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Acute Leukemia Classification based on Image Processing and Machine Learning Techniques

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Abstract

Acute leukemia is a fast-developing type of blood cancer that gets worse quickly in the children and adults and needs prompt treatment. Thus, this work displays an attempt that has been made to design a fast and cost-effective computer-aided system for acute leukemia diagnosis. The white blood cells in the microscopic images of blood smears are initially extracted by the Otsu's method and a cell separation algorithm is applied to break up the overlapped cells. Subsequently, several features are extracted from the whole cell, nucleus, and cytoplasm. The proposed system enhances the acute lymphoid, acute myeloid leukemia and their French, American and British (FAB) classification accuracy by applying the genetic algorithm to optimize the support vector machine kernel parameters and feature subset selection. The resulted overall accuracy of 100% for acute lymphoblastic leukemia subtypes and 90.32% for acute myeloblastic leukemia subtypes are achieved. Therefore, the current system yielded very promising results in terms of classification accuracy and the extent of acute leukemia subtypes that can be distinguished. However, future research is still needed to develop the diagnostic accuracy for acute myeloblastic leukemia subtypes.

Keywords: ***acute lymphoblastic leukemia, acute myeloblastic leukemia, support vector machine, genetic algorithm, feature subset selection.***

1. Introduction

Acute leukemia is usually characterized by uncontrolled proliferation of immature cells, either lymphoid or myeloid. Clinically it is categorized into two classes Acute Lymphoblastic Leukemia (ALL) and Acute Myeloblastic Leukemia (AML) [1]. Based on the morphology and cytochemical staining of blasts, French-American-British (FAB) divide ALL into three subtypes; L1, L2, and L3 while AML includes eight subtypes through M0 to M7, which are usually differentiated based on Peripheral Blood smear (PBS) test. However, the differentiation process subjected to human error and varies among observers depends upon their experience and interpretation. Thus, computer-aided diagnosis of acute leukemia based on image processing is suggested as an efficient method to overcome these drawbacks. According to the literature, most studies in this field can classify the cells in the blood smear images only as cancerous and non-cancerous cells with only a few some subtypes [2-8]. Hence purpose of this study is to extend the diagnostic process range to include the other subtypes except that of M6 subtype due to an insufficient dataset. After a literature review in section II. In details, the methodology used is described in section III, where the location of the cells and the nucleus are firstly determined. The morphological features such as color, shape and texture features are extracted. Then, the classification process is performed by using Support Vector Machine SVM kernel functions. Section IV used to summarize the obtained results which discuss in section V. Lastly, our conclusion and future work are summarized in section VI.

2. Related works:

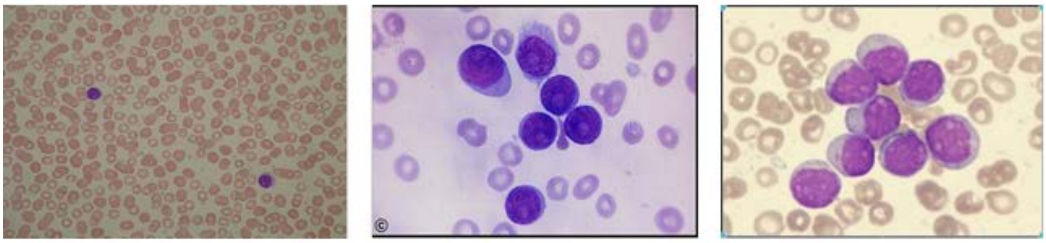
Various techniques have been used in the literature to improve the diagnostic process of non-healthy cells in the blood smear images. For instance, Rawat, J et al. (2015) [2] offered a system that can differentiate between healthy and non-healthy cells in an ALL-IDB dataset by using the shape and texture features as the input to the SVM classifier with achieving an accuracy of 89.8%. When Dumyan, S. and Gupta, A. (2017) [3] used Artificial Neural Network (ANN) classifier depend on the shape, texture, statistical and moment invariant features extracted from 36 blood smear images to identify ALL cells, the overall accuracy increased to 97.9%. Negm, A. et al. (2017) [4] proved that ANN and Decision tree classifier successfully discriminated the leukemia cells by using geometry, color and relative tissue features extracted from 642 images which are collected from a local hospital with achieved an accuracy of 99.519%. However, the study did not distinguish among the various FAB subtypes.

Due to the need of the pathologist and the difficulties faced those in the routine classification process of different acute leukemia subtypes, Rawat, J. et al. (2017) [5] used SVM classifier with a rich set of color, shape, and texture features with genetic algorithm for the recognition of FAB subtypes of ALL, i.e., L1, L2, and L3 as well as AML, i.e., M2, M3, and M5. The maximum accuracy was 97.1% and 98.5% for ALL and AML subtypes, respectively. Another attempt was introduced by Kasemi, F. et al. (2016) [6] which focused on the diagnostic methodology of AML subtypes, i.e., M2,M3,M4 and M5, by using SVM classifier with Hausdorff Dimension (HD), irregularity, texture, color and shape features extracted from 330 digital images admitted to Shariati hospital. The differentiation accuracy was 87%. While Reta, C. et al. (2015) [7] combined different classifiers to achieve accuracy of 90% in subtypes diagnosis due to the reduction in the number of false positives and false negatives presented different classifiers.

3. Methodology

3.1 Database Description:

In order to develop an efficient and robust computer-aided diagnosis system for acute leukemia, different staining images are used. The first collection of images has been taken from Acute Lymphoblastic Leukemia Image Database for Image Processing (ALL-IDB), where images have been captured with an optical laboratory microscope coupled with a Canon PowerShot G5 camera [8]. While the second one was collected from the American Society of Hematology (ASH) image bank that provides a high-quality web-based image library for hematological blood images labeled by an expert pathologist [9]. The third set of the collection was pictured from the Sutterstock image bank where is American stock photography offers the best quality images [10]. The last set of the collection was gathered from Pathpedia.com which is a comprehensive web-based resource for clinical and experimental pathology that offers hundreds of quality images [11]. The collection of this study database consists of 132 images of normal and acute leukemia blood smear images labeled by the pathologist. In details, it comprises of 50 images for normal patients, 27 images for ALL patients and 55 for AML patients. A total of 413 sub-images consist of 91 sub-images of normal cells, 106 sub-images of ALL cells and 216 of AML cells. Figure 1 displays an example of the sample images used in this study.



Healthy Cells ALL AML

Non-Healthy Cells

Fig. 1 Healthy and Non-healthy blood smear images

3.2 Proposed Computer-aided Diagnosis for Acute Leukemia:

The main diagram for acute leukemia diagnostic process in blood smear images is shown in Fig. 2. It consists of four stages; segmentation, feature extraction, feature subset selection, and classification. The segmentation stage is used to extract and identify the cells and their nucleus from different images. To differentiate among cells, the morphological features such as color, geometry and texture features are extracted by feature methods in the second stage. The informative features that reduce the accuracy are omitted in the following stage. The selected features are then processed by the classifier. The brief description of each stage is given in the next section of this study.

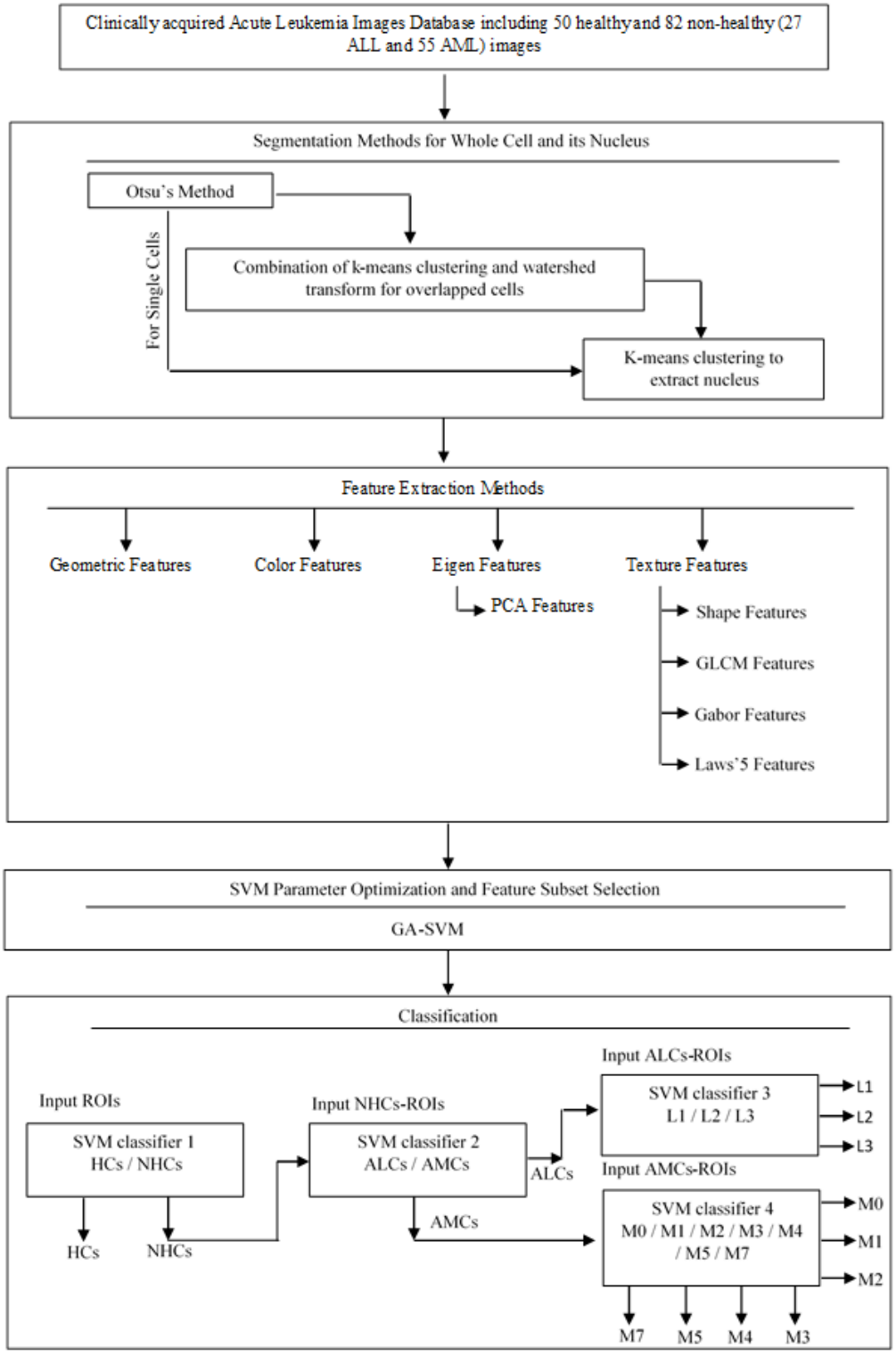


Fig. 2 Proposed approach for Diagnosis Acute Leukemia

3.2.1 Segmentation Stage

The segmentation stage is used to extract the leukocyte (White Blood Cells (WBCs)), i.e., the region of interest for acute leukemia diagnostic process from the input images [12]. The general steps used are described as follows.

In the first step, the blood smear image is acquired from the database and converted to the L*a*b* color space in the second step [13]. Then the Otsu's method is used to extract the WBCs from the b* component in order to produce the binary image. In the following step, the remaining background is eliminated by using morphological operations; filling holes and opening [14]. To identify the single and overlapped cells two measures; the total number of pixels of the object (area) and the ratio of the area of an object to the area of a circle with the same perimeter (compactness) are used [15]. To properly distinguish the overlapped cells, the value of less than 0.83 can be used as a threshold in the compactness measure. The area of the cell should be more than $7000/factor$, where the selected $factor$ depends on the dimension of each image. K-means clustering and modified watershed algorithm were used to separate the overlapping cells as described in Algorithm 1 [15, 16].

Algorithm 1

Step1: In the first step, the image is converted to the L*a*b* color space.

Step2: Then, k-means clustering is applied with a value of k=3.

Step3: To determine the nuclei in which cluster, the cluster with a minimum mean of b* layer is used as the nuclei cluster.

Step4: Morphological operations are used to save and smooth the shape of the nuclei.

Step5: A modified watershed transform is first applied to separate the nuclei.

Step6: Finally, the modified watershed transform is used to separate the cells based on the gradient method.

Step7: The boundary of each cell is smoothed by using the opening operation.

Finally, the nucleus of the produced cell is extracted by using the k-means cluster, then the cytoplasm is obtained by subtracting the nucleus from the whole cell in order to select the suitable features that can be used in the feature extraction stage. The outcome of the segmentation stage is shown in Fig. 3.

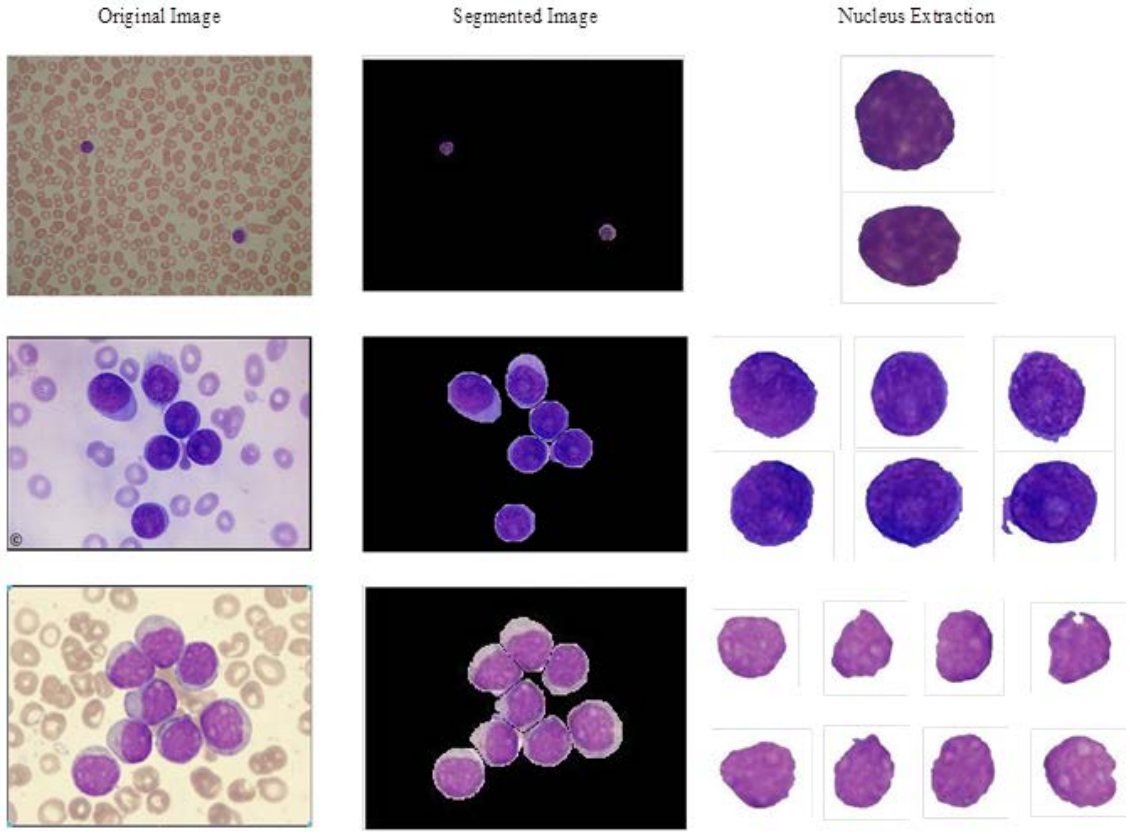


Fig. 3 The outcome of the segmentation stage

3.2.2 Feature Extraction Stage

Feature extraction is an important aspect in the pattern recognition and machine learning tasks in which the visual information, morphological changes in cells, shown in the peripheral blood smear is the first step for diagnosis acute leukemia [17]. Thus, the morphological features can be used as a magic tool to distinguish between normal and abnormal cells. In general, there are no specific features can be appropriately used for all kinds of computer vision application. Therefore, the current morphological features used for normal, ALL and AML cell differentiation are summarized in Table I [18].

On the basis of Table 1, the goal of this stage is to extract the distinct group of features such as color, geometry and texture features that can be used by pathologists to recognize acute leukemia cell.

Table 1: the morphological features in normal, myeloblastic and Lymphoblastic cells

Morphological Feature	**Normal**	**Myeloblastic**	**Lymphoblastic**
Size	Medium	Medium to large	Smaller to medium
Cytoplasm	Rough	Moderate	Scanty
Auer Rod	Absent	May be present	Absent
Nuclear Chromatin	Clogged	Fine	Coarse
nucleoli	Missing	Prominent, 1-4	Indistinct, 1-3

To achieve this goal, different types of features calculated from the sub-images have been extracted namely geometry, color, shape, statistical method (GLCM), transform domain-based model (Gabor), signal processing based (Law's mask) and PCA [19-21]. The brief description of the extracted features of the cell and its nucleus and cytoplasm is given in Table 2.

Table 2: Extracted features of cell and its nucleus and cytoplasm used

Method	**Region of Cell**	**Extracted Features**	**F_n**
Geometrical Features	Whole Cell & Nucleus	Area, Perimeter, Solidity, Eccentricity, Diameter, Extent, ConvexArea, MajorAxisLength, MinorAxisLength, Compactness, Convexity, Elongation, Rectangularity Cell-nucleus area ratio, Cell-nucleus perimeter ratio ,	28
	Cytoplasm	Area, Nucleus-cytoplasm area ratio	2
Color Features	Nucleus	Mean-red, Mean-green, Mean-blue, std-red, std-green, std-blue, Skewness-red, kewness-green, Skewness-blue, Kurtosis-red, Kurtosis-green, Kurtosis-blue, Energy-red, Energy-green, Energy-blue, Entropy-red, Entropy-green, Entropy-blue.	18
Texture Features			
Shape	Nucleus	Mean, Std, skewness, Kurtosis, Energy, Entropy	6
GLCM	Nucleus	Autocorrelation, Contrast, Correlation, Cluster Prominence, Cluster Shade, dissimilarity, Energy, Entropy, Homogeneity, Maximum Probability, Variance, Sum Average, Sum Variance, Sum Entropy, Difference Variance, Difference Entropy, Information Measure of Correlation 1, Information Measure of Correlation 2, Inverse Difference, Inverse Difference Normalized, Inverse Difference Moment Normalized.	80
Gabor	Whole Cell & Nucleus	Mean, Std	64
Laws'5	Nucleus	Mean, Std, Skewness, Kurtosis, Entropy for fifteen rotational invariant images	75
PCA	Nucleus	The first 10 Eigen values	10
Total number of features:			283

, where the std is the standard deviation, the GLCM is the gray level co-occurrence matrix and the PCA is the principle component analysis and F_n is the number of features.

3.2.3 Feature Selection Stage

In order to reduce the training time, decrease the associated overfitting risk and improved the classification accuracy, the unnecessary, redundant or irrelevant features should be removed from a high dimensional dataset. In machine learning, selecting informative features is done by feature selection methods such as Genetic Algorithm (GA) [22], Practical Swarm Optimization (PSO) [23], which at the same time use to optimize the SVM kernel function parameters in order to get the best classification accuracy [5]. Thus, in this study the GA which mimics the biological evaluation simultaneously used to optimize the SVM parameters and feature subset selection. The basic steps of the genetic algorithm are shown in Fig. 4. After careful observation of the several preliminary runs the initial genetic algorithm parameters used are listed in Table 3.

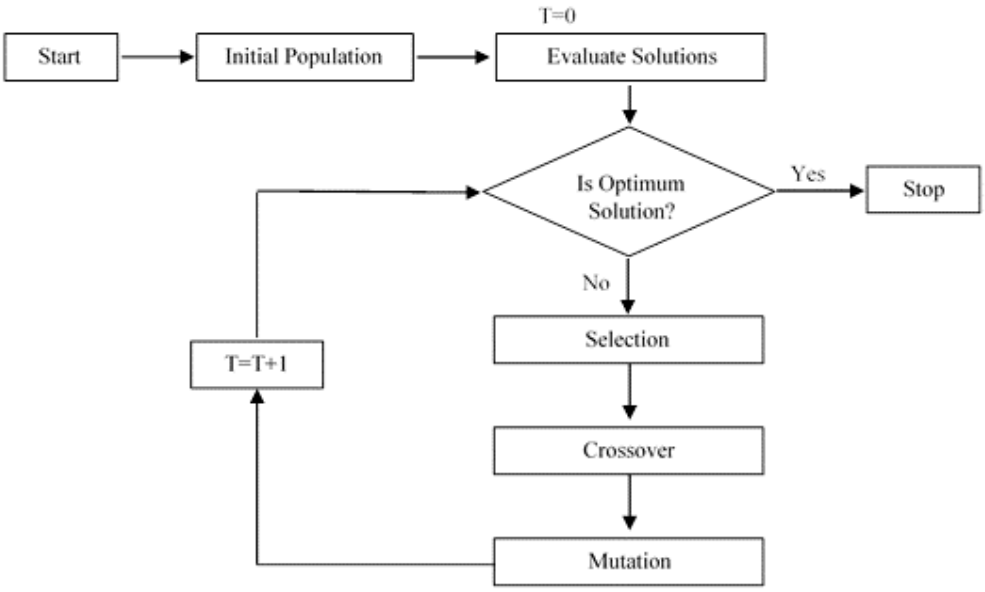


Fig. 4 The basic steps of the genetic algorithm used

Table 3. The initial Genetic Algorithm Parameters used

GA Parameter	Setting
C	$0 - 2^{20}$
γ	$2^{-20} - 0$
Generations Number	300
Population Size	100
Selection type	Tournament
Crossover type	Single-point crossover
Crossover Probability	0.8
Mutation Probability	0.1

3.2.4 Classification Stage

The main purpose of this stage is to discriminate the cancerous cells and find out various subtypes of acute leukemia. The classification stage of the current study is consisting of four modules; the first module used to recognize the non-healthy cells from healthy cells (NHCs/HCs). The second module is allocated to classify the non-healthy cells into Acute Lymphoblastic cells (ALCs) and Acute Myeloblastic cells (AMCs). In the third module, the ALCs are further classified into subtypes according to FAB classification, while the fourth module is dedicated to classifying the AMCs into their subtypes. These modules are designed by using the SVM classifier which is considered as a supervised learning model to construct an optimum hyperplane in the higher dimensional space [24]. Thus, the data points can be separated among different classes according to their labels with minimum expected risk. In the case of Non-Linear data separation, a kernel function is introduced to map the data points into the higher dimensional space. Consequently, to obtain a better classification performance, the kernel parameters C and γ for each set of training data should be set properly [25, 26].

4. Experiments and results

The proposed system was performed in Intel® Core™ i7-2670 QM CPU@ (2.20 GHz, 8 cores), 8 GRAM runs under windows 7 operating system and the development environment is MATLAB 2017 with Libsvm software [27]. A computer-aided system was designed for acute leukemia diagnosis from blood smear images. The conducted experiments and the classification performance are reported in this section. ALL and AML subtypes are diagnosed based on the presence of the non-healthy cells.

Experiment 1: Classification for HCs/NHCs cells using various SVM kernel functions

In this experiment, the classifier was designed for Healthy Cells/Non-Healthy Cells (HCs/NHCs) differentiation using various SVM kernel functions. The classifier performance of each kernel function is reported in Table 4. As can be seen from the table, the highest accuracy of 89.43% is achieved using the RBF kernel function. The obtained Cohen's kappa value is 62.70% for RBF, 59.57% for linear and 61.87% for polynomial kernel function using default parameters. While the f-measure is 84.02% for RBF, 80.79% for linear and 81.21% for polynomial kernel function. According to these results, RBF kernel function is selected for genetic algorithm implementation in order to enhance the classification accuracy. Table IV shows that achieved accuracy after applying the GA on the selected kernel function (RBF) is 99.19% with Cohen's kappa value of 97.60% and the f-measure of 98.81%.

Table 4. Classification performance for HCs/NHCs cells using various SVM kernel functions

	default parameters			With optimization and feature selection
Kernel Function	**Linear**	**Polynomial**	**RBF**	**RBF**
Number of features	283	283	283	132
Parameter C	1	1	1	1028771
Parameter γ	1/k	1/k	1/k	$8.67*10^{-7}$
Accuracy %	87.8049	87.8049	89.4309	99.1870
Precision %	85.9524	83.6859	94.0367	99.4845

Sensitivity %	76.2153	78.8773	75.9259	98.1481
F-Measure %	80.7915	81.2105	84.0164	98.8118
Cohen's kappa %	59.5661	61.8723	62.7012	97.5953

where; k is the number of the features

Experiment 2: Classification for ALCs/AMCs using various SVM kernel functions

The classifier in this experiment was built to discriminate Acute Lymphoblastic Cells (ALCs) from Acute Myeloblastic Cells (AMCs) by using kernel functions and the classifier performance results are presented in Table 5. The highest accuracy of 83.16% is also achieved using the same kernel function (RBF). The Cohen's kappa statistic is 58.96% for RBF, 39.52% for linear and 56.78% for polynomial kernel function under default conditions. The f-measure is 80.15% for RBF, 70.01% for linear and 78.87% for polynomial kernel function. On the basis of these results, the genetic algorithm is used to find suitable kernel parameters with which the SVM classifier achieved the highest accuracy of 96.84%. Cohen's kappa statistic has significantly increased to 92.76% and the f-measure becomes 96.39%.

Table 5. Classification performance for ALCs/AMCs using various SVM kernel functions

	default parameters			**With optimization and feature selection**
Kernel Function	**Linear**	**Polynomial**	**RBF**	**RBF**
Number of features	283	283	283	143
Parameter C	1	1	1	985697.9
Parameter γ	1/k	1/k	1/k	$4.83*10^{-7}$
Accuracy %	74.7368	82.1053	83.1579	96.8421
Precision %	71.2857	81.1326	82.9710	96.7949
Sensitivity %	68.7752	76.7389	77.5202	95.9929
F-Measure %	70.0080	78.8746	80.1530	96.3922
Cohen's kappa %	39.5225	56.7835	58.9633	92.7573

where; k is the number of the features

Experiment 3: Classification for ALL subtypes using various kernel functions

The experiment was performed in the FAB classification of ALCs into L1, L2, and L3 classes using the default and optimized SVM kernels. The classifier performance of each kernel function is recorded in Table 6. From Table VI, we can clearly state that the RBF kernel achieved an overall accuracy of 87.10%. The calculated Cohen's kappa value is 80.35% for RBF, 75.67% for linear and 71.03% for polynomial kernel function. When the experimental procedures are not optimized. The f-measure is 87.99% for RBF, 85.12% for linear and 81.38% of the polynomial kernel. However, after applying the genetic algorithm to optimize the selected kernel function the classification accuracy greatly increased to the maximum value of 100% with the Cohen's kappa statistic of 100% and f-measure also improved to the maximum value of 100%.

Table 6. Classification performance for ALL subtypes using various kernel functions

	default parameters			With optimization and feature selection
Kernel Function	**Linear**	**Polynomial**	**RBF**	**RBF**
Number of features	283	283	283	135
Parameter C	1	1	1	478200.46
Parameter γ	1/k	1/k	1/k	$3.95*10^{-7}$
Accuracy %	83.8710	80.6452	87.0968	100.0000
Precision %	85.6061	80.9091	89.1534	100.0000
Sensitivity %	84.6296	81.8519	86.8519	100.0000
F-Measure %	85.1150	81.3777	87.9876	100.0000
Cohen's kappa %	75.6672	71.0280	80.3487	100.0000
where; k is the number of the features				

Experiment 4: Classification for AML subtypes using various kernel functions

This experiment was designed for the FAB classification of the AMCs into M0 through M7 except M6 classes using the default and optimized SVM kernels. The performance values of the designed classifier are reported in Table 7. From Table VII, it can be observed that the highest accuracy of 69.35% is obtained by the RBF kernel function. The calculated Cohen's kappa coefficient value is 63.77% for RBF, 61.41% for linear and 55.81% for polynomial kernel function using default parameters. The f-measure is 71.84% for RBF, 67.79% for linear and 61.00% for polynomial kernel function. When we used the genetic algorithm to optimize the selected kernel function, the classification accuracy has gained increased to 90.32% with Cohen's kappa value of 88.51% and the f-measure becomes 91.12%. The value of the classification accuracy strongly depends on the feature subset selection and the SVM kernel parameter optimization.

Table 7. Classification performance for AML subtypes using various kernel functions

	default parameters			With optimization and feature selection
Kernel Function	**Linear**	**Polynomial**	**RBF**	**RBF**
Number of features	283	283	283	138
Parameter C	1	1	1	165169.16
Parameter γ	1/k	1/k	1/k	$2.21*10^{-7}$
Accuracy %	67.7419	62.9032	69.3548	90.3226
Precision %	70.6633	62.9252	74.7240	92.7171
Sensitivity %	65.1361	59.1837	69.1610	89.5692
F-Measure %	67.7872	60.9971	71.8350	91.1159
Cohen's kappa %	61.4068	55.8104	63.7650	88.5079
where; k is the number of the features				

5. Discussion:

From the above experiment results, the computer-aided system works essentially perfectly for acute leukemia subtypes diagnosis. It shows that the obtained results significantly enhanced after applying the genetic algorithm. Comparing these results with those from work of Negm, A. et al. (2017)[4] which use ANN and Decision Tree classifier rather than SVM, we see that these authors achieved approximately the same results for discrimination of healthy and cancerous cells. In the case of AML subtypes classification process Rawat, J. et al. (2017)[5] achieved better results of 98.5% than the present study of 90.32%, we believe this difference is due to their extremely low number of AML subtypes. However, the present study achieved the highest accuracy for the 3-classes classification of ALL subtypes of 100%. The promising results obtained from this study indicate that the computer-aided system can be efficiently used by the pathologist for acute leukemia diagnosis.

6. Conclusion

An acute leukemia diagnosis is an important challenge amongst the most Hematopathology issues. Thus, a computer-aided diagnostic system is utilized for the detection of acute leukemia subtypes by using Otsu's method to extract the WBCs. The k-means clustering and the modified watershed algorithm are used to separate the overlapped cells. Then both whole-cell and nucleus have been extracted. The GA is applied to optimize the SVM kernel parameters and feature subset selection. The overall accuracy of the developed computer-aided system is 99.19% for healthy and non-healthy cells on selected 132 subset features. The discrimination accuracy for ALL and AML types is 96.84% is gained with 143 subset features. The highest accuracy obtained from FAB subtypes of ALL is 100% is gained using 135 subset features while the maximum accuracy for the FAB subtypes of AML is 90.32% achieved by using a radial basis kernel function with 138 subset features. It concludes that the proposed system could be efficiently employed as a diagnostic tool to give help for FAB subtypes detection, i.e., L1, L2, L3 as well as M0, M1, M2, M3, M4, M5 and M7.

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