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PSO for Acute Lymphoblastic Leukemia Classification in blood microscopic images

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***Abstract*—** Leukemia means malignant neoplasm of the blood or bone. Leukemia affects both children and adults. It is a leading cause of death in present world. To avoid this problem we use Acute Lymphoblastic Leukemia (ALL) for save human life. To find it's through Microscopic. Blood and bone marrow tissue sample is performed by hematologists. Visual examinations of blood samples are often slow and limited by subjective interpretations and less accurate diagnosis. It was accomplished through segmentation, feature extraction and classification. This paper aims at proposing a quantitative microscopic approach toward the discrimination of lymphoblasts (malignant) from lymphocytes (normal) in blood samples. To use Particle Swarm Optimization (PSO) for accurate and authentic of ALL. This method is very useful to improve the all diagnostic accuracy by analyzing morphological and textual features from the blood image. Experimental results are obtained and compared over the available image data set.

Keywords - Acute lymphoblastic leukemia - Cell morphology – Quantitative - PSO Classification.

1 Introduction:

According to the American Cancer Society, cancer or malignant neoplasm is the world's leading cause of death followed by cardiovascular diseases. Cancer can be group of diseases characterized by: (i) uncontrolled cell division which prohibits programmed cell death and contributes to abnormal growth of tissues, (ii) ability to metastasize (spread), and (iii) eventually compromising the cellular function of the person, which successively may lead to death [1]. Cancer can affect any part of the body, although some cancers are more common or less common than others. According to the Centers for Disease Control and Prevention, 12.7 million people find out each year around the world that they have cancer and 7.6 million people die from cancer. And as per the joint study conducted by Centre for Global Health Research at St. Michael's Hospital, Toronto, and Indian national institutions in India, cancer alone accounted for 8 % of the 2.5 million total male deaths and 12 % of the 1.6 million total female deaths in the year 2010 [2].

Hematological malignancies are heterogeneous group of diseases which includes various forms of leukemia, lymphoma, and myeloma and are characterized by the malignant uncontrolled growth of hematopoietic cells [3]. The development of such malignancies results from an accumulation of genetic mutations in genes involved in regulating cell differentiation and proliferation, leading to aberrant control of these processes. It has been reported that approximately 75,000, 45,000, and 20,500 persons were diagnosed with lymphoma, leukemia, and myeloma, respectively, in 2011 in the USA alone [4]. In India, for the year 2010 approximately the total number of individuals suffering from blood cancer was estimated to be 104,239 [5]. And according to Indian Council of Medical Research (ICMR) by the year 2020, the total number of cancer cases of lymphoid and hematopoietic system is expected to go up to 77,190 for males and 55,384 for females. Even though leukemia starts in the bone marrow and lymphoma in the lymphatic system, both are considered as malignancies of the blood. The duo can affect people of all ages; however, leukemia is more common in children and young adults and people over the age of 60. The majority of leukemia deaths occur in low- and middle-income countries including India, where most of the patients are diagnosed in later stages. In India, leukemia is the most common childhood cancer with relative proportion varying between 25 and 40 % [6] and is the present subject of our study. Both acute lymphoblastic leukemia (ALL) and acute myeloblastic leukemia (AML) differ much in terms of nucleus chromatin and cell morphology. Image-based differentiation of benign and malignant cell samples is mostly based on cell morphology, texture, and color due to histochemical stain.

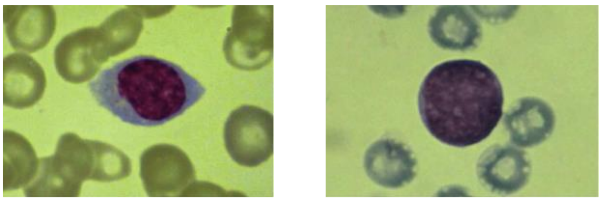
Definite genetic processes contribute toward malignant transformation of cells and their progeny forming a clone of leukemic cells [7]. Such neoplastic proliferations of hematopoietic cells are known as leukemia. Based on the severity of the disease, leukemia can be acute or chronic. Acute leukemia can be defined as neoplasms with more than 20 % of blasts in the peripheral blood/bone marrow and is a group of disorders which, if untreated, results in death in few weeks. Acute leukemia comprises a large number of leukemia's, and its practical classification is always difficult.

However, it can be categorized on the basis of morphologic findings, genetic abnormalities, putative etiology, cell of origin, immunophenotypic qualities, and clinical characteristics. Acute leukemia can be broadly classified into two types:

– Acute myeloblastic leukemia (AML)
– Acute lymphoblastic leukemia (ALL)

Due to advancement in treatment modalities, it is always necessary to subclass the leukemia to assess the prognosis and for the suitable planning of the treatment. The most widely used protocols for leukemia sub categorization are World Health Organization (WHO) classification and French, American, British (FAB) [8]. But, both fundamentally divide leukemia's as myeloid and lymphoid types, depending on the origin of the blast cell. Acute lymphoblastic leukemia (ALL) is the single most common pediatric malignancy accounting for one-fourths of all childhood cancers, thus considered as our current research focus. ALL affects both children and adults; however, primarily it is a childhood disease with peak prevalence between the age of 2 and 5 years. According to WHO, ALL subtypes are based on whether the precursor cell is a T or B lymphocyte, whereas FAB classification of ALL is based on morphology and histochemical staining and can be L_1, L_2, or L_3 subtypes.

Currently, microscopic examination of blood samples (peripheral blood/bone marrow) is a standard procedure for a confirmative screening and subtyping of ALL. However, regardless of advanced techniques like flow cytometer, immunophenotyping, and molecular probing, morphological evaluation of stained blood films still remains an economical procedure for the initial screening of ALL [9] across the globe. ALL diagnosis involves distinguishing a healthy lymphocyte from a malignant lymphocyte (lymphoblast) and can be difficult, even for an expert hematologist if the morphological features are not well developed or partially present. Nevertheless, there is always a chance of variability in human-reported diagnosis due to several factors, i.e., improper manual staining, operator fatigue, and inter-observer and intra-observer differences. Analysis of blood samples for hematological inferences is purely qualitative and is based on clinicopathological experience of the observer. As is the case at most regional cancer centers in India, visual diagnosis is often time-consuming and cumbersome as the number of cases per day is quite high across the country. Manual procedures are often subjected to unacceptable inter- and intra-observer variations [10], resulting in nonuniformity in diagnosis. Due to the prevalence of such uncertainty in manual screening of ALL, the conventional hematological evaluation needs to be strengthened using quantitative microscopy. Such automated procedures aim at avoiding painful biopsies and will facilitate early and precise diagnosis of leukemia. The representative blood microscopic images consisting of a lymphocyte (healthy) and a lymphoblast (malignant lymphocyte) are depicted in Fig. 1.



(a) Lymphocyte **(b)** Lymphoblast

Fig. 1 Representative blood microscopic images containing a lymphocyte and lymphoblast.

A brief overview of classifiers is

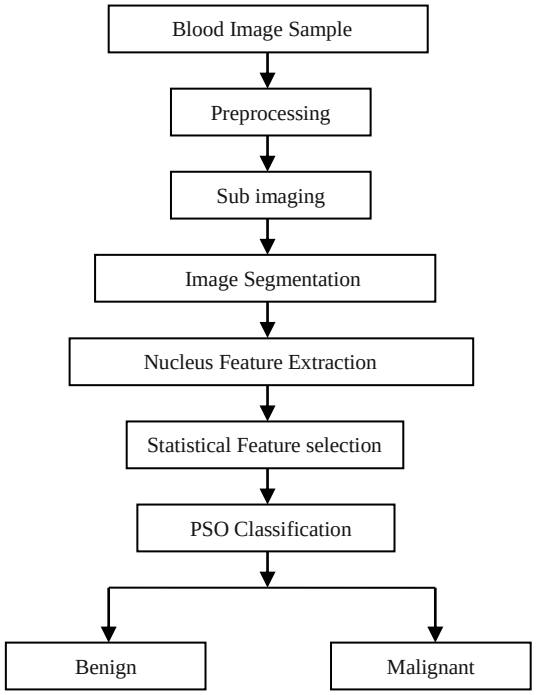


Fig. 2 Block diagram of the proposed ALL diagnosis system.

2 Methods:

2.1 Image acquisition:

Blood microscopic images of Leishman [11]-stained peripheral blood or bone marrow samples were optically grabbed by Zeiss Observer microscope (Carl Zeiss, Germany) under 100X oil-immersed setting and with an effective magnification of 1,000 at Ispat General Hospital, Rourkela, India. Each grabbed digital image is represented using three fundamental colors (red, green, and blue) and is stored in an array of size 1,024 X 1,024.

2.2 Preprocessing:

The presence of noise and acquisition of blood microscopic images under uneven lighting conditions necessitates

preprocessing. This is achieved using filtering and contrast enhancement.

2.3 Sub imaging:

Peripheral blood smear images are relatively larger with more than one leukocyte per image. However, the desired region of interest (ROI) must contain a single lymphocyte only for the detection of ALL. This is desired since each lymphocyte in the entire blood smear image has to be evaluated for differentiating an immature lymphocyte (lymphoblast) from a mature one [12]. To crop a sub image around each nucleus, a bounding box is required to be drawn around a center point. The coordinates of the center point can be determined by averaging the coordinates of each pixel in the object. This center point is known as center of mass and is obtained for each nucleus using the binary version of the nucleus image. Once the coordinates of the center of mass are obtained for each nucleus, a rectangular sub image is cropped from the original image. This entire process results in sub images containing a single leukocyte only with an assumption that there are no touching cells. It should be observed that along with the red blood cells (RBC) each image can contain a combination of neutrophils, eosinophils, basophils, lymphocytes, or monocytes. The problem of leukocyte classification or automated differential blood count has been investigated by several researchers. Implementation of such schemes will serve as lymphocyte identifier module in our proposed system and will facilitate the complete automation of the ALL disease recognition system. However, as ALL is a disease of lymphocytes, we are interested in images that contain lymphocytes only. Therefore, in the present study each blood smear image in the available data set is assumed to contain a particular type of leukocyte, i.e., lymphocyte only along with RBC.

2.4 Image Segmentation:

The main idea of the image segmentation is to group pixels in homogeneous regions and the usual approach to do this is by ‘common feature. Features can be represented by the space of colour, texture and gray levels, each exploring similarities between pixels of a region. Segmentation refers to the process of partitioning a digital image into multiple regions (sets of pixels). The goal of segmentation is to simplify and change the representation of an image into something that is more meaningful and easier to analyze. Image segmentation is typically used to locate objects and boundaries (lines, curves, etc.) in images. The result of image segmentation is a set of regions that collectively cover the entire image, or a set of contours extracted from the image. Each of the pixels in a region are similar with respect to some characteristic or computed property, such as color, intensity, or texture. The segmentation is based on the measurements taken from the image and might be greylevel, colour, texture, depth or motion. Image segmentation techniques are categorized into three classes: Clustering, edge detection, region growing. Some popular clustering algorithms like k-means are often used in image segmentation adjacent regions are significantly different with respect to the same characteristic(s). Segmentation is mainly used in medical imaging, Face recognition, Fingerprint recognition, Traffic control systems. K-means is a fast and simple clustering algorithm, which has been applied to many applications. K-Means clustering algorithm is also one of the recent techniques that have been proposed in the area of blood cells analysis. K-Means algorithm is one of the clustering algorithms that classify the input data points into multiple classes based on their minimum distance. In medical imaging, many researchers have proven that K-Means clustering has produced good segmentation image due to its performance in clustering of huge datasets.

Image segmentation of blood images is the foundation for all automated image-based hematological disease recognition systems including ALL. Image segmentation is performed in L*a*b* (CIELAB) color space. This color space consists of a luminosity layer L and a set of chromaticity layers a and b. The color information is present in the a and b layers only. Transforming the blood microscopic images from RGB to CIELAB reduces the color dimension from three (RGB) to two (a and b) and facilitates faster color based image segmentation.

1. Let Irgb represent an original lymphocyte image in RGB color space.
2. Apply L*a*b* color space conversion on Irgb to obtain the L*a*b* image, i.e., Ilab.
3. Construct the input feature vector using a* and b* components of Ilab.

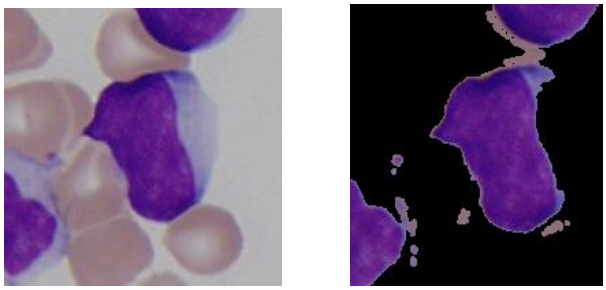


Fig. 3 Representation of Nucleus extraction from the original image.

2.5 Database Description:

The ALL-IDB2 version 1.0 is a collection of cropped area of interest of normal and blast cells that belongs to the ALL-IDB1 dataset. ALL-IDB2 images have similar gray level properties to the images of the ALL-IDB1, except the image dimensions.

The ALL-IDB2 image files are named with the notation ImXXX_Y.jpg where XXX is a progressive 3-digit

integer and Y is a Boolean digit equal to 0 if the cell placed in the center of the image is not a blast cell, and equal to 1 if the cell placed in the center of the image is a blast cell. Please note that all images labeled with Y=0 are from for healthy individuals, and all images labeled with Y=1 are from ALL patients.

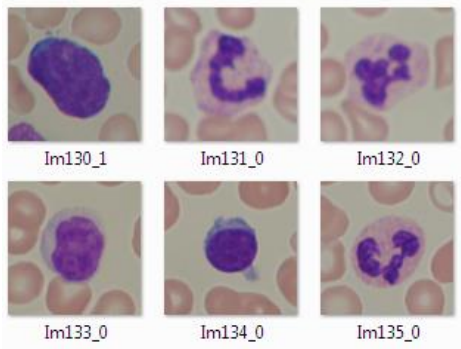


Fig. 4 Y=0 Representation of Healthy individuals .

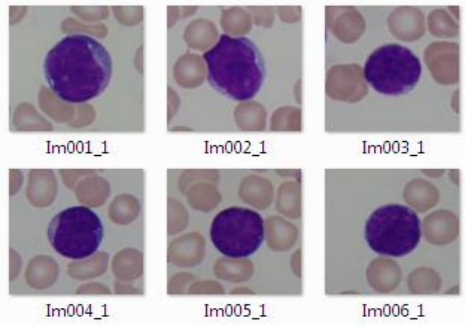


Fig. 5 Y=1 Representation of Patients.

3 Feature Extraction:

The criteria during diagnosis or in the follow-up of ALL are based on the percentage of lymphoblast present in the peripheral blood or bone marrow samples. The presence of more than 20 % of lymphoblasts in peripheral blood or bone marrow samples is labeled as ALL [7]. Morphologically, lymphoblast is characterized by large nucleus, having an irregular size and shape, the nucleoli are prominent, and the cytoplasm is scarce and intensely colored. Nucleus and cytoplasm of lymphoblast reflect morphological and functional changes in comparison with lymphocytes and play a main role in the assessment of malignancy in blood samples. The current visual criteria for the recognition of lymphoblasts in blood samples are summarized in and are followed by most of the hematologists across the globe. Analysis of the above table reveals marked differences in morphology among mature lymphocyte (small and large) and lymphoblast and is the basis of ALL diagnosis. As per expert's observation, it was noticed that in few samples the cell size of large lymphocytes equates to that of microblasts. In such samples, other morphological parameters, i.e., N/C ratio and nucleus chromatin distribution, are considered as essential discriminating factors for the diagnosis process. Further, it should also be remembered that the above features may not be distinct for the recognition of blasts individually. Accordingly, an amalgamation of all the features is adapted by expert hematologists for the final assessment of a PBS sample. Despite all, human evaluation of PBS is always subjective and time-consuming in nature. Therefore, to facilitate hematologists with a reliable tool for the diagnosis and follow-up of ALL, a set of novel quantitative features are presented here using an image processing approach.

Table 1: Features

Feature Index	Features
1	Nucleus Area
2	Nucleus Perimeter
3	Form Factor
4	Roundness
5	Compactness
6	Elongation
7	Fractal Dimension
8	Contrast
9	Correlation
10	Energy
11	Homogeneity

The basis for the differentiation of lymphocyte from lymphoblast as per experienced hematologists can be grouped as the following two types of characteristics, i.e., nuclear changes (variation in shape and size, chromatin pattern) and cytoplasmic changes (amount of cytoplasm and protein accumulation). In this work, we suggest some quantitative features for nucleus and cytoplasm region of a lymphocyte, which is correlated directly with the actual cytological features and aids in the computer processing of lymphocyte images. Among them, few features are directly measurable, while others can be computed from the measured data and each of them belongs to one of the three broad categories, i.e., morphological, textural, and color features[13].

1. Area (F1–F2): Individual area is computed by counting the total number of pixels present in the binary version of the nucleus and cytoplasm image, respectively.
2. Nucleus/cytoplasm ratio (F3): It is a measurement to indicate the maturity of a cell and is the ratio of the size of the nucleus to the size of the cytoplasm of that lymphocyte.

3. Cell size (F4): Entire cell area is computed by adding individual cytoplasm and nucleus area.

4. Perimeter (F5): The perimeter of the nucleus is obtained by counting the total number of pixels representing the nucleus boundary.

5. Form factor (F6): It is a shape parameter derived from the basic cellular measurements, i.e., area and perimeter. It can be mathematically defined as

$$\text{Form factor} = \frac{4 \times \pi \times \text{Area}}{\text{Perimeter}^2}$$

6. Roundness (F7): It is the degree to which the nucleus shape differs from that of a circle and can be defined as

$$\text{Roundness} = \frac{4 \times \text{Area}}{\pi \times \text{Maximum Diameter}^2}$$

7. Length/diameter ratio (F8): Length-to-diameter (L/D) ratio is the ratio of the major axis length and minor axis length of the nucleus region.

8. Compactness (F9): It is a numerical measure representing the degree to which a shape is compact.

9. Texture: Changes in the chromatin distribution reflects the organization of DNA in lymphocyte nucleus and is an essential diagnostic descriptor for classifying malignant lymphocytes (lymphoblast) from benign ones. Leishman staining of blood samples enables the visualization of chromatin distribution of lymphocyte nucleus in the form of texture. Genetic modifications are responsible for textural changes and are visible during the transition from normal to malignant. Such textural transformation can be quantified using Haralick's feature–based methods.

(a) Haralick's texture features: The gray-level co-occurrence matrix (GLCM) method is a way of extracting Haralick's texture features. A co-occurrence matrix is a two-dimensional matrix, in which both the rows and the columns represent a set of possible image values. GLCM can be defined as $Gd[i, j] = n_{i,j}$, where n_{ij} is the number of occurrences of the pixel (i, j) lying at distance d in the image. The co-occurrence matrix Gd has a dimension n 9 n, where n is the number of gray levels in the image. Statistical measures, i.e., contrast, correlation, homogeneity, energy and entropy are computed.

10. Color: Excessive pigmentation in lymphocyte nucleus results in hyperchromatism and is an important characteristic appearing in malignant lymphocytes. Chromatin abnormality results in increased staining capacity of nuclei. Such modification in DNA content of nuclei is visible in the form of change in color intensity in ALL. This color change during transition from normal to malignant is measured as mean color intensity in RGB and HSV color space, and a set of six features, i.e., lR, lG, lB, lH, lS, and lV, are computed to represent the change in color, where l represents the mean intensity for the red (R), green (G), blue (B), hue (H), saturation (S), and value (V) components, respectively. Similar measurement of color features was also performed for the cytoplasm region and is considered as a member of the feature vector for ALL recognition. It is observed that color features have low computational cost in comparison with texture features.

4 Classification:

In pattern recognition, classifiers are used to divide the feature space into different classes based on feature similarity. Depending on the number of classes, each feature vector is assigned a class label which is a predefined integer value and is based on the classifier output. Each classifier has to be configured such that the application of a set of inputs produces a desired set of outputs [14]. The entire measured data are divided into training and testing data sets. The training data are used for updating the weights, and the process of training the network is called learning paradigms. The remaining test data were used for validating the classifier performance.

4.1 Particle swarm optimization (PSO):

PSO is a population-based search algorithm and is initialized with a population of random solutions, called particles. Unlike in the other evolutionary computation techniques, each particle in PSO is also associated with a velocity. Particles fly through the search space with velocities which are dynamically adjusted according to their historical behaviors. Therefore, the particles have the tendency to fly toward the better and better search area over the course of search process. The PSO was first designed to simulate birds seeking food which is defined as a 'cornfield vector'. Assume the following scenario: a group of birds are randomly searching food in an area. There is only one piece of food in the area being searched. The birds do not know where the food is. But they know how far the food is and their peers' positions. So what is the best strategy to find the food? An effective strategy is to follow the bird which is nearest to the food. PSO learns from the scenario and uses it to solve the optimization problems. In PSO, each single solution is like a 'bird' in the search space, which is called 'particle.' All particles have fitness values which are evaluated by the fitness function to be optimized and have velocities which direct the flying of the particles (the particles fly through the problem space by following the particles with the best solutions so far). PSO is initialized with a group of random particles (solutions) and then searches for optima by updating each generation.

Each Particle I maintains the following information:

- X_i the current position of the particle,
- V_i the current velocity of the particle and
- Y_i the personal best position of the particle

The PSO algorithm can be summarized as follows:-

Step1: Initialize: Initialize parameters and population with random position and velocities.
Step2: Evaluation: Evaluate the fitness value for each particle.
Step3: Find the pbest: If the Fitness value of particle i is better than its best fitness value (pbest) in history, then set current fitness value as the new pbest to particle.
Step4: Find the gbest: If any pbest is updated and it is better than the current gbest, then set gbest to the current value.
Step5: Update velocity and position: Update velocity and move to next position according to equation (1) and (2) Step6: Stopping Criterion: If the number of iteration or CPU time are met, then stop; otherwise go back to step 2.

4.2 Radial basis functional neural network:

Radial basis functional network (RBFN) has gained considerable attention as an alternate to multilayer perceptron (MLP) trained by the back propagation algorithm [15]. The basis functions are embedded in a two-layer neural network, where each hidden unit implements a radial activated function. There are no weights connected between the input layer and hidden layer. Finding the appropriate RBF weights is called network training, and least mean square (LMS) learning algorithm is mostly used.

5 Performance analysis:

Performance evaluation is mandatory in all automated disease recognition systems and is conducted in this study to evaluate the ability of the above classifiers for the screening of leukemia in database images. In practice, performance metrics, i.e., accuracy, specificity, and sensitivity, are calculated from a confusion matrix which represents the differences in opinion between the hematologist and the classifier.

Table 2: Accuracy level

Classification Algorithm	Accuracy
BPN	92 %
RBFN	90 %
PSO	95 %

In this study, performance measure, i.e., accuracy, specificity, and sensitivity, is calculated to assess the diagnostic accuracy of the above classifiers and can be formulated in terms of TP, TN, FP, and FN. The performance measures can be written as:

$$\text{Accuracy} = \frac{TP + TN}{TP + FP + TN + FN} X \quad 100\%$$

$$\text{Sensitivity} = \frac{TP}{TP + FN} X \quad 100\%$$

$$\text{Specificity} = \frac{TN}{TN + FP} X \quad 100\%$$

In a binary classification problem, positive is considered as identified and negative as rejected. So in general, TP, TN, FP, and FN can be defined as:

TN (True Negative) – Correct Prediction as normal
FN (False Negative) – Incorrect prediction of normal.
FP (False Positive) – Incorrect prediction of abnormal.
TP (True Positive) – Correct prediction of abnormal.

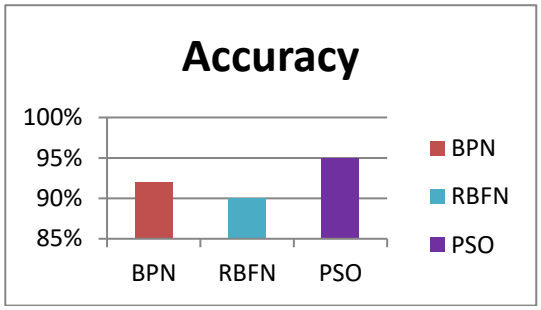


Fig.6 Representation of Accuracy Measure for PSO.

6 Results and discussion:

ALL is diagnosed on the basis of the presence or absence of unhealthy lymphocyte samples. Therefore, lymphocytes must be characterized as ‘‘unhealthy” or ‘‘healthy’’ cells in blood samples for the diagnosis of ALL. Experiments were conducted on the available lymphocyte images to demonstrate the efficacy of the image segmentation scheme and the segmented nucleus of lymphocyte and lymphoblast samples, respectively. However, we agree with the fact that much more research is necessary to completely fulfill the real clinical demand. Nevertheless, the results achieved demonstrate the potential of adopting a computer-aided approach for assisting hematologists in their final decision on suspected ALL patients. Average classification performance in terms of accuracy, sensitivity, and specificity of classifications such as PSO, BPN and RBFN was evaluated for set of features, and the comparative results are presented in Tables 2. It can be observed that the best overall accuracy of 95 is achieved with the proposed PSO classification algorithm.

7 Conclusion:

Diagnosis of ALL in children as well as adults is one of the most important hematopathology problems. Early screening of ALL is essential and can decisively modulate the treatment plan of suspected leukemia patients. Human screening of PBS samples is always time-consuming, subjective, and inconsistent while computer-aided diagnosis of ALL from images requires specific image processing and pattern recognition tools for precise screening. Average sensitivity and average specificity of greater than 90 % are also recorded

for the available images. The average recognition rate is much higher as required for automated acute leukemia detection. Results obtained stimulate future works that include sub classification of ALL.

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