

Mathematical Model of Computer Aided Detection for Acute Leukemia

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ABSTRACT: In the leukemia detection process, human errors, differences between observers based on their experiences and a huge variation in the time taken for diagnoses are some problems that need to overcome. Therefore, this paper proposes a computer-aided diagnostic mathematical model that assists in early detection of acute leukemia subtypes. The results showed that the conversion of images into $L^*a^*b^*$ color space produces uniformity in contrast compared to RGB color space. The resulted different features for each object indicate that the model can be used accurately to detect acute leukemia subtypes. To achieve this goal Lightness channel which gives a good contrast of the objects is selected to clearly extract the relevant object. The different features of selected objects suggest the ability to use the proposed model to distinguish the different acute leukemia subtypes. We hope the proposed model achieve a higher accuracy compared to available models in literature.

Keywords: Acute Leukemia, mathematical model, RGB color space, Lab color space, pre-processing, segmentation, feature extraction, theoretical test.

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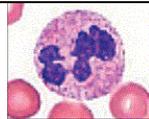
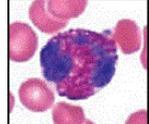
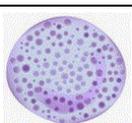
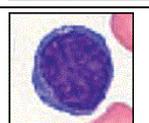
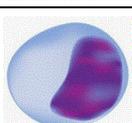
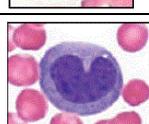
I. INTRODUCTION

Our body creates new cells continuously until growth is done, replace the dead cells and treat the damaged cells after injury by using certain genes. The damage to these genes leads to an abnormal behavior of cells called cancer. According to the World Health Organization, there were 8.8 million cancer deaths in 2015 compared to 8.2 million cases of 2012[1], which provides an overview of risk and cancer trends in the coming years.

Different types of cancers that effect the human body, including pancreatic cancer, lung cancer, colorectal, breast cancer, leukemia, etc. In leukemia cancer, tissues responsible for the production of blood cells including bone marrow and lymphatic system produces abnormal White Blood Cells (WBCs) or leukocytes. Theses abnormal leukocytes should die after a period of time but they don't and thus they become numerous in count[2]. There are five types of WBCs which classify based on granules into two main classes; granulocyte; that appears in the cytoplasm such as neutrophils of 40-70%, eosinophil of 5% and basophil of 0.5% and agranulocyte; that absent in the cytoplasm including lymphocytes of 20-50% and monocytes of 1-5%[3]. However, it easy to confuse these five types in the blood smear, thus we need to look to the morphology of nucleus. Table I shows the difference features of WBCs types according to granules staining and nucleus morphology[4].

The rapid development of the leukemia disease depends on how fast WBCs develop[5]. Therefore, leukemia also classify into two types: in **Acute Leukemia**; the abnormal blood cells (blasts) usually develop quickly and cannot do normal work. While, **Chronic Leukemia**; involves more mature blood cells that accumulate more slowly and can perform their normal function for a period of time. In diagnostic process, Leukemia is also named for the type of the WBCs that is affected. The rest of this paper is organized as follows. Section 2 discusses the literature review. Section 3 discusses subtypes of leukemia. Section 4 paper methodology. Section 5 provides a description of our proposed scheme in detail. Section 6 provides a brief analysis for our proposed model. Section 7 conclusion of our work. Section 8 future work.

Table I: Types of WBCs

Properties → WBCs Subtypes ↓	Microscope appearance	Diagram	Diameter (µm)	Nucleus	Granules
Neutrophil			12 - 14	Multi-lobed	Fine, faintly pink
Eosinophil			12 - 17	Bi-lobed	Stain bright red, or reddish - purple
Basophil			14 – 16	Bi-lobed or tri-lobed	Large blue
Lymphocytes			6 – 9 10 - 14	Deeply staining, eccentric	NK-cells and cytotoxic
Monocytes			Up to 20	Kidney shaped	None

https://www.histology.leeds.ac.uk/blood/blood_wbc.php

II. LITERATURE REVIEW

The significant amount of research work has been carried out to improve the diagnostic process of the acute leukemia by using the machine learning and image processing as a computer aided system. The detailed description of the literature for acute leukemia detection on the blood smear images are listed in Table II. From the literature the highest accuracy of the classification of healthy leukocytes and leukemia leukocytes is 99.5 obtained in the [6, 7] studies which were gained by various extraction features by using classifiers like Decision tree, Artificial Neural Network (ANN) and Support Vector Machine (SVM), respectively. However, in the first study [6] study did not discriminate between lymphoid and myeloid subtypes, and the observed accuracy achieved by the second study [7] decreased to 97.1 and 98.5 % during the classification process of acute leukemia subtypes. From the extensive study of literature, it can be seen that there are rare studies related to discriminate of different acute leukemia subtypes. So there is a need to build a reliable computer aided classification system to improve diagnostic process of the acute leukemia with high accuracy and in short time.

Table II: Studies carried out for the healthy leukocytes and acute leukemia classification

Authors, Year	Feature extraction method	Classifier used	Dataset used	No. of images	Accuracy (%)		
					Healthy or Leukemia	Leukemia subtypes	
						ALL	AML
Rawat, J. et al. 2015[8]	Shape and texture features	SVM	ALL-IDB	130	89.8	-	-
Negm, A. et al., 2017[9]	Geometry, color, texture and size features	Decision tree and ANN	-	642	99.519	-	-
Patel, N. and Mishra, A. 2015[2]	Color, geometry, texture and statistical features	SVM	ALL-IDB	27	93.57	-	-
Paswan, S. and Kumar, Y. 2017[10]	Color, texture, GLCM features and HD	KNN & SVM	ASH	100	61.11 & 83.33	-	-
Rawat, J. et al., 2017[7]	Color, geometric and texture features	SVM	ASH	240	99.5	97.1	98.5
Dumyan, S. and Gupta, A. 2017[11]	Shape, texture, statistics and moment invariants features	ANN	-	36	97.9	-	-

Kumar, P. and Vasuki, S., 2017[6]	GLCM, geometric and color features	SVM	-	70	90		
Priya, D. K. et al., 2015[12]	HD, LBP, shape and texture features	FFNN	ASH	80	98	-	-
Agaian, S. and Chronopoulos, A. T., 2014[13]	HD, color, shape and texture features	SVM	ASH	80	98	-	-
Sukanya, C. M. et al., 2016[14]	DRLBP and DRLTP	SVM	-	60	-	-	-
Kazemi, F. et al., 2016[15]	HD, shape, color and texture features	SVM	Shariati Hospital	330	98	-	87
Goutam, D. and Sailaja, S., 2015[16]	Texture features	SVM	ASH	90	98	-	-

GLCM is Gray Scale Co-occurrence Matrix, HD is Hausdroff dimension, LBP is Local Binary Pattern, DRLBP is Discriminative Robust Local Binary Pattern, DRLTP is Discriminative Robust Local Ternary Pattern, KNN is k-nearest neighbor, FFNN is feedforward Neural Network

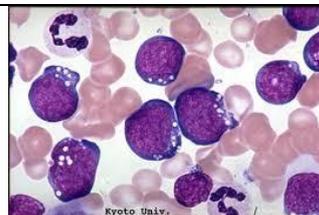
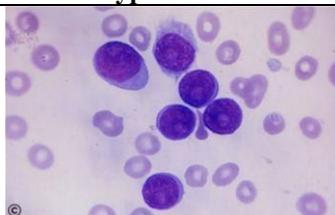
III. SUBTYPES OF LEUKEMIA

The routine examination of the blood smear under microscope classifies acute and chronic leukemia into four subtypes [5, 17, 18]; **Acute Myeloid Leukemia (AML)**, which starts in myeloid cells of bone marrow and quickly moves into the blood, is the most common type of leukemia diagnosed in both adults and children. **Acute Lymphocytic Leukemia (ALL)**, this type of cancer mostly spread in children under the age of 14 years. **Chronic Myeloid Leukemia (CML)**, is attributed to a defect in the Philadelphia chromosome that responsible of a genetic mutation in BCR ABL gene. This gene produces an abnormal protein called Tyrosine Kinase. **Chronic Lymphocytic Leukemia (CLL)**, as opposite of ALL is common in adults and characterized by the accumulation of small, mature-appearing lymphocytes in the blood, marrow and lymphoid tissues. However, the patient can feel good for several years without the need for any treatment.

The French American British (FAB) classification system divides ALL and AML into eleven subtypes, for ALL L1 to L3 and for AML M0 to M7 based on the cell morphology[19]. Table III and Table IV show the FAB classification of ALL and AML subtypes [20-22]

Table III: FAB Classification

ALL subtypes



L1: Lymphoblastic leukemia with homogeneous structure

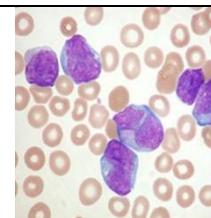
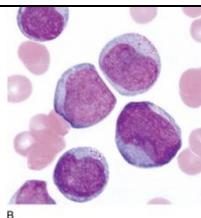
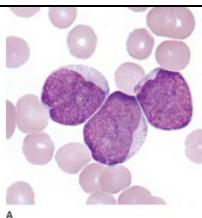
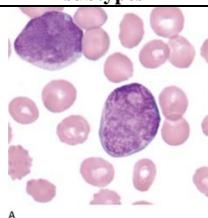
L2: Lymphoblastic leukemia with varied structure

L3: Burkitt's leukemia

<http://www.elsevier.es/en-revista-revista-medica-del-hospital-general-325-articulo-morphology-leukaemias-S0185106315000724>

Table IV: FAB Classification

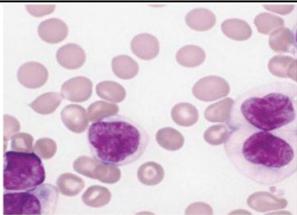
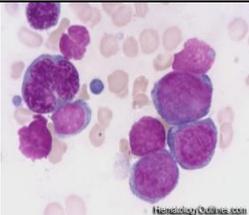
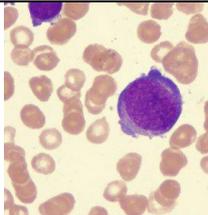
AML subtypes



M1: Acute myeloblastic leukemia

M2: Acute myeloblastic

M3: Promyelocytic

M0: Acute myeloblastic leukemia with minimal differentiation	without maturation	leukemia with maturation	leukemia
			
M4: Acute myelomonocytic leukemia	M5: Acute monocytic leukemia	M6: Acute erythroid leukemia	M7: Acute megakaryocytic leukemia
https://www.wikidoc.org/index.php/Acute_myeloid_leukemia_pathophysiology			

However, the downside associated with diagnostic techniques used by hematologist in blood test make a difficult to differentiate among different subtypes. Thus this paper aims to generate a successful model that be used to assist hematologist to detect acute leukemia blood cells.

IV. METHODOLOGY

In this section, the mathematical equations of image processing, which is programmed using MATLAB software, will be discussed. The proposed system for automated acute leukemia detection from blood smear images is shown in Figure 1.

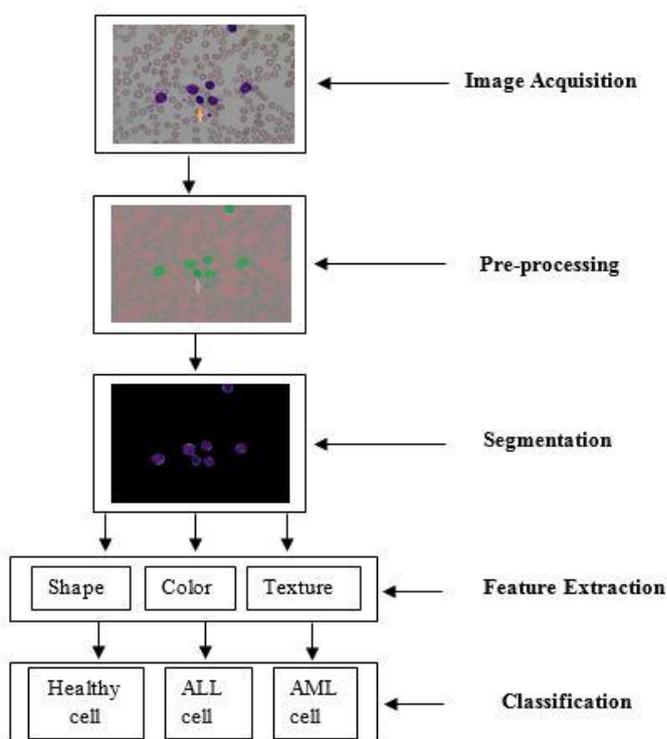


Figure 1. Flowchart of the steps will be achieved in the proposed mathematical model

V. DESCRIPTION OF OUR PROPOSED SCHEME

1.1. Image Acquisition

In this step, two data sets of acute leukemia images; Acute Lymphocytic Leukemia – Image Database (ALL-IDB)[23] and the American Society of Hematology (ASH) [24], captured with an optical laboratory microscope will be taken. This provides a wide range of high quality images for the following steps.

1.2. Pre-processing

The acquired image mostly contains some sort of noise and bluer regions. So before further processing, a median filter will be suggested to enhance the quality of the input image [25]. The non-uniformity in the contrast between cells and background prevents a right segmentation thus to facilitate the interpretation of the image and extract the object information, the RGB color space of the input image should be converted to the $L^*a^*b^*$ color space by using the basic equations [26].

Assuming that CC is denoted to each RGB color channel, which is normalized by divided by $2^{\text{bit depth}}$ (255). The following boundary conditions of $C_{R,G,B}$ is applied to the normalized CC to get the XYZ three dimensional space values as follows.

$$C_{R,G,B} = \begin{cases} \frac{CC}{12.92} & \text{if } CC \leq 0.04045 \\ \left(\frac{CC + 0.055}{1.055}\right)^{2.4} & \text{otherwise} \end{cases}$$

$$\begin{bmatrix} X \\ Y \\ Z \end{bmatrix} = \begin{bmatrix} 0.608 & 0.174 & 0.201 \\ 0.299 & 0.587 & 0.114 \\ 0.000 & 0.066 & 1.117 \end{bmatrix} \begin{bmatrix} R \\ G \\ B \end{bmatrix}$$

The transformation to CIELab is done by using a reference white point which is $(X_{ref}, Y_{ref}, \text{ and } Z_{ref})$

$$L = (116 * f(Y/Y_{ref})) - 16$$

$$a = 500 * [f(Z/Z_{ref}) - f(Y/Y_{ref})]$$

$$b = 200 * [f(Y/Y_{ref}) - f(X/X_{ref})]$$

where $f(x) = \begin{cases} x^{1/3} & \text{if } x > 0.008856 \\ (7.787 * x) + (16/116) & \text{otherwise} \end{cases}$

1.3. Segmentation

Although the b channel gives more localized blast cells without the background interfering, the L channel is selected in the theoretical test due to the higher contrast to identify the specific region of acute leukemia blast cells.

To detect the blast cell regions from L color channel subspace the Otsu's method is used [27] to calculate the optimum threshold that has the lowest weighted within-class variance. The value of each point in the selected channel is compared to the optimum threshold in order to get the binary image based on the following equation.

$$\forall (i,j) \in I_{output}, I_{output}(i,j) = \begin{cases} 1 & I(i,j) \geq T \\ 0 & I(i,j) < T \end{cases}$$

To extract the correct features of acute leukemia cells, the single cells crop from the binary image while the overlapped cells will be separated by using a watershed segmentation which is defined as follows[28].

$$Wshed(f) = D \cap \left(\bigcup_{i \in I} CB(m_i)\right)^c$$

where D is the topographical distance between two points p and q and can be given by:

$$T_f(p,q) = \inf_{\gamma} \int_{\gamma} \|\nabla f(\gamma(s))\| ds$$

$CB(m_i)$ is the catchment basin of the minimum and can be given by:

$$CB(m_i) = \{x \in D | \forall j \in I \setminus \{i\}: f(m_i) + T_f(x, m_i) < f(m_j) + T_f(x, m_j)\}$$

The resulted blast cell consists of two parts cytoplasm and nucleus. Therefore, we need to segregate the nucleus from the cytoplasm.

1.4. Feature Extraction

The aim of this step is to define a large set of data into feature set with a reduced dimension. The extracted features based on shape, texture and color from regions selected in the segmentation process; nucleus and whole cell,[29] provides valuable information for the classification of acute leukemia cells. In the following we will describe the three important features will be used in this study.

1.4.1. Shape Features: that provides information on image geometric features; such as area, perimeter, diameter, solidity, etc., from the cell and its nucleus. Then the Elongation, Eccentricity, Rectangularity, Convexity and Compactness [2] will be calculated as follows:

- Elongation:

$$\text{Elongation} = 1 - \frac{\text{minor axis}}{\text{major axis}}$$

- Rectangularity

$$\text{Rectangularity} = \frac{\text{area}}{\text{major axis} * \text{minor axis}}$$

- Eccentricity

$$\text{Eccentricity} = \frac{\sqrt{\text{major axis}^2 - \text{minor axis}^2}}{\text{major axis}}$$

- Convexity

$$\text{Convexity} = \frac{\text{perimeter}_{\text{convex}}}{\text{perimeter}}$$

- Compactness

$$\text{Compactness} = \frac{4 * \pi * \text{area}}{\text{perimeter}^2}$$

1.4.2. Texture Features: which study the nucleus chromatin structure and divides into two types; histogram-based features and GLCM features. In histogram-based features: a histogram plot displays the distribution of pixels among grayscale values. The common features such as mean, standard deviation, etc., and their equations are listed in the Appendix.

GLCM features: will be used to determine the spatial dependency, the relationship between pairs of pixels at a time, of grayscale values in the image by relying on the second order statistics [30-32] as:

$$G_{dx,dy}(i, j) = \sum_{x=1}^n \sum_{y=1}^m \begin{cases} 1, & \text{if } I(x, y) = i \text{ and } I(x + dx, y + dy) = j \\ 0, & \text{otherwise} \end{cases}$$

where i and j are the gray level values, x and y are the spatial position in the image and the offset (dx, dy) depends on the direction θ and distance D . The sum of the squared elements in the GLCM (energy), the measurement of the intensity between two neighboring pixels over the whole image (contrast), a correlation between two neighboring pixels over the whole image (correlation), and the measurement of the proximity of the distribution of elements in the GLCM to GLCM diagonal (homogeneity) will be handled by MATLAB function (graycomatrix) while, another set of texture features will be calculated. The equations for each of these features are listed in the Appendix.

1.4.3. Color Features: the mean values of the gray image will be produced for each color channel such as; mean, standard deviation, skewness, kurtosis, energy and entropy.

1.5. Classification

In the final stage, the calculated feature values will be used to categorize leukemia patients into ALL and AML subtypes. To do that, first the entire specific data will be divided into training and testing data sets. Second, the feature vector of training dataset will be assigned into the class label of ALL and AML subtypes. Finally, the values of the testing dataset will be checked with the previous calculated values in the training step. Based on the values of the input image the classifier classifies the test image into ALL and AML subtypes with their discrimination from healthy cells. To evaluate the efficiency of the classifier a confusion metric shown in Table V will be introduced.

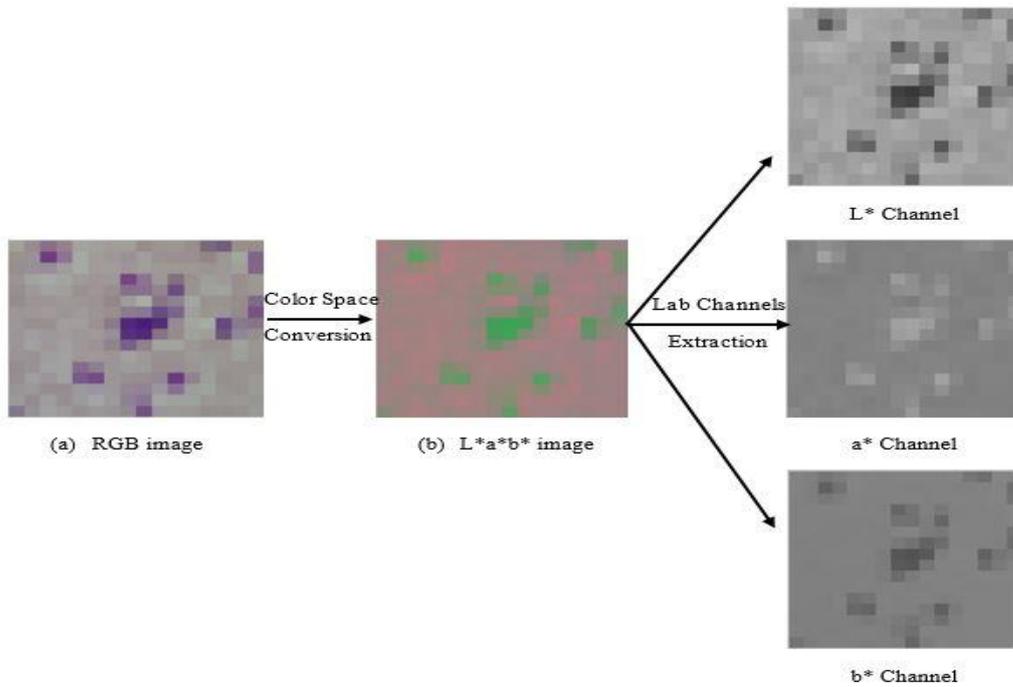


Figure 2. The Lab color space channels

As can be seen the objects are more contrasted in L* channel which provide a good chance to recognize the object region. To highlights the desired objects of the binary image resulting from the segmentation process using Otsu’s method, the complementation is done in Table VII and in Figure 3.

Table VII: Otsu’s method and its complementation

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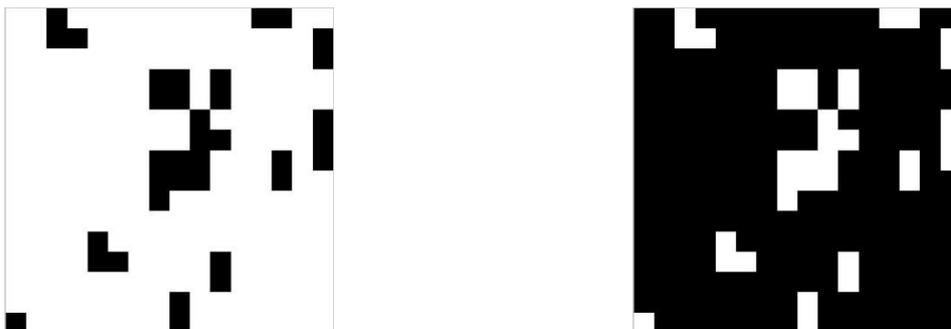


Figure 3. Segmentation process of binary image in left and complementation of binary image in right

These results suggest that the proposed model provides an easy way that will help to reflect the object in the input image and facilitate its feature extraction. In order to crop each object individually in the binary image and find out its features the connected objects are labeled after removing the boundary objects. The resulted cropped objects are shown in Figure 4.

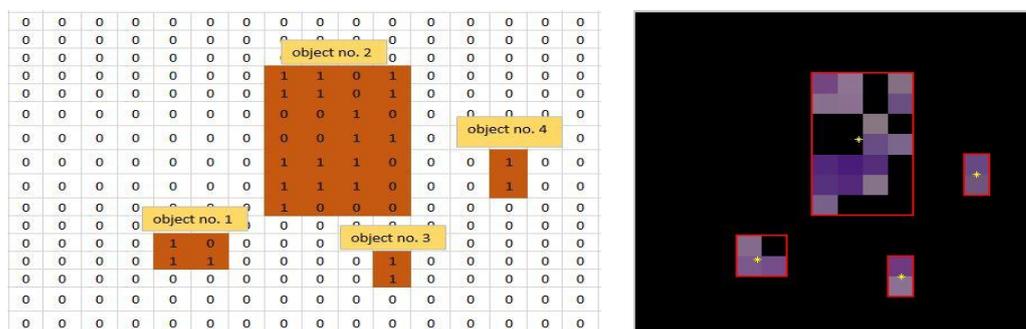


Figure 4. Labeling process of connected components, matrix in left and input image in right

In our proposed model the shape, color and texture features of the extracted objects are calculated in Table VIII.

Table VIII: Feature extractions from the image				
Feature Extracted	Object no. 1	Object no. 2	Object no. 3	Object no. 4
Shape Features				
Size	3	16	2	2
Perimeter	3.4142	23.3134	2	2
Diameter	1.95441	4.513517	1.595769	1.595769
Roundness	3.234098	0.369929	6.283185	6.283185
GLCM Features				
Energy	0.3888889	0.208984375	0.333333333	0.333333333
Contrast	3	3.28125	4.333333333	4.333333333
Homogeneity	0.750	0.622395833	0.527777778	0.527777778
Entropy	1.011404265	1.934941269	1.098612289	1.098612289
Color Feature				
Red Channel				
Mean	0.162527233	1.1225	0.163398693	0.140522876
Standard Deviation	0.230333408	1.42298981	0.233244523	0.19899036
Skewness	0.720604663	0.596676053	0.765236979	0.71543576
Kurtosis	-1.461442769	-1.444437345	-1.336341669	-1.47645753
Entropy	1.002718265	1.747389797	0.867563228	0.867563228
Energy	0.481481481	0.37125	0.5	0.5
Green Channel				
Mean	0.119854248	0.821875	0.111764706	0.103921569
Standard Deviation	0.170526871	1.120395961	0.169880585	0.14749391
Skewness	0.792842461	0.884306187	0.099784505	0.729693862
Kurtosis	-1.253016201	-0.907658972	-0.426357066	-1.43622791
Entropy	1.002718265	1.712732438	0.867553228	0.867563228
Energy	0.481431481	0.3725	0.5	0.5
Blue Channel				
Mean	0.182570806	1.329375	0.181699346	0.169934641
Standard Deviation	0.258229404	1.633036737	0.257768365	0.240419842
Skewness	0.707970853	0.426645669	0.726918996	0.709645388
Kurtosis	-1.497571742	-792889054	-1.444050126	-1.492821167
Entropy	0.848685558	1.630336516	0.867563228	0.867563228
Energy	0.50617284	0.37625	0.5	0.5

According to the results, each object can distinguish by different features. That is our proposed model is a promising strategy that can be used to characterize acute leukemia subtypes.

VII. CONCLUSION

Leukemia as a fatal disease caused due to exceed in the number of WBCs cells must be diagnosed early. So, this paper suggests an effective mathematical model which will be used to detect the acute leukemia subtypes from the blood smear images. The proposed model was tested mathematically. The result showed that the conversion of images into $L^*a^*b^*$ color space produce uniformity compared to RGB color space. The

proposed model suggested different features for each object indicating that the model can be used accurately to detect acute leukemia subtypes.

VIII. FUTURE WORK

The proposed model will apply to upgrade quality and accuracy of segmentation and classification tasks in order to gain more confidence diagnostic process. The associated problem of limited leukemia classification subtypes gives the proposed model an opportunity to seek a critical task to classify the various acute leukemia subtypes.

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APPENDIX: TEXTURE FEATURE EQUATIONS

Features	Equations
First Order Statistics	
Mean	$\mu = \sum_{i=1}^{N_g} iH(i)$ <p>where: N_g is the number of the non-zero histogram bins and $H(i)$ is the first order histogram.</p>
Standard Deviation	$\sigma = \sqrt{\sum_{i=1}^{N_g} (i - \mu)^2 H(i)}$
Skewness	$s = \sigma^{-3} \sum_{i=1}^{N_g} (i - \mu)^3 H(i)$
Kurtosis	$k = \left(\sigma^{-4} \sum_{i=1}^{N_g} (i - \mu)^4 H(i) \right) - 3$
Entropy	$- \sum_{i=1}^{N_g} H(i) \log_{25} H(i)$
Energy	$\sum_{i=1}^{N_g} H(i)^2$
Second Order Statistics	
Energy	$\sum_{i=1}^{N_g} \sum_{j=1}^{N_g} [g(i,j)^2]$ <p>where $g(i,j)$ denote to the co-occurrence matrix</p>
Contrast	$\sum_{i=1}^{N_g} \sum_{j=1}^{N_g} i - j ^2 g(i,j)$
Correlation	$\sum_{i=1}^{N_g} \sum_{j=1}^{N_g} \frac{(i - \mu_x)(j - \mu_y)g(i,j)}{\sigma_x \sigma_y}$ <p>where μ is the mean of $g(i,j)$, $\mu_x(i)$ is the mean of the row i, $\mu_y(j)$ is the mean of column j, $\sigma_x(i)$ is the standard deviation of row i, $\sigma_y(j)$ is the standard deviation of column j</p>
Homogeneity	$\sum_{i=1}^{N_g} \sum_{j=1}^{N_g} \frac{g(i,j)}{1 + i - j }$
Entropy	$- \sum_{i=1}^{N_g} \sum_{j=1}^{N_g} g(i,j) \log_{25} [g(i,j)]$
Sum of square variance	$\sum_{i=1}^{N_g} \sum_{j=1}^{N_g} (i - \mu)^2 g(i,j)$
Inverse difference moment	$\sum_{i=1}^{N_g} \sum_{j=1}^{N_g} \frac{g(i,j)}{1 + i - j ^2}$
Sum average	$\sum_{i=2}^{2N_g} [i g_{x+y}(i)]$ $g_{x+y}(k) = \sum_{i=1}^{N_g} \sum_{j=1}^{N_g} g(i,j), \text{ where } i + j = k \text{ and } k = 2,3, \dots, 2N_g$
Sum variance	$\sum_{i=2}^{2N_g} (i - \text{sum_entropy})^2 g_{x+y}(i)$
Sum entropy	$- \sum_{i=2}^{2N_g} g_{x+y}(i) \log_{25} [g_{x+y}(i)]$

Difference variance	$\sum_{i=0}^{N_g-1} i^2 g_{x-y}(i)$ $g_{x-y}(k) = \sum_{i=1}^{n_x} \sum_{j=1}^{n_y} g(i,j), \text{ where } i-j = k \text{ and } k = 0, 1, \dots, N_g - 1$
Difference entropy	$-\sum_{i=0}^{N_g-1} g_{x-y}(i) \log_2[g_{x-y}(i)]$
Information measure of correlation I	$\frac{H - HXY1}{\max(HX, HY)}$ $H = -\sum_{i=1}^{n_x} \sum_{j=1}^{n_y} g(i,j) \log_2[g(i,j)]$ $HXY1 = -\sum_{i=1}^{n_x} \sum_{j=1}^{n_y} g(i,j) \log_2(g_x(i)g_y(j))$ $HXY2 = -\sum_{i=1}^{n_x} \sum_{j=1}^{n_y} g_x(i)g_y(j) \log_2(g_x(i)g_y(j))$
Information measure of correlation II	$IMC_{II} = \sqrt{1 - e^{-2(HXY2-H)}}$

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