Automated Mitotic Cell Detection and Classification for Breast Cancer Histopathological Images

R. Geetha , M. Sivajothi

Abstract: ***Breast cancer tops the list of life-threatening disease with greater mortality rates for women population. However, the mortality rates caused by breast cancer can be minimized by inculcating periodical screening. Histopathological images are utilized by the pathologists for diagnosing or staging the cancerous growth. As the histopathological images are so intricate, it is quite difficult to analyse the images manually. Understanding the involved difficulty, this work presents an automated mitotic cell detection and classification for breast cancer histopathological images. The performance of the proposed approach is analysed in terms of standard performance measures such as accuracy, sensitivity, specificity and time consumption. The performance of the proposed approach outperforms the existing approaches.***

Keywords: ***Histopathological images, breast cancer, mitotic cell detection.***

I. INTRODUCTION

Cancer is one of the dangerous diseases being observed all through the world. Recent statistical reports that the mortal rates due to cancer is about 7,48,821 in the year 2018. Though there the cancerous growth can be detected in different organs such as oral cavity, lung, oesophagus, breast, cervix and so on. Among all these kinds of cancer, breast cancer is the leading type of cancer among women. The report states that about 14% of the cancer in women is observed to be breast cancer. The mortality rate of women owing to breast cancer is about 87,090 [1]. The entire women population suffers from this incessant disease.

However the mortality rate can be reduced to some extent, when the breast cancer is detected at an early stage by means of periodical screening. Recognizing the seriousness of this dreadful disease, the computer technology has rendered remarkable contribution to the medical science. The computer aided system helps in assisting the healthcare professional for diagnosing and treating various diseases [2].

As far as cancer is concerned, the biopsy sample is utilized for analysis and is usually attained with the help of histopathological images. The term histopathology is ‘histos’, ‘pathos’ and ‘logy’ refer to tissue, disease and analysis respectively [3]. Basically, the histopathological images are captured to analyse the biopsy in the digital format. These digitized images help in detecting the cell size and abnormalities found in the tissues.

Advanced image processing techniques pave way for detecting the abnormalities found in the histopathological images by employing image processing activities such as image pre-processing, segmentation, feature extraction and classification. The image pre-processing is the first and foremost step of any operation in image processing activity. The pre-processing phase aims to denoise or enhance the quality of images. The segmentation is the second important phase, which attempts to segregate the nuclei from the image and the potential features are extracted in the feature extraction phase. Finally, the classification or decision is made in the classification phase.

In the existing literature, there are several systems meant for detecting breast cancer, however the existing works based on histopathological images are scarce. Additionally, most of the existing approaches nuclear polymorphism, tubule formation and count of mitotic cells [4-14]. Mitosis is the most important process, which intends to decompose the cells and is the important measure to grade the severity of cancer. The mitotic cell detection is a complex process, as the mitotic cells present in histopathological images show varying colour, shape and texture features. Mitotic cells share more degree of resemblance with normal cells and lymphocytes. Hence, it is quite complex to detect mitotic cells from the histopathological images.

Understanding the necessity and benefits of mitotic cell detection, this article presents an automated system by extracting different potential features from the images. The proposed approach is based on four significant phases, which are histopathological image pre-processing, segmentation, feature extraction and classification. The images are pre-processed by employing top and bottom hat transformation. The nuclei are detected and segmented with the help of LACM and its parameters are set by Artificial Bee Colony (ABC) algorithm. The shape and textural features are then extracted, in order to ensure better mitotic cell detection ability. Some of the contributions of this work are as follows.

- The breast cancer detection techniques based on histopathological images are quite scarce in the existing literature and this work operates over histopathological images.
- The proposed work does not require any prior knowledge about the histopathological images.

Revised Version Manuscript Received on 22 December, 2018

R. Geetha, Research Scholar, Department of Computer Science, Manonmaniam Sundaranar University, Tirunelveli, Tamil nadu, India

Dr.M. Sivajothi, Associate Professor, Department of Computer Science, Sri Parasakthi College for Women, Courtallam, Tamil nadu, India

- It is difficult to detect mitotic cells from the histopathological images, as the histopathological images show intricate structure. This work utilizes the shape and textural properties of the images to distinguish between the normal and mitotic cells.
- All the processes involved in the proposed approach are automatic and the attributes of LACM is set by the bio-inspired algorithm ABC. This increases the reliability of the system.
- The performance of the proposed approach is satisfactory in terms of accuracy, sensitivity and specificity rates, when compared to the existing approaches.

The rest of the article is organized as follows. Section 2 discusses the related review of literature with respect to mitotic cell detection in breast cancer histopathological images. The proposed automated mitotic cell detection technique is elaborated in section 3 and the performance of the proposed approach is analysed in section 4. Finally, the concluding remarks of this article are summarized in section 5.

II. REVIEW OF LITERATURE

This section reviews the state-of-the-art related literature with respect to mitotic cell detection on breast cancer histopathological images.

In [15], the mitotic cells are detected in multispectral histopathological images. Initially, the mitotic and non-mitotic cells are taken out from the histopathological image. The training and the test samples with similar spatial and spectral properties are then obtained. Classifiers such as Support Vector Machine (SVM), Random Forests (RF), Naïve Bayes (NB), k-Nearest Neighbour (k-NN) are employed for training different clusters and the results are evaluated.

An automated mitotic cell detection and segmentation technique is proposed for multispectral histopathological images in [16]. This work is based on three different modules, which are discriminative image generation, mitotic cell detection and segmentation and classification. The initial phase forms a multispectral image with the help of Linear Discriminant Analysis (LDA), which considers the images from ten spectral bands. Bayesian modelling and local region thresholding techniques are employed to detect and segment mitotic cells. The features are extracted from the mitotic cells with the dimension of 226.

In [17], a technique to detect mitosis in histopathological images meant for grading breast cancer is proposed. This work utilizes an area morphological scale for segmenting the cells and the scale is formed by increasing the relative entropy between the mitotic cells and the background. Finally, the segmented cells are classified as mitotic and non-mitotic by utilizing random forest classifier.

In [18], the mitotic cells are detected and segmented in histopathological images for diagnosing cancer. This work is based on three steps and they are pre-processing, mitotic cell detection, segmentation and classification. The mitotic cells are detected and segmented with the help of Bayesian modelling and local region thresholding techniques. The classification is then attained by utilizing Bayesian and SVM classifiers.

In [19], a technique to distinguish between mitotic and non-mitotic cells for breast cancer histopathology images is presented on the basis of wavelet based statistical features. This work extracts the objects of interest by representing the images in wavelet transformation and the employed wavelet is Dual-Tree Complex Wavelet Transform (DT-CWT). Five basic statistical features are extracted from each and every sub-band of the wavelet. SVM is employed as the classifier to distinguish between the cells.

A learning based mitotic cell detection technique in histopathological images is presented in [20]. This work proposes a hierarchical learning workflow for detecting the mitosis in breast cancer automatically. Initially, a pixel-wise classifier is utilized to distinguish between the mitotic and non-mitotic cells. The classification is carried out by utilizing shape and the texture features.

In [21], a computer aided system is proposed for detecting and classifying between mitotic cells by using SVM classifier. This work reviews different techniques meant for detecting mitotic cells followed by which the SVM based automated mitotic cell detection technique is proposed for histopathological images.

A mitosis detection scheme based on Convolutional Neural Network (CNN) features is proposed in [22]. Automated mitosis detection is presented for diagnosing and grading cancer with the help of histopathological images. The cell structures are found out by performing clustering operation and blob analysis. The cellular image patches are extracted from the images and the CNN features are extracted and the features are reduced with the help of Principal Component Analysis (PCA) and Local Discriminant Analysis (LDA). Finally, SVM classifier is employed to classify between the mitotic and non-mitotic cells in histopathological images.

Motivated by these existing works, this work intends to present a system to detect and classify between the mitotic cells in histopathological images of breast cancer. The goal of this work is to increase the sensitivity and specificity rates. The following section elaborates the proposed approach in detail.

III. PROPOSED AUTOMATED MITOTIC CELL DETECTION IN BREAST CANCER HISTOPATHOLOGICAL IMAGES

This section describes the proposed automated mitotic cell detection scheme in addition to the work overview.

A. Overview of the Work

Digital pathology is one of the most difficult research areas, as the diagnostic procedures rely on the pathologic analysis. The cancerous growth can be graded based on the severity and it can be better performed by histopathological analysis. It is quite difficult to analyse the histopathological images manually, as it exhibits intricate details.

The following figure 1 shows the overall flow of the proposed approach.

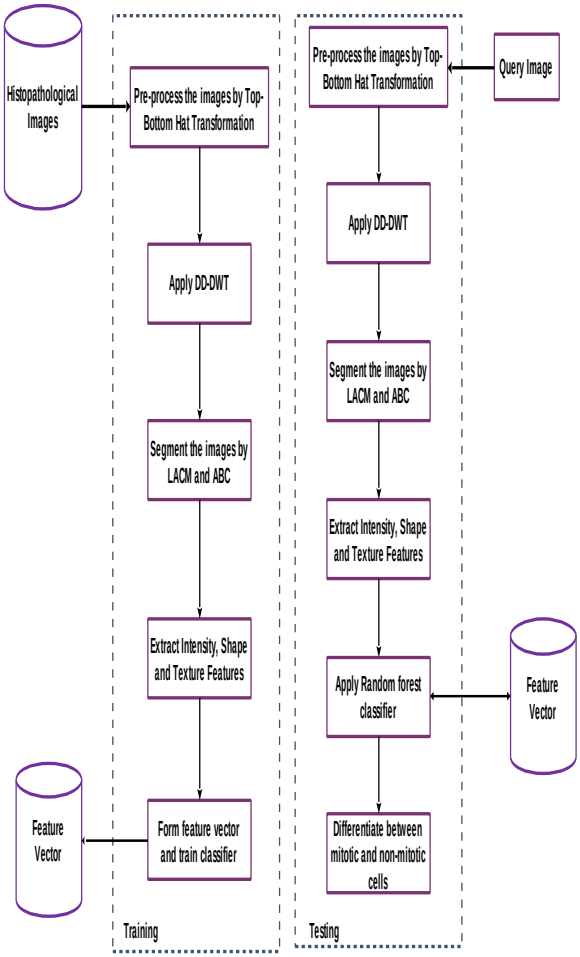

Fig.1. Overall flow of the proposed approach

This analysis is usually carried out by the pathologists by exploring numerous samples of a single patient. This process involves more human effort and the accuracy rates may be affected. Besides this, the mitotic cells do not share same structure, which makes the process extremely tough to differentiate between the mitotic and non-mitotic cells.

Understanding the difficulty involved in manual histopathological image analysis, this article proposes an automated histopathological analytic system that can distinguish between the mitotic and non-mitotic cells effectively. The proposed work can assist the pathologists in detecting the mitotic cells, which saves time and increases the efficiency.

The proposed approach relies on four significant phases and they are histopathological image pre-processing, nuclei segmentation, feature extraction and classification. The image pre-processing is attained by performing top and bottom hat transformation, such that the contrast is adjusted between the foreground and background respectively. The nuclei of the cell are then extracted from the cells however, segregating the area of interest from the background is a complex task. The potential shape and texture features are then extracted from the segmented nuclei and the classification is performed by random forest classifier. All the involved phases are described in the following sub-sections.

B. Histopathological Image Pre-processing

Pre-processing is the basic operation of all advanced image processing activity, as it prepares the image to be suitable for the forthcoming processes. When the histopathological images are considered, clumsy structure with minute details is observed. This makes the process of segmentation tougher and hence, the pre-processing activity intends to differentiate between the foreground and background of the histopathological images.

This work pre-processes the histopathological images with the help of top and bottom hat transformation, which can distinguish between the cell background and foreground content by increasing the contrast. The top hat transformation highlights the objects present in the background and the bottom hat transformation works in the reverse mode. Let f be an image and the top and bottom transformation (TB_t) is carried out in the following way.

$$TB_t = f + TH_t - BH_t \quad (1)$$

$$TH_t = f - (f.open) \quad (2)$$

$$BH_t = (f.close) - f \quad (3)$$

In the above equations, $f.open$ and $f.close$ denotes the morphological opening and closing of the image. By this way, the contrast of the histopathological image is improved. Yet, the background and foreground parts of an image are not segregated. As stated earlier, the size of the nuclei is not static, the area of interest is chosen by multi-resolution technique. The sample original and pre-processed images are illustrated in figure 2.

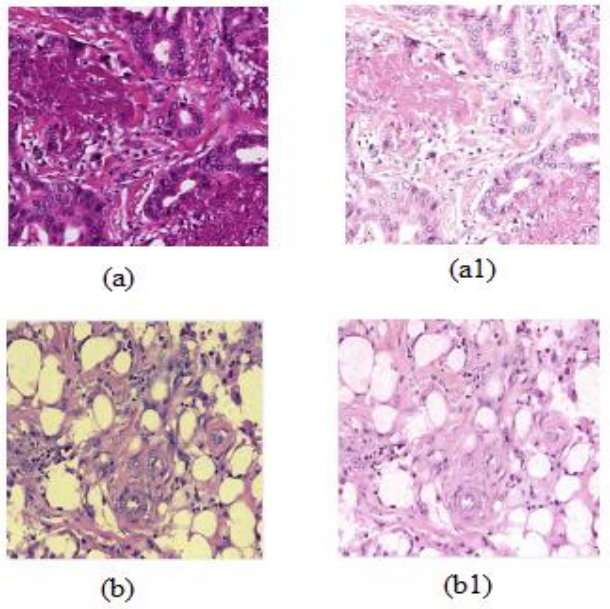

Fig.2. (a,b) Sample original images (a1,b1) Pre-processed images

Published By:
Blue Eyes Intelligence Engineering
& Sciences Publication

This work applies Double Density Discrete Wavelet Transform (DD-DWT), owing to the properties of degree of directionality, shift invariance and reduced degree of redundancy. The three channel filter bank is formed on the basis of a scaling function $\varphi(t)$ and two different wavelets $\Psi_1(t)$ and $\Psi_2(t)$. The scaling and wavelet spaces v_j and $w_{i,j}$ are represented by the following equations.

$$v_j = Span\{\varphi(2^j t - n)\} \quad (4)$$

$$w_{i,j} = Span\{\Psi_i(2^j t - n)\} \text{i} = 1,2 \quad (5)$$

$$\varphi(t) = \sqrt{2}h_0(n)\varphi(2t - n) \quad (6)$$

$$\Psi_i(t) = \sqrt{2}h_i(n)\varphi(2t - n), i = 1,2 \quad (7)$$

In the above equation, $h_0(n)$ are low frequency filters and $h_i(n)$ in which $i = 1,2$ are high frequency filters. The application of DD-DWT helps in analysing the histopathological images better and paves way for better segmentation process.

C. Nuclei Segmentation on Histopathological Images

The nuclei of cells are segmented by means of Localized Active Contour Model (LACM). However, it is hard to determine the nuclei of the cells during the initial phases of mitosis. This issue is addressed by incorporating a bio-inspired algorithm called ABC, which can detect the centre point of the nucleus. The ABC algorithm is employed to detect three different thresholds, such that the nuclei can be differentiated from the cytoplasm, stroma and vacuoles. Initially, the LACM is applied over the image to detect the nuclei by considering the energy information of the pixels with respect to a specific radius *r*.

The energy information is computed both in local and global regions with respect to the neighbourhood pixels of the nuclei. The energy curve is computed by $E(c)$, which is presented as follows.

$$E(c) = \int N_{(x,y)} En_{ex}(c) + \delta\beta \quad (8)$$

In the above equation, $N_{(x,y)}$ denotes the neighbourhood regions, β and δ denotes the curvature of the curve (c), contour's smoothness respectively. The local energies are calculated with respect to the internal and external portions of the contour.

$$E(c) = -\frac{1}{2}[(AI_{in} - AI_{ex})^2] + \beta \quad (9)$$

In the above equation, AI_{in} and AI_{ex} are the average intensities of the internal and external portions of the contour. The success probability of the food source is given by eqn.10.

$$SP_i = \frac{E(c)_i}{\sum_{fs=1}^{i} E(c)_{fs}} \quad (10)$$

Hence, the nuclei are detected and segmented with the help of LACM algorithm. ABC algorithm is employed to choose the thresholds. The ABC algorithm involves four important phases and they are parameter initialization, employed, onlooker and scout bees phases. The initialization phase creates the initial parameters and the stopping criterion of the algorithm. The employed bee phase looks for the food source with better quality nearby the detected food source. The quality of the food source is determined by the fitness value and the information about the food source is shared with the onlooker bees.

The onlooker bees select the high quality food source, based on the information provided by the employed bees. Once a new food source is found, the quality of the food source is compared with the existing food source by greedy selection. Finally, the employed bees change their nature to scout bees, when the high quality food source cannot be detected. The search for food source continues, until the high quality food source is detected [23,24]. As the convergence time of ABC is more, LACM is utilized for detecting and segmenting the nuclei, for which the thresholds are selected by the ABC algorithm. Figure 3 depicts the sample segmented nuclei results of the proposed approach. The ABC algorithm for threshold selection is presented as follows.

ABC Algorithm for Optimal Threshold Selection

Input : LACM applied images

Output : Optimal thresholds to attain segmentation
Begin
Initialize parameters;
Randomly distribute the food source;
Calculate the fitness of the food source by eqn.(9);

//Employed bee
Detect a food source and calculate its fitness;
Calculate the success probability of the food source by eqn.10;

//Onlooker bee phase
Choose a food source f_i and calculate the fitness;
Match the existing and new fitness values;
If(new fitness>old fitness value)
Discard the old fitness value and save the new f_i;

Select the top three values and declare them as thresholds;
Produce binary mask image (bm)
End;

By this way, the centre points of the nuclei are detected from the cells and differentiated with the help of threshold. The computed bm image helps in segmenting the nuclei with the perfect boundary with the help of LACM technique. The feature extraction phase of this work is presented as follows.

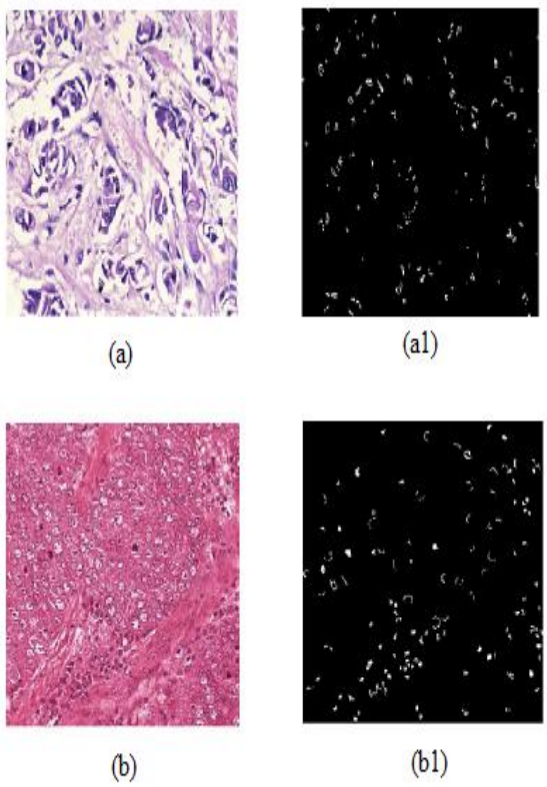

Fig.3. (a,b) Original images (a1,b1) sample nuclei segmentation results

D. Feature Extraction

As the histopathological images contain rich texture information with varying shapes, the segmented nuclei are processed with the phase of feature extraction. This work extracts the intensity, texture and shape based features for distinguishing between the mitotic and non-mitotic cells. The intensity based features such as mean, variance, kurtosis and skewness are extracted from the segmented nuclei. The overall algorithm of this work is presented as follows.

Proposed automated mitotic cell classification algorithm

Input : Breast cancer histopathological images
Output : Mitotic cell classification
//Training
Begin
For all train images
Do
Pre-process the images by applying top, bottom hat transformation;
Apply DD-DWT for better analysis;
Segment the images by LACM and ABC algorithms;
Extract intensity, shape and textural features from the segmented nuclei;
Form feature vector and save;
Train the random forest classifier with the feature vector;
End do;
End for;
End;
//Testing
Begin
For a query image
Do
Pre-process the image by applying top, bottom hat transformation;
Apply DD-DWT for better analysis;
Segment the images by LACM and ABC algorithms;
Extract intensity, shape and textural features from the segmented nuclei;
Form feature vector fv_i;
Apply random forest classifier;
Return result;
End do;
End for;
End;

In addition to this, the shape based features such as area, perimeter and the haralick features are extracted to represent the textural features [25]. The features are extracted in four varying directions such as $0°, 45°, 90°$ and $135°$. The total count of features utilized is 20. The feature vector is then formed to train the classifier.

E. Classification

The mitotic and non-mitotic cells are classified with the help of random forest classifier. Let R be the total count of random trees in the forest and the training set be denoted as TS. During the process of training, each and every tree is allotted with the weight $W_i^0 = 1$; where $i = \{1, Q\}$. The probability of class label cl for image β is indicated by $p_i^{cl}(\beta)$ and is determined by the tree i. The weight of the tree is computed by

$$W_i = W_i^0 - \frac{1}{TS}\sum_{k=1}^{TS}\left|p_i^{\bar{cl}}(k) - p_i^{cl}(k)\right|; i = \{1, Q\} \quad (11)$$

In the above equation, $p_i^{\bar{cl}}(k)$ is the ground truth class label. During the testing phase, the classification is performed as follows. Let b be the total count of classes for the input data k, then the classification is performed by

$$\bar{cl} = \underset{c}{argmax} \sum_{i=1}^{T} W_i\, p_i^{cl}(k); i = \{1, Q\} \quad (12)$$

This kind of classification yields better classification results, owing to the weight allocation and the trees with minimal weights cannot attain better results. The sample classification results of the proposed approach are presented in figure 4.

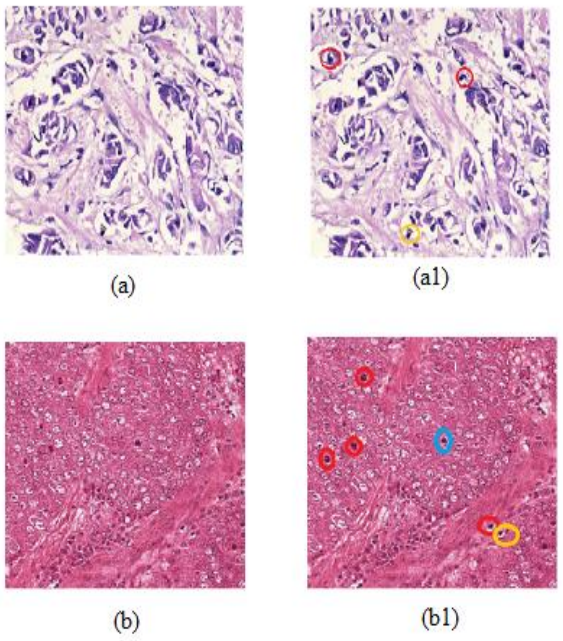

Fig.4. (a,b) Original images (a1, b1) sample classification results

This strategy helps in attaining better accuracy rates and the performance of the proposed approach is evaluated in the following section.

IV. RESULTS AND DISCUSSION

The performance of the proposed approach is evaluated in terms of accuracy, sensitivity, specificity and the results are compared with the existing approaches. The proposed work is implemented in MATLAB 2013a environment on a standalone computer with 16 GB RAM. The performance of the proposed approach is evaluated over a publicly available dataset mitosis detection [26]. Accuracy is the most important performance metric which indicates the reliability of the proposed algorithm. The greatest accuracy rate signifies the better classification ability of the system to differentiate between mitotic and non-mitotic cells. The accuracy rate is computed by the following equation.

$$A = \frac{TP+TN}{TP+TN+FP+FN} \times 100 \quad (13)$$

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

$$Sen = \frac{TP}{TP+FN} \times 100 \quad (14)$$

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.

$$Spec = \frac{TN}{FP+TN} \times 100 \quad (15)$$

The experimental results of the proposed approach are depicted in graphical format as follows.

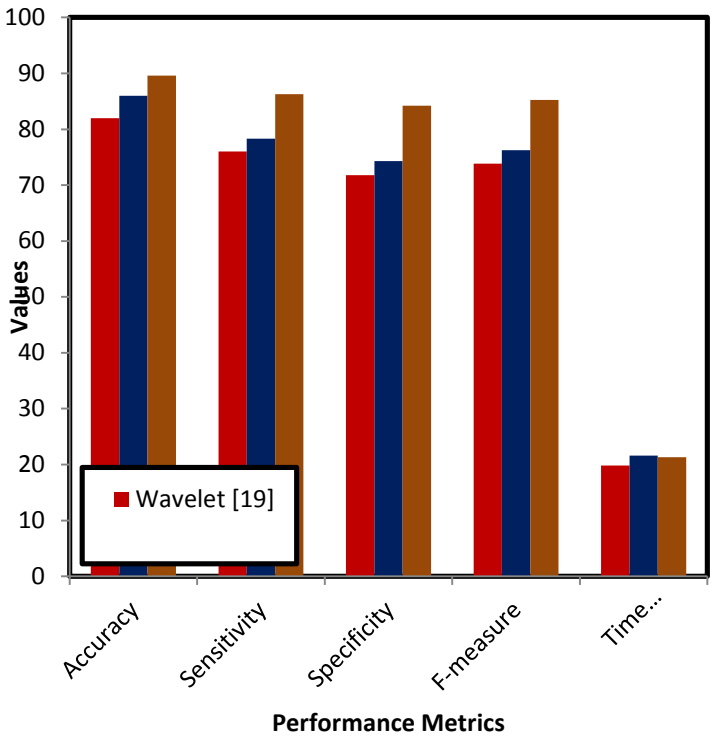

Fig.5: Performance analysis of the proposed approach

The attained experimental results are tabulated in table 1.

Performance Metrics/Feature extraction techniques	Wavelet based [19]	Mitosis detection [17]	Proposed
Accuracy (%)	82	86	**89.6**
Sensitivity (%)	76	78.3	**86.3**
Specificity (%)	71.8	74.3	**84.2**
F-Measure (%)	73.84	76.24	**85.23**
Time Consumption (s)	**19.8**	21.6	21.3

Table 1: Experimental Results of the Proposed Approach

From the experimental results, it is evident that the performance of the proposed approach is satisfactory in terms of standard performance measures. The results are presented by executing the proposed algorithm for fifteen times and the average values are presented. The greater sensitivity and specificity rates of the proposed approach prove that the false negative and false positive rates are minimal. Hence, the mitotic cells are differentiated in a better way with the help of clear-cut segmented nuclei.

On time consumption analysis, it is observed that the time consumption of the proposed approach is a bit greater than the existing approaches. The main reason for the increased time consumption is the automated segmentation and feature vectors. However, the time consumption of the proposed approach is tolerable. The concluding remarks of this article are presented in the following section.

V. CONCLUSION

This article presents an automated mitotic cell detection scheme for breast cancer histopathological images. Mitosis is a significant process through which the severity of the cancer can be graded. Hence, this work differentiates between the mitotic and non-mitotic cells and can serve as an aid for the pathologists for better diagnosis. The proposed work is based on four main phases and they are image pre-processing, segmentation, feature extraction and classification.

The images are pre-processed to increase the prominence of background and foreground details, which is achieved by top and bottom transformation. The foreground part is extracted with the help DD-DWT. The process of segmentation is carried out with the help of LACM and optimized by ABC algorithm. The intensity, shape and texture features are extracted from the segmented region and the random forest classifier is imparted with the knowledge about mitotic cells. The performance of the proposed approach is tested in terms of accuracy, sensitivity, specificity and compared with the existing approaches. In future, this work is planned to be extended to multi-spectral histopathological images. Additionally, the feature selection techniques may be incorporated to reduce the time and memory consumption.

REFERENCES

1. http://cancerindia.org.in/cancer-statistics/
2. Yasmin M, Sharif M, Mohsin S. Survey paper on diagnosis of breast cancer using image processing techniques. Res J Recent Sci 2013;2(10):88–98.
3. Mohan H. Textbook of Pathology, 7th ed.. New Delhi, India: Jaypee Brothers Medical Publishers (P) Ltd.; 2014.
4. J. R. Dalle, W. K. Leow, D. Racoceanu, A. E. Tutac, and T.C. Putti, “Automatic breast cancer grading of histopathological images,” in Proceedings of the IEEE International Conference on Engineering in Medicine and Biology Society, pp. 3052–3055,
5. 2008.
6. L. Latson, B. Sebek, and K. A. Powell, “Automated cell nuclear segmentation in color images of hematoxylin and eosin-stained breast biopsy,” Analytical and Quantitative Cytology and Histology, vol. 25, no. 6, pp. 321–331, 2003.
7. M. Veta, P. J. van Diest, R. Kornegoor, A. Huisman, M. A. Viergever, and J. P. W. Pluim, “Automatic nuclei segmentation in H&E stained breast cancer histopathology images,” PLoS ONE, vol. 8, no. 7, Article ID e70221, 2013.
8. E. Cosatto, M. Miller, H. P. Graf, and J. S. Meyer, “Grading nuclear pleomorphism on histological micrographs,” in Proceedings of the 19th International Conference on Pattern Recognition (ICPR ’08), pp. 1–4, Tampa, Fla, USA, December 2008.
A. Fakhrzadeh, E. Sporndly-Nees, L. Holm, and C. L. L. ¨Hendriks, “Analyzing tubular tissue in histopathological thin sections,” in Proceedings of the 14th International Conference on Digital Image Computing Techniques and Applications (DICTA’12), pp. 1–6, Fremantle, Australia, December 2012.
9. Basavanhally, E. Yu, J. Xu et al., “Incorporating domain knowledge for tubule detection in breast histopathology using O’Callaghan neighborhoods,” in Medical Imaging: Computer Aided Diagnosis, vol. 7963 of Proceedings of SPIE, Lake Buena Vista, FLa, USA, February 2011.
10. M. Khan, H. El-Daly, and N. M. Rajpoot, “A gamma-gaussian mixture model for detection of mitotic cells in breast cancer histopathology images,” in Proceedings of the IEEE International conference on Pattern Recognition, pp. 149–152, 2012.
11. Sommer, L. Fiaschi, F. A. Hamprecht, and D. W. Gerlich, “Learning-based mitotic cell detection in histopathological images,” in Proceedings of the 21st International Conference on Pattern Recognition (ICPR ’12), pp. 2306–2309, November 2012.
12. H. Irshad, S. Jalali, L. Roux, D. Racoceanu, L. J. Hwee, and G. Le Naour, “Automated mitosis detection using texture, SIFT features and HMAX biologically inspired approach,” Journal of Pathology Informatics, vol. 4, p. 12, 2013.
13. C. Cires¸an, A. Giusti, L. M. Gambardella, and J. Schmidhuber, “Mitosis detection in breast cancer histology images with deep neural networks,” in Medical Image Computing and Computer-Assisted Intervention, pp. 411–418, Springer, Berlin, Germany, 2013.
14. H. Huang and H. K. Lee, “Automated mitosis detection based on exclusive independent component analysis,” in Proceedings of the IEEE International Conference on Pattern Recognition, pp.1856–1859, 2012.
15. Huseyin Cukur ; Gokhan Bilgin, "Detection of mitotic cells in multispectral histopathological images", 25th Signal Processing and Communications Applications Conference, 15-18 May, Antalya, Turkey, 2017.
16. Cheng Lu ; Mrinal Mandal, "Toward Automatic Mitotic Cell Detection and Segmentation in Multispectral Histopathological Images", IEEE Journal of Biomedical and Health Informatics, Vol.18, No.2, pp.594-605, 2014.
17. Angshuman Paul ; Dipti Prasad Mukherjee, "Mitosis Detection for Invasive Breast Cancer Grading in Histopathological Images", IEEE Transactions on Image Processing, Vol.24, No.11, pp.4041-4054, 2015.
18. G. Logambal ; V. Saravanan, "Cancer diagnosis using automatic mitotic cell detection and segmentation in histopathological images", Global Conference on Communication Technologies (GCCT), 23-24 Apr, Thuckalay, India, 2015.
19. Tao Wan ; Xu Liu ; Jianhui Chen ; Zengchang Qin, "Wavelet-based statistical features for distinguishing mitotic and non-mitotic cells in breast cancer histopathology", IEEE International Conference on Image Processing, 27-30 Oct, Paris, France, 2014.
20. Christoph Sommer ; Luca Fiaschi ; Fred A. Hamprecht ; Daniel W. Gerlich, "Learning-based mitotic cell detection in histopathological images", Proceedings of the 21st International Conference on Pattern Recognition, 11-15 Nov, Tsukuba, Japan, 2012.
21. H Amitha ; I. Selvamani ; D. Anto Sahaya Dhas, "Developement of computer aided system for detection and classification of mitosis using SVM", International Conference on Inventive Computing and Informatics, 23-24 Nov, Coimbatore, India, 2017.
22. Abdulkadir Albayrak ; Gokhan Bilgin, "Mitosis detection using convolutional neural network based features", IEEE 17th International Symposium on Computational Intelligence and Informatics, 17-19 Nov, Budapest, Hungary, 2016.

23. Dervis Karaboga, Beyza Gorkemli, Celal Ozturk, Nurhan Karaboga, A comprehensive survey: artificial bee colony (ABC) algorithm and applications, Artif Intell Rev, 2012.
24. Dervis Karaboga, Celal Ozturk, A novel clustering approach: Artificial Bee Colony (ABC) algorithm, Applied Soft Computing 11 (2011) 652–657.
25. R. M. Haralick, K. Shanmugam, and I. Dinstein, ``Textural features for image classication," IEEE Trans. Syst., Man, Cybern., vol. SMC-3, no. 6, pp. 610-621, Nov. 1973.
26. http://tupac.tue-image.nl/node/3