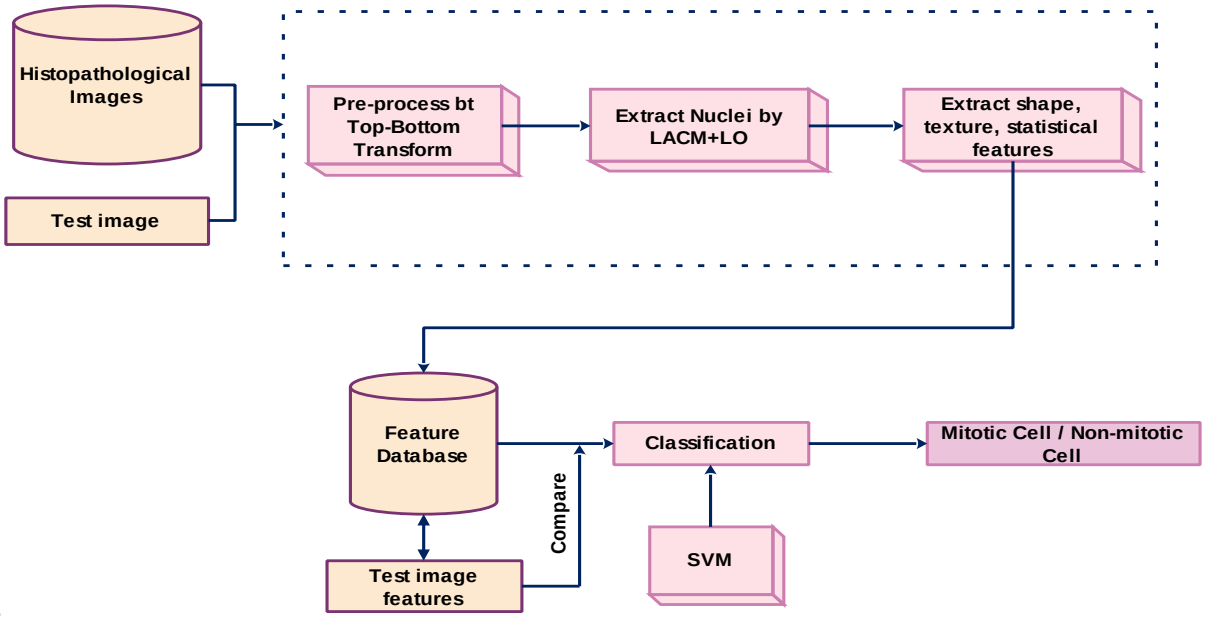

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Fig.1. General flow of the proposed work

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The objective of the work is attained by segregating the work into four vital modules and they are histopathological image pre-processing, nuclei segmentation, feature extraction and decision making. The image pre-processing module of this work aims to normalize the stains in the image for better image analysis. The nuclei are then extracted by Localized Active Contour Model (LACM) combined with Lion Optimization (LO) algorithm for initial parameter selection. The features are then extracted to train the Support Vector Machine (SVM) classifier. All these modules are explained one after the other.

3.2 Histopathological Image Pre-processing

This work applies the top and bottom transformation as in [1], to distinguish between the foreground and background areas of the histopathological image. As soon as the transformation is done, curvelet is applied on it. Curvelet is an improvised version of ridgelet transform (RT_f) and is denoted by

$$RT_f(a,b,\theta) = \int\int \psi_{a,b,\theta}(x,y) I(x,y) dxdy \quad (1)$$

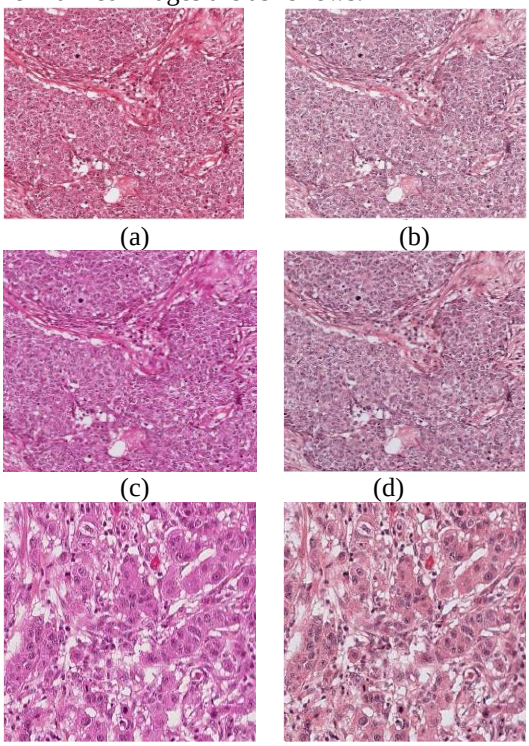
In the above equation, the input image is denoted by $I(x,y)$ and ψ is the ridgelet function which is computed by the following equation (2).

$$\psi_{a,b,\theta}(x,y) = a^{-1/2}\psi\left(\frac{x\cos\theta + y\sin\theta - b}{a}\right) \quad (2)$$

The curvelet sub-bands of the input image are computed by modifying the ridgelet in various scales and orientations. The sub-bands of curvelet are then analysed for energy by the following equation.

$$E(a,\theta) = \sum_x \sum_y |Sb_{a,\theta}(x,y)| \quad (3)$$

The resultant pre-processed histopathological images after performing top and bottom hat transformation and normalized images are as follows.



(a) (b) (c) (d) (e) (f)

Fig.2. (a,c,e) Input histopathological images (b,d,f) Pre-processed histopathological images

The above presented figure shows the original input and the pre-processed histopathological images. The stain normalized images are shown in figures 1a, 1d and 1f. Hence, the process of pre-processing makes the cell components clearly distinguishable. When the pre-processing operation is performed, the nuclei are extracted by the following segmentation process.

3.3 Nuclei Segmentation by LACM and LO

Normal segmentation procedure does not work for histopathological images, due to its tight content package. However, LACM performs well in detecting the nuclei being present in the image. Usually, the nuclear membrane tends to fade in the initial stages of mitosis, such that the nuclei and the background areas of the image are disseminated together. This makes the process of nuclei detection tougher and hence the choice of initial points helps in tackling the scenario, which is done by LO.

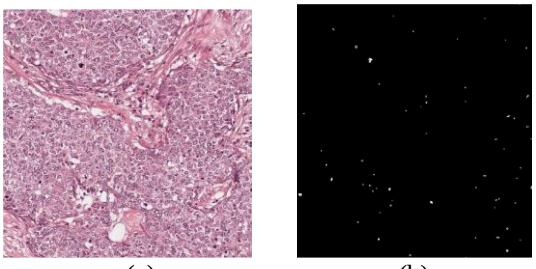
The LO algorithm is a metaheuristic algorithm, which is based on the real mannerism of lions. By nature, the lions are communal animals, which are classified under two classes such as local lions and roving lions [23, 24]. The local lions dwell by creating groups called pride. Approximately, each and every pride is composed of four to five lionesses, their cubs with one or two matured lions.

When the male cubs mature, then they are driven out from the pride. These ejected matured male lions roam around as roving lions. A potent roving lion may bother the local lion at any time just to get into the pride. Suppose, when the roving lion wins over the local lion, then the defeated lion is ejected from the pride. Hence, the pride can accommodate only the fitter individuals and the rest are ejected for every time period. Based on this idea, the feasible thresholds are detected by the LO algorithm and is presented as follows.

Proposed Nuclei Detection algorithm

```
Input: Pre-processed images
Output: Nuclei detection
Begin
For all images
 Initialize the population of lions and other parameters;
 Circulate the prey;
 For each pride of lions
  Randomly select a lioness for hunting;
  Compute the fitness of the lions by eqn.9 in [1];
  Compute the probability of success by eqn.10 in [1];
  Arrange the fitness values in ascending order;
  Disregard the lions with greater value;
 Apply LACM;
   End for;
  For each roving lion
   Perform the same steps as in pride of lion;
   Compute fitness value;
   Compare the fitness value of roving lion and the pride of
lion;
    If (fitness(roving lion) < fitness(lion in pride)
     Exchange the lion to pride;
     Discard the roving lions with greater value;
Apply LACM;
Compare and swap the lions if better value is found;
      Save the best solution;
    End if;
   End for;
 End;
While(termination condition not met)
End;
```

The nuclei are detected and extracted with the help of the fitness value, which indicates the local energy levels with respect to the contour. With this idea, the nuclei are detected and segregated, as shown in figure 3.



(a) (b)

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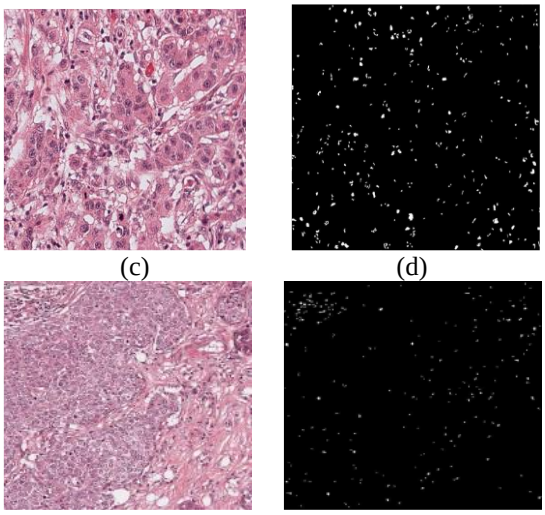


(c) (d)

(e) (f)

Fig.3. (a,c,e) Pre-processed images (b,d,f) nuclei detected images

Hence, the nuclei are detected and segmented with the help of the combination of LACM and LO algorithm. Now, the process of feature extraction proceeds as follows.

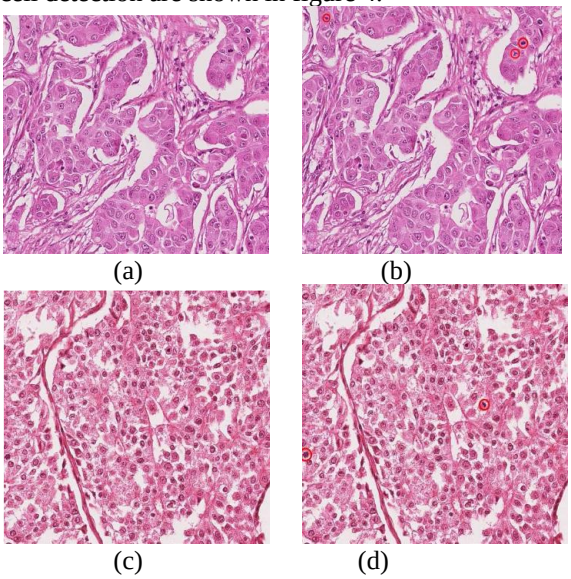
3.4 Feature Extraction

Features play an important role to distinguish between the mitotic and non-mitotic cells. The feature extraction of this work is based on three sets of features such as shape, texture and statistical features. Fifteen different shape based features such as area, perimeter, eccentricity, centroid and so on are extracted [25].

The texture features are extracted by means of 22 features of Gray Level Co-occurrence Matrix (GLCM) [26] and 11 features of Gray Level Run Length Matrix (GLRLM) [27]. Finally, 10 first and second order moments which include mean, standard deviation, skewness, kurtosis, energy, entropy and median are computed. For every color channel, 58 features are computed and hence a total of 174 features are extracted. The so extracted features are utilized to train the SVM classifier.

3.5 SVM Classification

SVM is a popular classification algorithm which distinguishes between the entities by means of a boundary, which is termed as hyperplane. This work employs a binary SVM, as this work involves two classes such as mitotis and non-mitosis cells. Some of the sample images for mitotic cell detection are shown in figure 4.



(a) (b)

(c) (d)

Fig.4. (a,c) Original images (b,d) Mitosis cell detected images

The proposed work utilizes a non-linear kernel based on Radial Basis Function (RBF) kernel function $K(a_i, a_j)$, which is applied to a higher dimensional feature space FS related to the input space Rd through the mapping, as defined in [28].

$$K\ (a_i, a_j\ )\ =\ exp\ \left(\frac{-\|A_i - A_j\|^2}{2\sigma^2}\right) \quad (4)$$

The SVM detects the most feasible hyperplane for separating the entities in the feature space FS of the train samples, such that $\alpha \in Rd$ and corresponding classes can be defined as $b \in \{-1, 1\}$ as denoted by

$$W(\alpha) = \sum_{i=1}^{N} \alpha_i - \frac{1}{2}\sum_{i=1}^{N} \sum_{j=1}^{N} \alpha_i \alpha_j b_i b_j k(A_i A_j) \quad (5)$$

Based on the restrictions $\sum_{i=1}^{N} \alpha_i b_i = 0$ and $0 < \alpha_i < c < b_i$. Here, the attribute C helps in mentioning the threshold to distinguish between the entities. The distance between a sample and the hyperplane is measured as the output of the SVM.

$$f(a) = \sum_{i=1}^{N} \alpha_i k(a_i, a) + b \quad (6)$$

Where the sample a is alloted to the mitosis class if $f(a) > 0$.

In the proposed work, the positive class is mitotis and negative class indicates non-mitotic cells. The optimization objective function for Support Vector Machines is described as

$$min_\theta\ C \sum_{i=1}^{m} [b^{(i)} cos\ t_1\ (\theta^T a^{(i)}) + (1 - b^{(i)})\ \cos t_0\ (\theta^T a^{(i)} + \frac{1}{2} \sum_{i=1}^{n} \theta^2 \quad (7)$$

Suppose, when the parameter vector 'θ transpose times a'is greater or equal than 0, it is classified as positive else it is set as negative. The RBF kernel is employed for training and testing dataset. While training the classifier, the parameters C (regularization parameter) and gamma (parameter of RBF) are focussed.

Greater value of C results in the lower bias and greater variance. Selecting a smaller C value tends to increase the bias and lower variance respectively. When choosing the gamma value, larger gamma value leads to features greater bias and lower variance and the smaller gamma works opposite, as cited in [29]. Hence, the mitotic and non-mitotic cells are classified and the performance of the work is analysed as follows.

4. RESULTS AND DISCUSSION

The performance of the proposed mitotic cell detection and classification approach is implemented 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 [30] 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 mitotis. Sixty percent of the data are utilized for training and the remaining forty percent is employed for testing.

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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 mitosis detection [21], CW [20] and RF [1] in terms of accuracy, sensitivity, specificity and time consumption. 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 rate is calculated by

$$A = \frac{TP+TN}{TP+TN+FP+FN} \times 100 \quad (8)$$

The sensitivity and the specificity rates of any algorithm must be greater, such that the classification results are reliable and is computed by

$$Sen = \frac{TP}{TP+FN} \times 100 \quad (9)$$

The specificity rate must be preferably greater, because it shows the potential of the classification algorithm that it can differentiate between the mitotic and non-mitotic cells.

$$Spec = \frac{TN}{FP+TN} \times 100 \quad (10)$$

The F-measure rate is computed by the following equation.

$$F_m = \frac{2 \times Sen \times Spec}{Sen+Spec} \quad (11)$$

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.

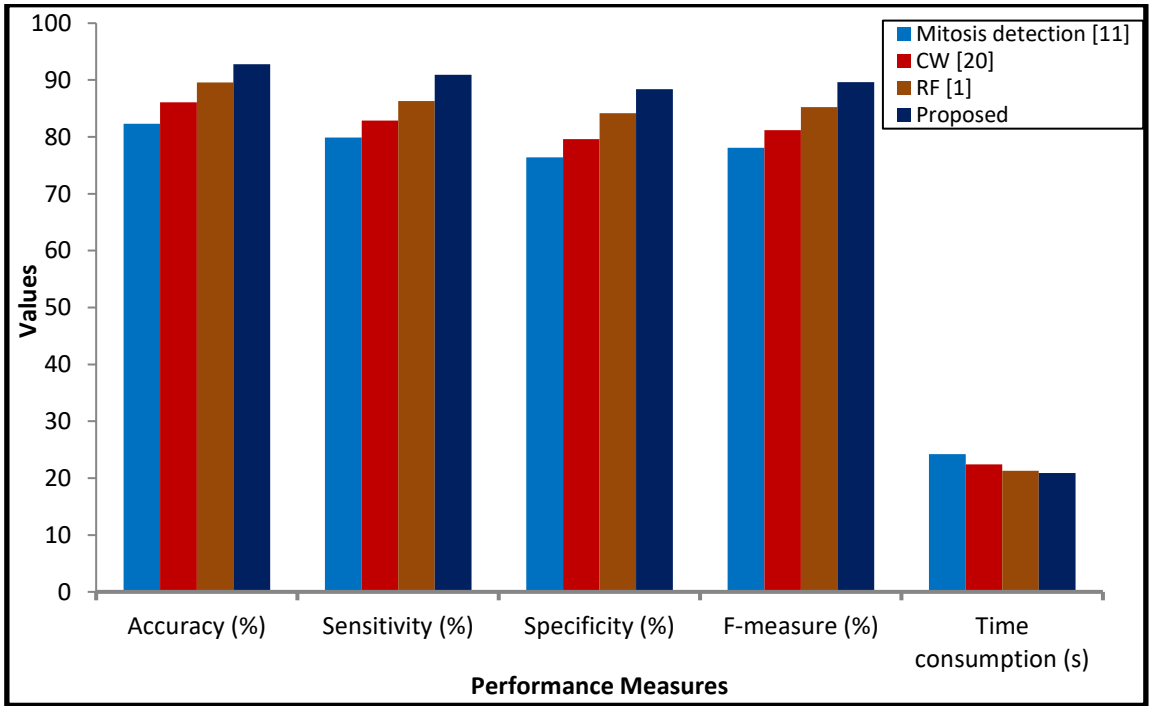

Fig.5. Performance evaluation of the proposed work with the existing approaches

From the experimental analysis, it is observed that the performance of the proposed work is satisfactory in terms of all the considered performance measures. The proposed work proves better performance in detecting and classifying the mitotic cells with the help of appropriate pre-processing and nuclei extraction technique. As the initial stages of the work performs better, the crispy set of features are extracted from the detected nuclei and the SVM performs classification in recognizing the mitotic cells. Hence, the performance of the work is satisfactory and the paper is concluded in the following section.

5. CONCLUSIONS

This paper presents a system to differentiate between mitotic and non-mitotic cells of histopathological images of breast tissues. This work utilizes histopathological images for better analysis and decision making. Understanding the difficulty associated with the histopathological image processing, this work organizes itself in four major modules such as pre-processing, nuclei extraction, feature extraction and mitotic cell classification. The performance of the mitotic cell detection is compared with the existing approaches and the performance of the proposed work is observed to be satisfactory. In future, this work is planned to be extended by considering the nuclei based features and the optimal features can be selected from the extracted features for training the classifier.

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