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Mitosis Detection from Breast Cancer Histology Slide Images using Particle Swarm Optimization and Support Vector Machine

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Abstract

This paper introduces a new strategy for the purpose of automatic mitosis detection from breast cancer histopathology slide images. In this method, a new approach for reducing the number of false positive using Particle Swarm Optimization (PSO) is proposed. The proposed system is implemented on the histopathology slide images acquired by Aperio XT scanner (scanner A). In PSO algorithm the number of false positive objects or non-mitosis are defined as a cast function and by the minimization it the most of the non-mitosis candidates will be removed. Then some color, texture features such as co-occurrence and run–length matrices are extracted from the rest of candidates and finally mitotic cells are classified using specific support vector machine (SVM) classifier. The simulation results prove the claims about the high performance and efficiency of the proposed system.

Keywords: breast cancer; classification; feature extraction; mitosis detection; Particle Swarm Optimization (PSO); Support vector classification (SVM); Complete Local Binary Pattern (CLBP)

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1. Introduction

Nowadays, one of the most prevalent type of cancers which mostly leads to dead is breast cancer [1]. Due to the world health organization (W.H.O.) standardizations, there is a system known as Nottingham which is used for breast cancer grading. According to this system, three morphological features known as nuclear polymorphism, tubular constructions formation and number of mitosis cells are used for grading breast cancer [2]. The diagnosis about the grade of breast cancer is done based on the pathology studies by pathologists over histopathology cancerous tissue slides. In recent years, many research on breast cancer has been proposed that provided an automated Computer Assisted Diagnosis (CAD) systems that assists pathologist for breast cancer grading. In some of researches, automatic breast cancer detection systems based on the three breast cancer grading features have been presented [4-6]. However, most of the researches on breast cancer histopathology images usually consider only one of nuclear polymorphism [5,7-9], tubule formations [10,11], mitosis cells [12-16]. Amount of dividing cells known as mitosis is essential feature for breast cancer grading. Pathologists by using scanners count the number of mitoses in 10 distinct HPF (High Power Field) histopathology images and based on number of mitosis in 10 HPF reported score related to the number of mitoses is as Eq. (1) [6].

$$MC = \begin{cases} 1 & N < 9 \\ 2 & 10 < N < 19 \\ 3 & N > 19 \end{cases} \quad (1)$$

Where N is the total number of mitoses in 10 HPFs.

In the field of extraction and counting the number of mitosis in breast cancer histopathology slide images, several automatic methods have been proposed [12-16]. Some of these methods are used multispectral histopathology images for detect and count mitosis [17,18]. Khan et al. proposed a method for automatic counting of mitotic cells from histopathology slide images in which a statistical Gamma-Gaussian Mixture Model (GGMM) is used to estimate the probability density function of mitosis and non-mitosis cells. By estimating pdfs of mitosis and non-mitosis candidates are extracted. Then, by training SVM classifier with the statistical features that are extracted by Gabor filter, the mitoses are detected [12].

Somer et al. proposed another method [13] in which the mitoses are detected due to two level classification: level one, random forest classification to identify candidates and level two, SVM classification to classify candidates and diagnosis mitosis from non-mitosis objects. In another mitosis detection system, use Blue-ratio mapping to map the original histopathology image from RGB to blue ratio color space [14]. In the Blue-ratio color space, the pixels belonging to the blue color channel have bigger value than the other two color channels (R and G). Therefore, by using this mapping, the nuclei of cells which have significant blue color content, can be extracted by a simple thresholding. At this method by applying Laplace of Gaussian filtering to the blue-ratio image and thresholding the resulted image, initial candidates for mitosis objects are extracted. Then, by extracting different features such as co-occurrence and run-length matrices from each candidates and by using classifiers the mitoses are detected [14]. In some researches, for mitosis detection purpose, Artificial Neural Networks (ANNs) [15] and exclusive independent component analysis (EICA) [16] have been employed. In some other more recently proposed papers such as [19-21], specific features with object-wise extraction

considerations are proposed. This approach leads to better discrimination results between mitotic and non-mitotic objects. But in general, some important challenges facing automatic mitosis detection from histopathology images are existed that reduce accuracy of mitosis detection. These challenges can be reviewed as following section.

The organization of the rest of this paper is as follows. In Section 2 challenges facing the mitosis detection is described. Section 3 describes the proposed mitosis detection system consists ofcandidate extraction, candidate selection, feature extraction and classification and mitosis detection subsections. Experimental results to demonstrate effectiveness of our mitosis detection system are presented in Section 4. The paper ends with a few concluding remarks. (Section 5).

2. Challenges Facing the Mitosis Detection

In general, there are two challenges in front of automatic detection of mitosis cells in histopathology images that both of them related the nature of histopathology images. The first problem is that the mitotic cells existing in a histopathology image normally have diverse color, shape and texture, On the other hand mitosis cells have a great deal of similarities with non-cancerous cells and lymphocytes. The second challenge in front of appropriate mitoses detection is the high number of extracted candidates. In the other words as the resolution of histopathology images is high and there are many other objects similar to mitoses; therefor, the number of extracted candidates is high.

In this paper, an automatic mitosis detection system is proposed that will overcome the challenges in front of mitosis detection. To overcome the first challenge, we extract different features based on color, texture, shape of mitosis. Also to overcome the second challenge, a method that omits the large number of non-mitosis candidates is introduced. In the proposed method, the number of non-mitosis candidates is defined as a cast function of TBLO optimization algorithm. So by minimization this optimization problem the large number of non-mitosis candidates are omitted.

3. Method

Figure 1 shows the block diagram of the proposed system for automatically detection of mitotic cells.

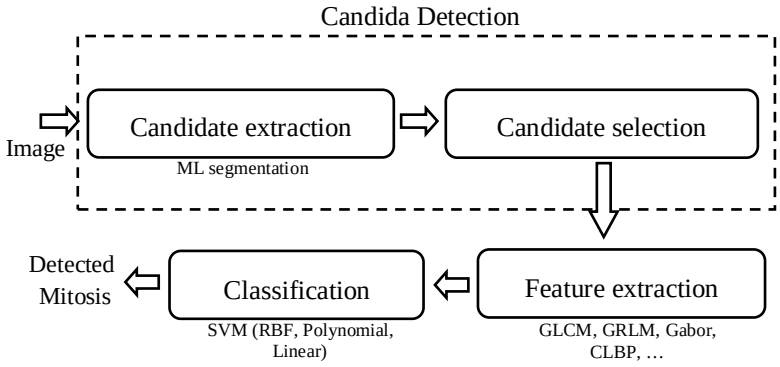


Figure. 1. The proposed framework for mitosis detection

In this system first a preprocessing stage is applied to the original image which includes Gaussian filtering for image smoothing then in the second stage the distribution parameter of mitosis and non-mitosis gray levels are estimated based on Maximum Likelihood algorithm. By using ML algorithm and calculating a threshold that removes background, the initial candidates are extracted which their number is too high. Then an approach is proposed to reduce the high number of extracted non-mitosis candidates. After candidate selection procedure, color and texture features are extracted from remaining candidates and representative features are used to train a Support Vector Machine (SVM) classifier using different kernels. The trained classifier is then used to classify the test candidates.

3.1. CANDIDATE EXTRACTION USING MAXIMUM LIKELIHOOD (ML)

In this subsection, the ML algorithm is used to estimate statistical probability density functions of mitosis and non-mitosis grey levels. In fact by using training data, ML estimates the parameters of probability density functions related to mitosis and non-mitosis. As the parameters are estimated by ML, proper thresholds could be calculated for candidate extraction. Assuming that x' as the grey level of mitosis pixel and y' as the grey level of non-mitosis pixel and also by assuming the independency of mitosis and non-mitosis grey levels, the probability density function of mitosis and non-mitosis grey levels can be defined as equations (2) and (3), where X', Y' are the grey levels of all mitosis and non-mitosis pixels.

$$p(X';\theta_{X'}) = p\left(x_1', x_2', \ldots x_N';\theta_{x'}\right) = \prod_{k=1}^{N} p(x_k';\theta_{x'}) \quad (2)$$

$$p(Y';\theta_{Y'}) = p\left(y_1', y_2', \ldots y_M';\theta_{y'}\right) = \prod_{k=1}^{M} p(y_k';\theta_{y'}) \quad (3)$$

The ML estimates parameters so that the mitosis and non-mitosis pdfs be at their maximum values. According to Figure 2 [12], the histogram or pdf of pixels belonging to mitosis and non-mitosis are similar to Gaussian function. Gaussian probability density function have two parameters, mean (μ) and covariance (∑). Thenthese two parameters of Gaussian pdfs are estimated by ML as Eqs. (4) and (5).

$$\mu_{x'} = \frac{1}{N}\sum_{i=1}^{N} x_i' \quad , \quad \Sigma_{x'} = \frac{1}{N}\sum_{i=1}^{N}(x_i' - \mu_{x'})^2 \quad (4)$$

$$\mu_{Y'} = \frac{1}{M}\sum_{i=1}^{M} y_i' \quad , \quad \Sigma_{Y'} = \frac{1}{M}\sum_{i=1}^{M}(y_i' - \mu_{y'})^2 \quad (5)$$

Where N is the number of mitotic pixels and M is related to the number of non-mitotic ones.

As histopathology are color images comprising of RGB components, therefore, it is necessary that the mean and covariance parameters of mitosis and non-mitosis be estimated for separate R, G and B components, separately. Therefore, mean and covariance of mitosis and non-mitosis probability density functions have six $\mu_{X,R}$, $\mu_{X,G}$, $\mu_{X,B}$, $\sum_{X,R}$, $\sum_{X,G}$, $\sum_{X,B}$ components. As seen in Figure 2, by considering the intersection of mitosis and non-mitosis pdfs, it is possible to find thresholds for each color component and by using thresholding the candidates can be extracted. For example, for the R color component, threshold can be computed from the equation Eq.

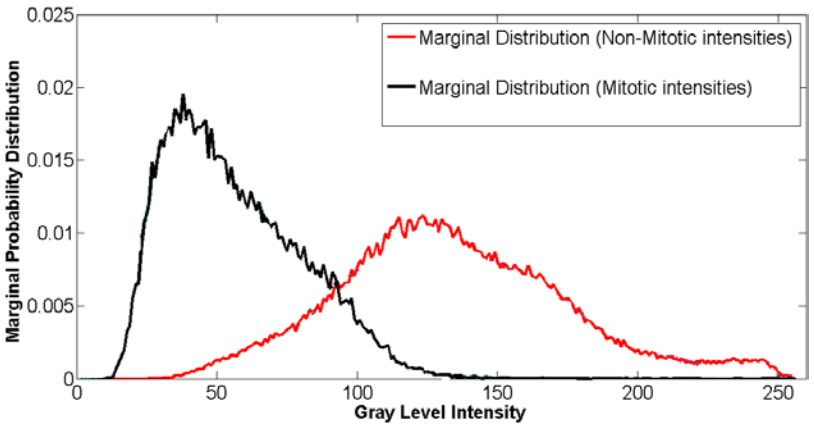


Figure. 2. Pdfs of mitosis and non-mitosis grey levels

$$\Rightarrow \quad T_R = \frac{\sigma^2_{x',R}\mu_{y',R} - \sigma^2_{y',R}\mu_{x',R} + \sqrt{\sigma^2_{x',R}\sigma^2_{y',R}\left(\mu_{x',R} - \mu_{y',R}\right)^2 + 2\left(\sigma^2_{x',R} - \sigma^2_{y',R}\right)ln(\frac{\sigma_{x',R}}{\sigma_{y',R}})}}{\sigma^2_{x',R} - \sigma^2_{y',R}{}^2} \quad (6)$$

By obtaining the three predetermined thresholds, it is possible to extract initial candidates. According to this approach, three binary image including the mask of initial candidates are obtained due to the Eq. (7).

$$C_l = \begin{cases} 1, & \text{if} \quad P_l(i,j) > T_l \\ 0, & \text{otherwise} \end{cases} \qquad l \in R, G, B \quad (7)$$

Where $P_x(i,j)$ is the grey level of the pixel in coordinates (i,j). For each thresholds, three binary images known as C_R, C_G and C_B, are obtained. Since for the future processing and also extracting the mitosis, it is necessary that one binary image comprising the mask of initial candidates be achieved. Thus, among the three images C_R, C_G and C_B, we select the best one that having fewer segmentation error. Error of segmentation is defined as Eq. (8).

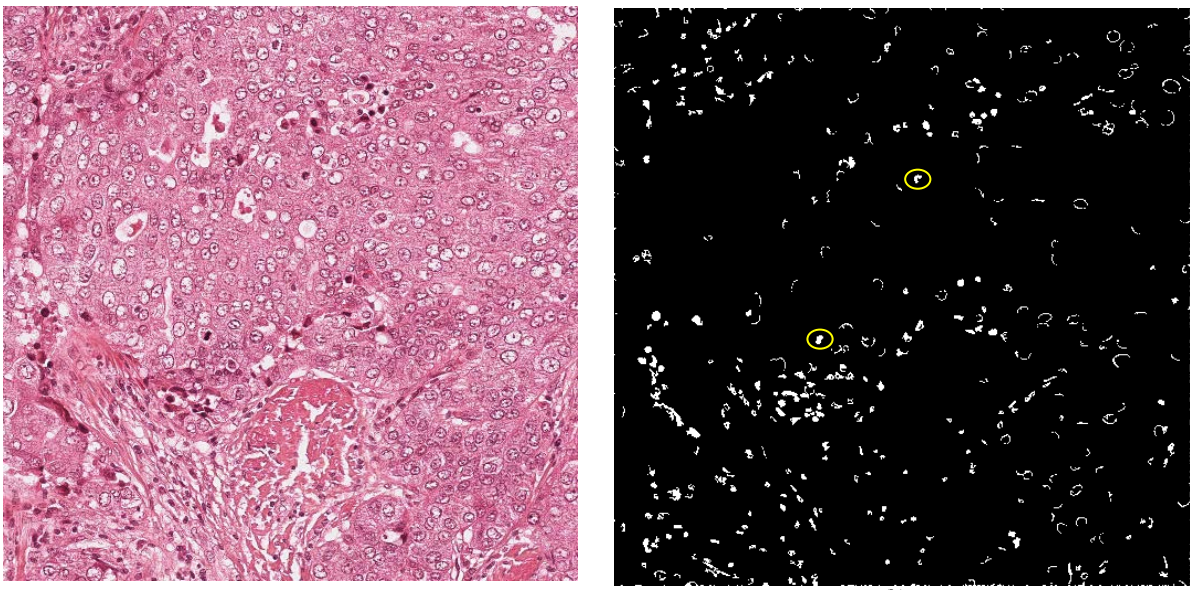
$$E_l = \sum_{i=1}^{n}\sum_{j=1}^{m} \text{xor}(C_l(i,j), Gr(i,j)) \ , \qquad l \in R, G, B \quad (8)$$

Where $Gr(i,j)$ is the mitosis ground truth binary mask and n, m are length of image in x and y directions. The candidates extracted by ML segmentation method for a sample breast cancer high power field (HPF) slide image is shown in Figure 3.a.In this histopathology image there are two mitoses, while the number of extracted candidates by ML algorithm is 356 (Figure 3.b).

3.2. CANDIDATE SELECTION

As seen in Figure 3, the number of candidates extracted by ML segmentation method is usually too high. In some other mitosis detection systems also this problem exist. Although, in candidate detection stage of some presented mitosis detection system, statistical methods such as GMMM [12], pixel based classification [13] or mapping such as Blue Ratio is used to have low number of non-mitosis candidates, however, the number of

extracted non-mitosis candidates usually is too large. This dilemma leads to the low accuracy of mitosis detection.



(a) (b)

Figure. 3. Detected candidates using ML algorithm;
(a) a sample histopathology image that have six mitoses (b) candidates extracted from ML algorithm

In the system proposed in this paper, a new approach toward reducing the number of non-mitosis candidates is proposed. In the proposed method, the number of non-mitosis candidates will be considered as cost function of an optimization algorithm. Minimum the cost function will lead to the omission of a great number of non-mitosis objects as unwanted candidates. For this purpose, mean of grey levels is computed for each segmented candidates due to the Eq. (9).

$$M_k = \sum_{i=0}^{255} i \; p(x_k = i) \quad (9)$$

Where M_k is the mean and $p(x_k=i)$ relates to the histogram of kth candidate. By computing M_k for all candidates, the two vectors $\bar{M}_m$ (mean of mitosis candidates) and $\bar{M}_{nm}$ (mean of non-mitosis candidates) are obtained according to Eqs. (10) and (11).

$$\bar{M}_m = [M_{m1}, M_{m2}, \ldots M_{mL}] \quad (10)$$

$$\bar{M}_{nm} = [M_{nm1}, M_{nm2}, \ldots M_{nmP}] \quad (11)$$

Where *L* and *P* stand for the number of mitosis and non-mitosis candidates, respectively.

If it is assumed that there are *L+P* candidates in which *L* and *P* stand for the numbers of mitosis and non-mitosis candidates, respectively, then by computing $T_r$due to the Eq. (12), it is possible to eliminate a part of non-mitosis candidates. The number of non-mitosis candidates (N_r) which can be omitted is computed according to Eq. (13).

$$Tr = \max\left(\bar{M}_m\right) \quad (12)$$

$$Nr = p_r(\bar{M}_{nm} > Tr) \quad (13)$$

The main purpose is to provide a method to increasing the number of eliminated non-mitoses candidates. For this reason, a weighting factor hi is assigned to the grey levels. The weighted mean is calculated as Eq. (14).

$$M'_k(h_i) = \sum_{i=0}^{255} h_i \times i \times p\left(x_k = i\right) \quad , \quad h_i \in [0 \quad 1] \quad (14)$$

Due to this consideration, new vectors $\bar{M}'_m(h_i)$ and $\bar{M}'_{nm}(h_i)$ will be obtained but the values of hi weights would not be clear. To solve this problem, hi must be calculated so that the histograms of Nr or removed non-mitosis candidates have the maximum value. The maximum value of the Nr is P. For computing the weighting values hi, a cost function f, which must be minimized, is defined as Eq. (15).

$$f\left(h_i\right) = P - N_r = P - p_r\left(\bar{M}'_{nm}(h_i) > T_r\right) \quad (15)$$

Solving this problem is not possible with deterministic methods, therefore to find an appropriate answer for h_i, heuristic Particle Swarm Optimization (PSO) is employed. PSO is a biologically inspired computational search and optimization method developed in 1995 by Eberhart and Kennedy [22] based on the social behaviors of birds flocking or fish schooling. The algorithm of PSO emulates from behavior of animals societies that don't have any leader in their group or swarm, such as bird flocking and fish schooling. Typically, a flock of animals that have no leaders will find food by random, follow one of the members of the group that has the closest position with a food source (potential solution). The flocks achieve their best condition simultaneously through communication among members who already have a better situation. Animal which has a better condition will inform it to its flocks and the others will move simultaneously to that place. This would happen repeatedly until the best conditions or a food source discovered. The process of PSO algorithm in finding optimal values follows the work of this animal society. Particle swarm optimization consists of a swarm of particles, where particle represent a potential solution.

In Table 1, the steps of PSO algorithm are shown consecutively [22]. Due to that is not largely affected by the size and nonlinearity of the problem and can converge to the optimal solution in many problems where most analytical methods fail to converge, PSO has become a very attractive optimization technique and has been successfully applied to many real world problems [22].

Table 1-PSO algorithm steps

Implementation steps of PSO algorithm	
Step 1:	Definition of size of population and boundary of optimal solution and generate initial population
Step 2:	Determine the global best solution in all particles (G_{best})and define population as best population (P_{best})
Step 3:	Update location(X_i) and speed(V_i) of each particle due to the following $X_{i+1} = X_i + V_{i+1}$ $V_{i+1} = \text{rand} \times C_1 \times \Delta x_1 + \text{rand} \times C_2 \times \Delta x_2 + \omega \times V_i$ $\Delta x_1 = P_{best} - X_i \quad , \quad \Delta x_2 = G_{best} - X_i$ Where rand is random variable between (0,1) and C_1, C_2, ω are the parameters of PSO algorithm and are selected as: $C_1, C_2 > 0$, $0.4 < \omega < 0.9$
Step 4:	Replacing the new population with the old population if $Cost(X_{i+1}) < Cost(X_i)$
Step 5:	Exit if maximum iteration is performed else go to step 2.

By using training datasets and implementing PSO optimization, the optimal value of hi weights and threshold Tr can be obtained and it would be possible to omit a large number of non-mitosis candidates in the mitosis candidate extraction phase. If we assume that in the test phase, there are a total number of Nt candidates, according to Eq. (16), the candidates that their weighted means are greater than the threshold Tr are omitted and the remaining candidates are passed to the next processing stages and final mitotic detection phase.

$$\text{Candida}_k = \begin{cases} \text{removed} , & M_k^{'} > T_r \\ \text{remained} , & \text{otherwise} \end{cases} \quad k = 1, 2, ..., N_t \quad (16)$$

Where $M_k^{'}$ is the weighted mean of Kth candidate which is achieved from Eq. (14).

3.3. FEATURE EXTRACTION

For detecting and discriminating mitotic from non-mitotic candidates some features based on color, texture and shape are extracted from the remaining candidates. As there are many similarities between mitotic cells with non-mitotic, the extracted features must be discriminant. The features that we extract are as follow: 14 haralick features derived from grey level co-occurrence matrices (GLCMs) [23], 11 features obtained from Run length matrices (CLRLMS) [24] , features achieved from Complete Local Binary Pattern (CLBP) with radius R = 2 and the number of neighboring pixels p = 16 [25] , 4 statistical features comprising of grey level mean, variance , third and fourth moments, 32 mean and energy features obtained from two level decomposition of packet wavelet [26] , 32 energy features obtained from Gabor filtering in 8 directions and 4 frequencies [27]. Since the histopathology images are RGB then the features are extracted from the three color components, therefore the final length of feature vectors will be 330.

3.4. CLASSIFICATION AND MITOSIS DETECTION

According to the extracted feature vectors by training an SVM classifier, the mitosis classification and detection is executed. During the SVM classification, the input feature data are projected to a higher order space. By this mapping which is usually done based on a kernel, the SVM is able to discriminate the feature vectors by optimal hyper planes in higher order space. It is proved that in SVM for calculating optimal hyper planes, equation Eq. (17) must be solved where a_i are Lagrange coefficients and x_i are related to the data of each class and y_i are the output of the SVM classifier and $K(x_i.x_j)$ is the kernel function [28].

$$\max_{\substack{a_i \geq 0 \\ \sum_{i=1}^{n} a_i y_i = 0}} \left\{ \sum_{i=1}^{n} a_i - \frac{1}{2} \sum_{i,j=1}^{n} y_i y_j a_i a_j K(x_i.x_j) \right\} \quad (17)$$

In general, the kernel functions may be linear, Gaussian (Radial Basis Function), homogeneous and inhomogeneous polynomials and also sigmoid kernel [25].In this paper, three different types of kernels i.e. Gaussian (RBF), polynomial & linear are used for mitosis detection. SVM algorithm is very sensitive to the entity of the chosen training and testing data therefore a k-fold cross validation is applied to the randomly selecting training and testing data and accordingly the SVM classifier is used many times. In this approach, data F are divided into K parts. Then, k-1 parts of the F are used as training dataset (*Ftr*) and the remaining part (*Fte*) is used as testing dataset. This procedure is repeated k times and at each step, new *Ftr* and *Fte* dataset are generated and the classification becomes accomplished. The mean accuracy obtained through the k repetition of SVM classifier is considered as the final mitosis detection accuracy.

4. Result and Discussions

The database employed for simulations is related to ICPR 2012 mitosis detection contest [29] that includes 35 breast cancer histopathology slide images which are acquired by Aperio XT scanners with 40x magnification. The resolution of histopathology images is 2084x2084 pixels. The total numbers of mitoses among 35 database images is 236. For training SVM classifier and achieving the results, we use k-fold that the parameter k and the number of iteration are set to 5 and 100, respectively.

For evaluating the results, there are some specific accuracy measurement criteria known as precision, recall and F-measure which are defined as equations (18) to (20). Precision criterion describes how many of the final classified candidates are real mitoses. This criterion is defined due to the equation (18) in which the TP (True Positive) parameter is the number of truly detected mitoses. The FP stands for the False Positive that relates to the number of non-mitoses that are misclassified as mitosis. The less the amount of FP is, the greater the precision will be. Recall or sensitivity criterion explains that how much the algorithm is successful in detection more numbers of mitosis correctly or in fact, how much it is successful to avoid losing real mitosis candidates existing in the original image. This criterion is defined as Eq. (19) in which FN (False Negative) stands for the number of last misclassified mitosis objects. The less the numbers of FN is, the higher the sensitivity criterion will be. Moreover, F-measure is the harmonic mean of the two previous criteria which measures the reconstruction degree between precision and recall criteria.

$$\text{Precision} = \frac{T_P}{T_P + F_P} \quad (18)$$

$$\text{Recall} = \frac{T_P}{T_P + F_N} \quad (19)$$

$$\text{F-score} = \frac{2 \times \text{Precision} \times \text{Recall}}{\text{Precision+Recal}} \quad (20)$$

4.1 EFFICIENCY OF THE PROPOSED MITOSIS DETECTION SYSTEM

The results obtained by the proposed method are discussed and compared with the results of other algorithms from two aspects. First, from the aspect of the number of extracted candidates and second, from the aspect of mitosis detection accuracy.Based on the F-measure criteria, the efficiency of the candidate extraction stage in the proposed method is compared with candidate extraction stage of other mitosis detection systems such as Laplace of Gaussian filtering method [14] and pixel-wise classification [13]. In candidate extraction stage of the proposed mitosis detection system, the training datasets are employed and the PSO optimization algorithm with the initial population number of N=500 under 1500 iterations is performed. The number of initial candidates achieved by ML estimation for testing datasets is about 6956. By the means of proposed method that remove the most of the non-mitosis candidates, the number of remaining candidates after reduction is rebated to 950 which means that about 86 percent of non-mitosis candidates are omitted. Chart1 compares the efficiency of the candidate extraction stage in proposed method with two other systems based on the precision, recall and F-measure criteria. As the results show, performance of the proposed algorithm in eliminating the non-mitotic candidates isbetter than existing algorithms so that resulted in 8.84% precision, 93.33% recall and 16.15% F-measure.Chart2 show mitosis detection result of proposed system based on different SVM kernels.Because of overlapping of the feature vectors belonging to mitosis and non-mitosis classes, the RBF kernel, that project the data to a higher order space nonlinearly, has better classification results than the linear and polynomial kernels. Based on the precision, recall and F-measure criteria, the efficiency of the proposed mitosis detection method is compared with results of other mitosis detection systems in Chart3 that our system result in 78.57% F-measure. As seen in Chart3, in the proposed system, because of the using non-mitosis candidate reduction algorithm, the output FP is very low and this fact leads to the improvement of precision and F-measure.

The result of the proposed mitosis detection system for a breast cancer histopathology image is shown in Figure 4 In histopathology image that is shown in Figure 4.a, there are two mitoses, while the number of extracted candidates by ML algorithm is about 356 candidates (Figure 4.b). Because of that in candidates extraction stage based on ML algorithm, number of non-mitosis candidates is much more than mitosis candidates, classification results tend to non-mitosis or false positives. To overcome this problem, by employing the proposed candidate selection algorithm, the number of candidates is reduced to 97 (Figure 4.c). According to results, about 72.75% of non-mitosis candidates are omitted. In fact about 72.75% of the candidates of sample histopathology image that can be false positive, is reduced. In Figure 4.d the result of mitosis detection by proposed system is shown. The green circles show true positives, red circles show false positive results.

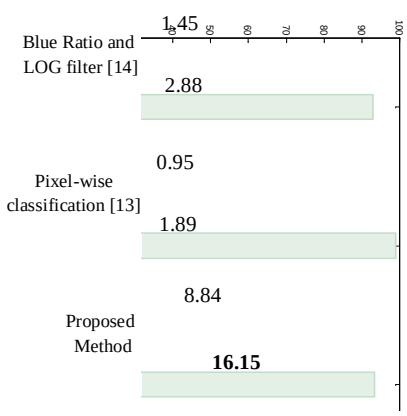


Chart 1. Candidate extraction efficiency in different algorithms

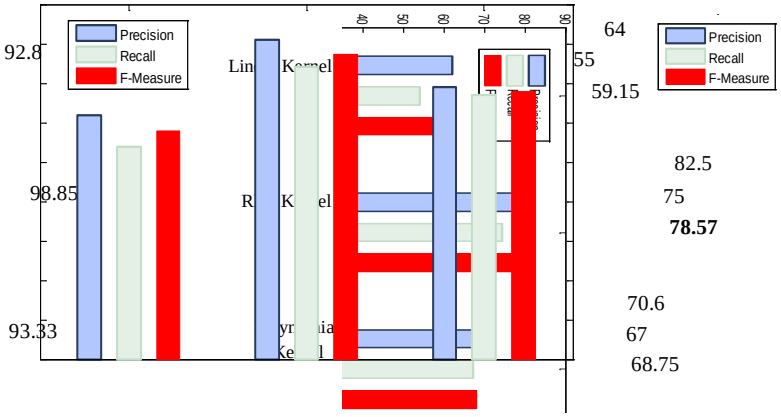


Chart 2. Result of proposed mitosis detection system to different SVM kernel

output FP is very low and this fact leads to the

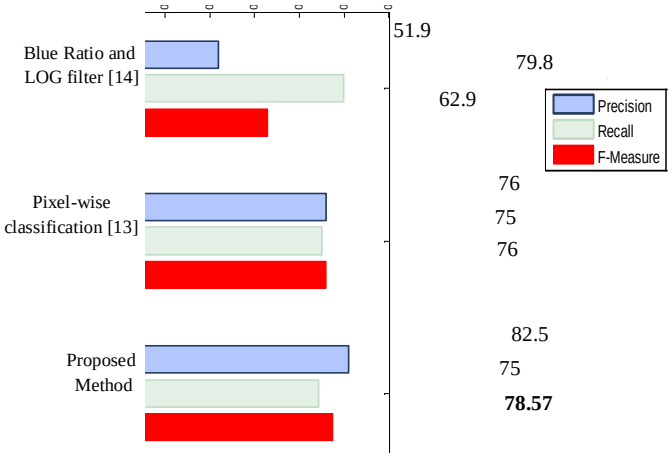


Chart 3. Result of mitosis detection in different algorithms

5. Conclusion

In this paper, an intelligent system for mitosis detection in breast cancer histopathology slide images is proposed. In the proposed system, by using ML algorithm that estimates the pdfs of mitosis and non-mitosis grey levels, the candidates of mitosis are extracted. Because the most extracted candidates are non-mitosis, to reduce false positives results, a candidate selection algorithm is proposed. In this algorithm by defining a cost function and minimizing it using PSO algorithm, the large number of non-mitosis candidates are removed. Then by using different feature extraction methods color, shape and texture features are extracted and by training the SVM classifier with different kernels, the mitosis is detected. We evaluated the performance of the proposed mitosis detection system in terms of F-measure over a set of 35 breast histology images. Results show the performance of proposed mitosis detection system that result in 78.57 % F- measure.

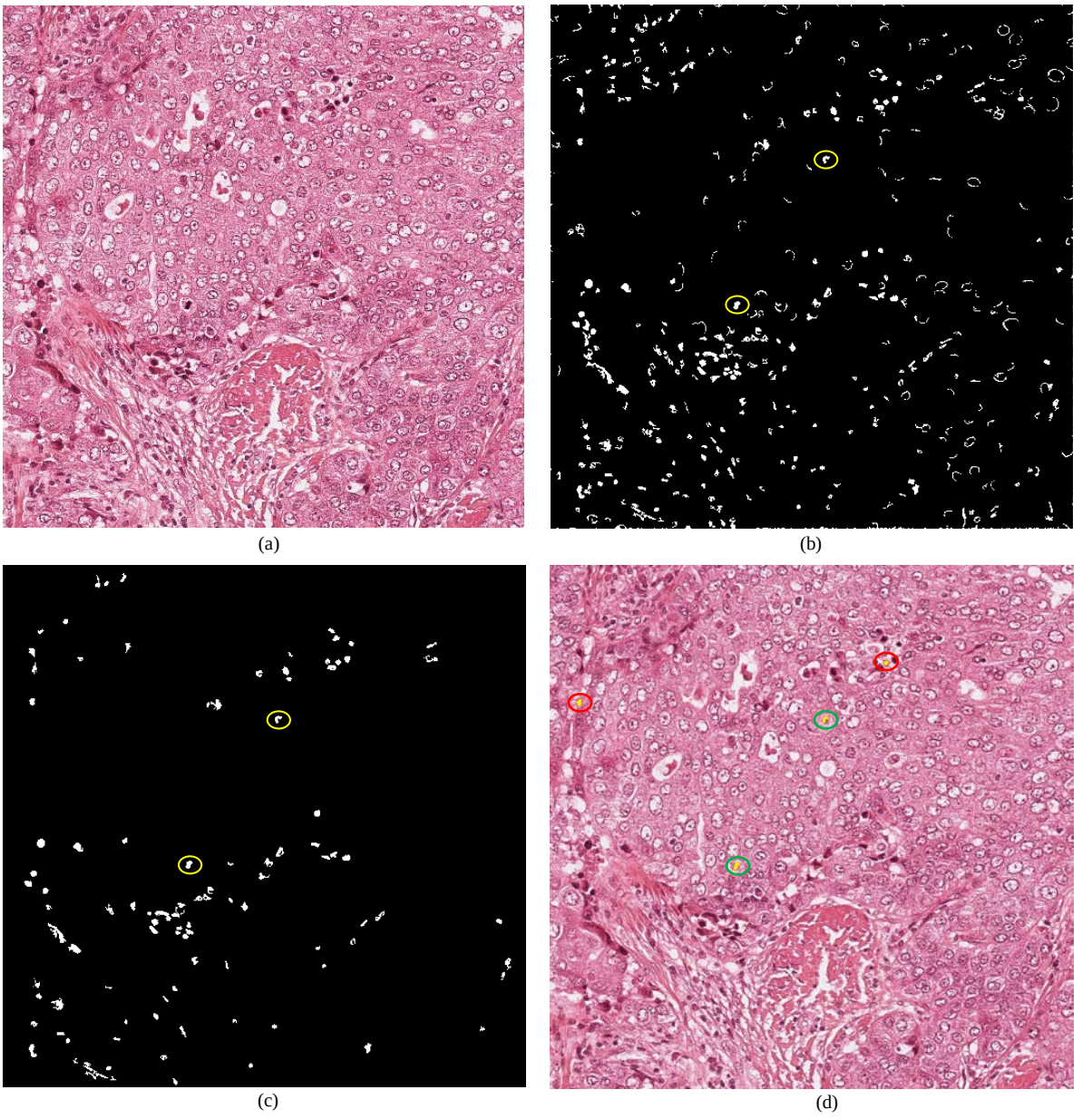


Figure. 4. The proposed mitosis detection results; (a) sample breast cancer histopathology image, (b) detection candidates using ML algorithm, (c) selection of desired candida and remove the most of non-mitosis candidates, (d) result of mitosis detection: green circles are true positive results, red circle shows false positive one.

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