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COMPARISON OF DEEP LEARNING ALEXNET AND SUPPORT VECTOR MACHINE TO CLASSIFY SEVERITY OF SICKLE CELL ANEMIA

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ABSTRACT

Sickle cell anemia (SCA) is a serious hematological blood disorder, where affected patients are frequently hospitalized throughout a lifetime. Most of the patient's life span reduced, and some become addict based on the nature of strong analgesic that is taken by the concern patients, which they all have strong side effects. The existing method of severity classification for SCA patient is done manually through a microscope which is time-consuming, tedious, prone to error, and require a trained hematologist. The affected patient has many cell shapes that show important biomechanical characteristics of patient severity level. The main purpose of the study is to develop an automated severity level classification method of SCA patients by comparing deep learning AlexNet and Support Vector Machine (SVM) to enable present the percentage of each cell present in blood smear image. Hence, having an effective way of classifying the abnormalities present in the SCA disease based on the level of patient severity to give a better insight into managing the concerned patient's life. The study was performed with 182 SCA patients (over 11,000 single RBC images) with 14 classes of abnormalities and a class of normal cells to develop a shape factor quantification and general multiscale shape analysis to classify the patient based on severity level. As a result, it was found that the proposed framework can detect 85.4% abnormalities in SCA patient blood smear in automated manner when compared with Support Vector Machine (SVM) method with 71.9%. Hence, the system classifies the severity of SCA patient automatically and reduce the time and eye stress with performance AlexNet model performance of 95.1% accuracy, 99.1% specificity, and 98.5% precision value.

Keywords: AlexNet model, Support Vector Machine (SVM), Red blood cells and Sickle cell anemia.

INTRODUCTION

Sickle cell anemia (SCA) is a type of inherited RBC disorder connected with abnormal hemoglobin Sickle (HbS). When HbS molecules polymerize into RBCs based on lack of oxygen, they greatly affect the adhesion, shape, and size properties of the RBCs. The red blood cells become easily damaged with a wide proportion of diverse shapes in the cell population (Fasano et al., 2015), which makes this problem a perfect prospect for the examination of morphological heterogeneity. RBCs are biconcave shape. All the sides of the cell surface curve inward like the interior of a sphere. This shape gives RBCs the ability to move through tiny blood vessels to deliver oxygen to the organs and tissues. RBCs are also a key factor in determining human blood type. Blood type is decisive by the presence or absence of certain identifiers on the surface of RBCs. The diameter of red blood cells

varies from 7 to 8 microns. Each red blood cell has around 280 million hemoglobin molecules, and also the lifetime of each healthy person RBCs cell is 100 to 120 days. Then RBCs get destroyed in the spleen while for the SCA patient last for 10 to 20 days (Elsalamony, 2016). Hence, SCA is affected by several risks of life-threatening complications such as organ damage over time, stroke, and high mortality rate.

Globally, 1.62 billion population are affected by anemia, which is equivalent to 24.8% of the population, the majority, including SCA (Garg, Nigam, Agrawal, Nigam, & Agrawal, 2016). Approximately 5% of the worldwide population are carriers of the gene's trait for hemoglobin disorders. Hemoglobin disorders are genetic blood diseases caused due to the inheritance of unhealthy/abnormal hemoglobin genes from both healthy parents. More than 300,000 babies are born with hemoglobin disorders every year worldwide (Vishwas Sharma, 2017). The main key challenge of SCA is the variability in its clinical severity level from one patient to another. Available methods for treating SCA are mostly supportive and focus on symptom control but lack disease prediction in different clinical stages (Milton et al., 2015). Recent progress in machine learning and computer image processing techniques could provide an effective method in monitoring the severity level of SCA patients.

Several studies have been reviewed in this study, among which include the application of machine learning on SCA patients using different approaches but not considering the severity level detection based on RBCs shape abnormalities. Robert *et al*. work based on the possibility to determine sickle cell severity considering the clinical event of thirty-three patients, which was suggested that the severity of sickle cell could be detected based on hemolytic anemia and microvascular occlusion which are directly caused by abnormalities in sickle cell red blood cells. The SCA severity could detect by considering the patient shape abnormalities presence in sickle cell anemia patients (Robert P. Hebbei, M.D., Marc A. B. Boogaerts, M.D., John W. Eaton, Ph.D., and Martin H. Steinberg, 1980). Sebastiani *et al*. work to generate a predictive model of sickle cell severity disease using the Bayesian network modeling approach to consider seven clinical events with 13 laboratory tests. Based on automated characteristics and the demographic treatment information in 3380 affected patients, in which the method shows an association between clinical events and laboratory test that regulate the risk of mortality rate in SCA. The laboratory test considered in this study is expensive by the majority of the patient and is not available in some rural areas (Sebastiani et al., 2007). Sebastiani *et al*. worked on observational study of single nucleotide polymorphism (SNPs) that is to say variation of deoxyribonucleic acid (DNA) and also the patient genotype to detect the severity considering their laboratory characteristics such as hemoglobin, age, gender and reticulocyte levels also the clinical variability was considered based on the medical history of the patients. The study considers 1,265 patients and classifies them based on mild and severe. The study used a genome-wide association to understand genetic diversity that accounts for the phenotypic heterogeneity of sickle cell anemia, as estimated by an integrated model of severity. The main challenge of the study is that patient medical data is incomplete due to the emergency nature of the sickness (Sebastiani et al., 2010). Mengjia *et al*.(Xu et al., 2017) worked to develop an automated RBC shape classification method to detect the abnormality region of interest (ROI) from the smear image of sickle cell patients and separate the overlapped cells by using an

improved random walk method. The work moved further by using the extracted ROI and automated cropping, the abnormality into patches to normalize the RBCs size, and apply deep convolutional neural network for classification purposes, which achieved 87.6% accuracy. The work used eight patients with seven thousand patches of an image divided into three experimental sets. Data augmentation was introduced on the image in which the drawback of the study is that severity was not achieved, more data needed for the image categories, teardrop cell was not considered in the study, and a standard library containing diverse SCA RBC categories is needed for SCA image processing research. Aliyu *et al*. compare SVM and deep learning AlexNet models to classify a normal and four abnormal cells which observed SVM performs better than AlexNet but concludes RBCs data are not available to use the state of the art model and recommend data collection for RBCs disease detection for the straight forward AlexNet model that can detect much more abnormalities for SCA patients study(Aliyu et al., 2018) Aliyu *et al*.(Abdulkarim Aliyu Hajara, Azhar Mohd, & Sudirman Rubita, 2019) used form factor and perimeter features as descriptors to detect normal and four abnormal cells, but SCA patients have abnormalities that are more than the ones predicted in the study.

The main focus of this paper is to develop an automated severity level classification of SCA patients using deep learning AlexNet model based on RBCs shape abnormalities. The rest of this paper is organized as follows: Section II is the background of SCA with cell abnormality, Section III is the materials and methods, section IV is the results and discussion, and section V is the conclusion and recommendation.

SICKLE CELL ANEMIA (SCA)

Sickle cell anemia describes a group of hereditary blood disorders that have a significant impact on the lives of affected individuals. The patient with SCA has a problem with hemoglobin. Hemoglobin is a protein in red blood cells that carries oxygen throughout the body. With SCA, the hemoglobin forms into stiff rods within the red blood cells. These changes the shape of the red blood cells. SCA comprises unhealthy hemoglobin called sickle hemoglobin or hemoglobin S, which contributes to the cells manufacturing many abnormalities in the form of shape and size depending on the level of the patient's disease. The red blood cells of sickle cell patients usually die after 10-20 days, and the bone marrow cannot make new RBCs quickly to replace the dying ones (National Institute of Health, 2014). Sickle cell anemia includes sickle hemoglobin S (SS), Sickle beta-thalassemia, and sickle hemoglobin C (SC) disease (Allan F. Platt, 2016). SCA has no established cure in adult patients (Ballas, 2018).

Severe Sickle Cell (HbSS)

Sickle cell hemoglobin (HbSS) disease or homozygous SS disease, is an inherited autosomal recessive disorder resulting in qualitative mutation of the hemoglobin structure in red blood cells (RBCs). The mutation of normal hemoglobin A ($\alpha_2\beta_2$) to hemoglobin S ($\alpha_2\ \beta_2^{6val}$) is caused by the amino acid substitution of valine (GTG) for glutamic acid (GAG) on the sixth position of the β chain. The sickling process occurs under deoxygenated conditions in which hemoglobin S polymerizes, forming aggregates called tactoid that give the resulting product a rigid structure. Nearly half of all patients with sickle cell anemia experience vaso-occlusive crisis (abdominal and joint/bone pain accompanied by fever) caused by masses of sickle cells trapped in the

blood vessels due to decreased deformability of RBCs from tactoid formation, sickle cell hemoglobin (SS) has several characteristic laboratory findings. The peripheral blood smear results demonstrate the presence of elliptical, sickle, teardrop, and oval cells. Neutrophilia and thrombocytosis may also be observed (McPherson, 2017).

Severe Sickle Cell (HbSβ)

S/ß thalassemia results from the absence of ß-chain production that causes red blood cell (RBC) instability due to excess β chains, leading to abnormal erythropoiesis. S/ß thalassemia can differentiate from HbSS based on RBC morphologic characteristics and hemoglobin electrophoresis results. HbSS and HbSβ-thalassemia are clinically very similar and, therefore, commonly referred to as SS, these genotypes associated with the most severe clinical manifestations (Ballas, 2018). S/ß thalassemia is characterized by oval, teardrop, fewer sickle cells, and elliptical shape, but other abnormalities may be present.

Mild Sickle Cell (HbSC)

HbSC disease, RBC comprised of approximately 50% HbS and 50% HbC; however, the presence of HbC associated with increased potassium chloride (KCl) cotransport activity, which induces loss of potassium ion (K+) and intracellular water, in turn facilitating the polymerization of HbS(Nagel RL, Fabry ME, 2003). The main morphological characteristics of RBCs in HbSC patients show very few sickle cells, elliptical shape with many stomatocyte cells and dense microcytic, SC2, or reticulocyte cells in some patients. Hence, due to the low solubility of HbC induces intra erythrocyte crystal formation that may also identify in the blood smear (Costa, 2016). Table 1 shows a summary of the sickle cell severity level.

MATERIALS AND METHODS

This paper presents a framework that includes image acquisition, image preprocessing, the trained AlexNet model, trained Support Vector Machine model and graphical user interface (GUI) to present the severity result.

Table 1: Summary of Sickle Cell Severity Based on Cell Morphological Feature

SCA Severity Clinical Classification	Abnormality Involved	Sickle Cell Severity Classification
Hemoglobin SS(HbSS)	Sickle cell, reticulocyte, oval, Teardrop, elliptical	Severe and clinically similar to HbSβ [14]
Haemoglobin Sβ (HbSβ)	Sickle cell, teardrop, oval and elliptocyte [14]	Severe and Clinically similar to HbSS [14]
Haemoglobin SC (HbSC)	Sickle cell or elliptical with either reticulocyte/target, SC2, stomatocyte, microcytic cell [8]	Mild class [16]

SCA Patient Image Acquisition

The blood specimens were obtained from 182 different patients in Murtala Muhammad Specialist Hospital (MMSH) and Aminu Kano Teaching Hospital (AKTH) Nigeria with approved ethic numbers of MOH/off/797/T.1/849 and NHREC/21/08/2008/AKTH/EC/2307 respectively. For the preparation of a stained blood smear, a drop of blood was dripped on a glass slide at an angle of 25°. The blood smear was air-dried and stained with Giemsa. The stained slides of RBCs were then captured using a microscope (Hundwetzlar H600) that connected with a 3M pixel Amscope camera (FMA050) using a 40× magnification objective lens.

Image Preprocessing

The original dataset image sample in Fig. 1 undergoes preprocessing by firstly converting the image to greyscale, then thresholding used Otsu method of thresholding in equation (1)

$$\boldsymbol{t^* = \mathbf{arg}max_t \delta_b^2(\mathbf{t})} \quad (1)$$

$\boldsymbol{t^*}$ is the optimal threshold that maximize the functions $\boldsymbol{\delta_b^2}$ which is based on second order statistic Mathematically, the operation can are expressed as binary image using equation (2)

$$\boldsymbol{g}\,(\mathrm{x, z}) = \begin{cases} \mathbf{1}\ \boldsymbol{if}\ \ \boldsymbol{f(x,z) > T} \\ \mathbf{0}\ \boldsymbol{if}\ \boldsymbol{f(x,z) \leq T} \end{cases} \quad (2)$$

Deep Learning AlexNet Model

AlexNet was first proposed by Alex Krizhevsky *et al.* in the 2012 ImageNet Large Scale Visual Recognition Challenge (ILSVRC-2012) (Hinton, 2012). The AlexNet architecture model of LeNet-5 architecture (Y.LeCun, B.Boser, J.S.Denker, D.Henderson, R.E.Howard, W.Hubbard, 1989) comprised of a stack set of convolution layers superseded by one or more fully connected layers. Fig. 2 shows that the convolution layers may have had a pooling layer and normalization layer right after them, and all the layers commonly had Rectified Linear Unit (ReLU) non-linear activation units associated with them. AlexNet architecture (Russakovsky et al., 2015) comprises of 5 convolution layers, three fully connected layers, and one softmax layer. The first two convolution layers that are convolution one and convolution two are followed by a pooling layer and a normalization layer. The fifth convolution layer is also followed by a single pooling layer. The last fully-connected layer right before the softmax layer tagged fully convolution eight (fc8), has eight outputs in this adopted version, equalling the number of classes or labels. The outputs are fed as input to the softmax layer, which exponentially normalizes them, thereby given out a distribution of values across the eight classes that add up to 1. AlexNet was successful based on some practical strategies like the ReLU non-linearity layer and the dropout regularization technique. The ReLU, as shown in equation (3), is a half-wave rectifier function, which can significantly accelerate the training phase and prevent overfitting. The dropout technique can be regarded as a kind of regularization by stochastically setting a number of the input neurons or hidden neurons to be zero, to reduce the co-adaptations of the neurons, which are usually utilized in the fully connected layers in the AlexNet architecture.

$$f(z_i) = \max(0, z_i) \quad (3)$$

where z_i represents the input of the nonlinear activation function on the i^{th} channel.

The pooling layer further transforms the output of the activation step by reducing the dimensionality of the features map considering the output of the small region of neurons into a single output. The AlexNet comprises of 5 convolution layers and three fully connected layers with a softmax layer as the final layer. Each single convolution layer C_{Li} has maps of the same size for the two directions of x & y of the image, given as B_{ix} and B_{iy} with kernel sizes D_{ix} and D_{iy} respectively. Then, given the number of pixels to skip during the transverse at both directions denoted as H_{ix} and H_{iy}, the final output map size can be given in equations (4) and (5), respectively as:

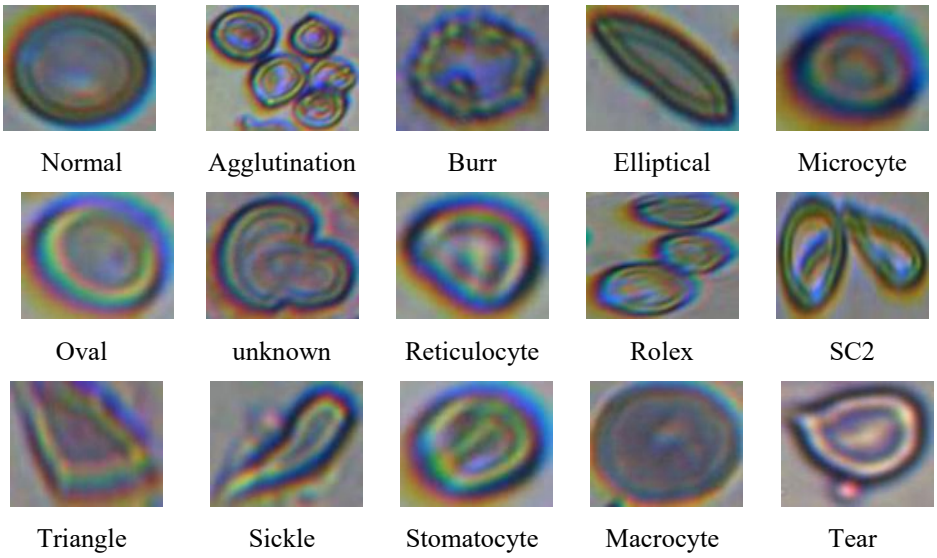

Figure 1: Dataset of Normal and Abnormal RBC for Classification

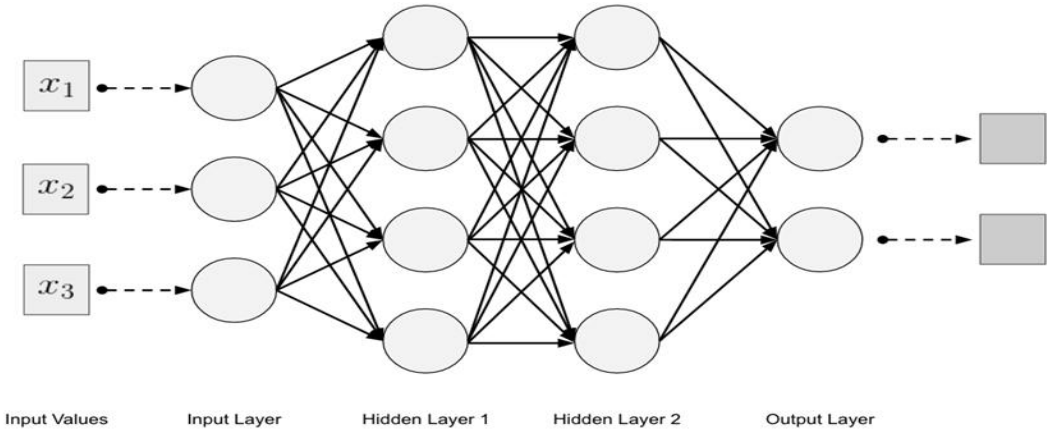

Figure 2: The AlexNet Architecture

$$B_{ix}^{L} = \frac{B_{ix}^{L-1} - D_{ix}^{L}}{H_{ix}^{L}+1} + 1 \quad (4)$$

$$B_{iy}^{L} = \frac{B_{iy}^{L-1} - D_{iy}^{L}}{H_{iy}^{L}+1} + 1 \quad (5)$$

Additionally, several researchers who apply the AlexNet pretrained model in image classification, but fewer areas in medical images are used, like an author who investigated the shape of red blood cells in microcapillary poiseuille flow to enable unbiased studies on drugs influence in flow properties of single RBCs (Kihm, Kaestner, Wagner, & Quint, 2018). Another researcher used the AlexNet model to classify malaria (Ave, Carpenter, & St, 2017). But AlexNet is a simple, typical, foundational, and one of the state-of-the-art CNN architecture models. The model is not used in sickle cell anaemia patients, and based on the reviews AlexNet error rate is less (Ballester & Araujo, 2014).

Support Vector Machine

The interesting method of feature selection is the application of the linear Support Vector Machine(SVM) (I. Guyon, 2003). The simplest way of application of the SVM network for feature selection is training the network using only one feature. The predictive power of the single feature for a classification task is characterized by the value of error function minimized by a one-dimensional linear SVM trained to classify learning samples based on only one feature of interest. The smaller this error, the better is the quality of the feature.

The ranking of the features may also be done for all features working together. The method is based on the idea that the absolute values of the weights of a linear classifier trained on the whole set of features produce a feature ranking (Elisseeff, 2003). The feature associated with the larger weight is more important than that associated with the small one. For the classification stage, the researchers used the Support Vector Machine as part of the classification method to choose the best classifier. MATLAB software was used for developing this classification method using Support Vector Machine (SVM) with Radial Basis Function (RBF).

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The training samples $\{y_i x_i\}_{i=1}^{N}$, with the label $y_i \epsilon\ (-1, +1)$, indicate the class in which the feature vector $x_i \epsilon\ R^d$ belongs. SVM has to separate hyperplane with maximum-margin in higher feature space induced by kernel function $k(x, z)$. The normal form of SVM classifier is defined in equation (6):

$$F(x) = \sum_{i=1}^{n} \alpha_i y_i\, k(x, v_i) + b \qquad (6)$$

where $\{v_i\}_{i=1}^{n}$ are referred to as support vectors, which are a small set of training data near the separating hyperplane, x is the feature vector and is normalized to the unit length before the training, and the classification and b are the kernel constants.

Feature vector x is normalized to unit length before training and classifying. The RBF kernel can be written in equation (7):

$$x = e^{-2\gamma} e^{2\gamma x^T z} \qquad (7)$$

The first term $e^{-2\gamma}$ is constant and thus, the RBF kernel is the second term $e^{2\gamma x^T z}$. In the simplified form of RBF kernel, the value of variable $2\gamma x^T z$ is bounded within $[0, 2\gamma]$, as $0 \leq x^T z \leq 1$ is always true due to L2-norm normalization. Therefore, if the kernel parameter can take small values, the simplified RBF kernel $e^{2\gamma x^T z}$, is approximated by second-order polynomial approximation, Equation (8)

$$k(x, z) \approx a + c\,(2\gamma x^T z) + q\,(2\gamma x^T z)^2 \qquad (8)$$

SCA severity classification using graphic user interface

The graphical user interface (GUI) is a tool to interact with the user to present the severity classification system. The GUI system required command to classify the severity level of a patient. The trained Alex Net classifier is used to classify normal and 14 abnormalities. Hence, conditions set to the GUI are based on the presence of an elliptical

cell or sickle cell with one of these cells, namely microcyte, stomatocyte, or sc2 cell classified into mild. Then the patient classified as severe based on the presence of four cells namely sickle cell, oval, teardrop, and elliptical, but other abnormalities may appear on the patient slide.

Accuracy, Sensitivity, Specificity And Precision

The The accuracy, sensitivity, specificity, and precision for sickle cell detection are determined using equation 9, 10, 11, and 12 respectively. The proportion of true-false, positive-negative, was carried out. The accuracy of the named cell detection system is measured in the percentage of true-positive (TP), false positive (FP), true negative (TN), and false-negative (FN).

where,

TP - Number of named cells correctly identified as an abnormal cell on the blood smear image

TN - Number of named cells correctly identified as a normal cell on the blood smear image FP - Number of named cells incorrectly identified as an abnormal cell on the blood smear image

FN - Number of named cells incorrectly identified as a normal cell on the blood smear image

$$\text{Accuracy} = \frac{TP+TN}{TP+TN+FP+FN} \quad (9)$$

$$\text{Sensitivity} = \frac{TP}{TP+FN} \quad (10)$$

$$\text{Specificity} = \frac{TN}{TN+FP} \quad (11)$$

$$\text{Precision} = \frac{TP}{TP+FP} \quad (12)$$

RESULTS AND DISCUSSION

Image sample

Image sample in Fig. 3. is the acquired images from SCA patient. The input image then undergo image resizing.

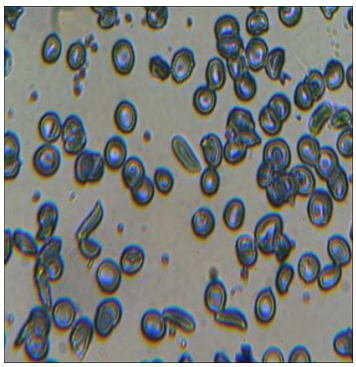

Figure 3: Sample of SCA patients acquired image

Comparison between Deep learning AlexNet Model and Support Vector Machine

This is based on the dataset that has a total of 182 patient's blood smear slides and 3 images were captured from each slide that gives total of 546 images in the dataset. Approach using support vector machine (SVM) model (Chy & Rahaman, 2018) was implemented to record the sickle cell detection accuracy. This result was then used to evaluate and compare with the proposed deep learning AlexNet model method. The main different between the proposed method and support vector machine classification method is in the feature extraction. The support vector machine model requires feature extraction such as eccentricity, major axis, minor axis, perimeter, entropy, mean, standard deviation and variance and was manually done. The proposed method does not require manual feature extraction. Furthermore, the proposed method classifies the patient severity level while the existing method did not classify the patient severity level due to lack of dataset. This helps the proposed method to improve the performance

of the model by increasing the accuracy rate of the detection and introduce severity level classification. SVM model present 71.9% overall accuracy, while deep learning AlexNetmodel with same dataset having 85.40% overall accuracy. Table 2. Shows the performance result based on accuracy.

Severity result

The experiment training datasets were used with different categories of SCA patient's RBC blotch images in JPEG format, with over 11,000 cells of fifteen classes dataset. The classification of the cells and patient automated condition is displayed in Fig. 4 and Table 3 gives the severity comparison of SVM and AlexNet Model based on accuracy, sensitivity, specificity and precision.

Table 2: Red blood cell detection performance comparison based on accuracy

Red blood cells	SVM method accuracy [25] (%)	Proposed method accuracy (%)
Agglutination	88	93
Burr	63	100
Macrocyte	92	92
Microcyte	81	94
Normal	51	87
Oval	40	86
Reticulocyte	69	100
Rolex	88	72
SC2	79	70
Sickle	79	67
Tear	63	100
Triangle	76	72
Unknown	80	68
Elliptical	62	80
Stomatocyte	80	100
Average	71.9	85.4

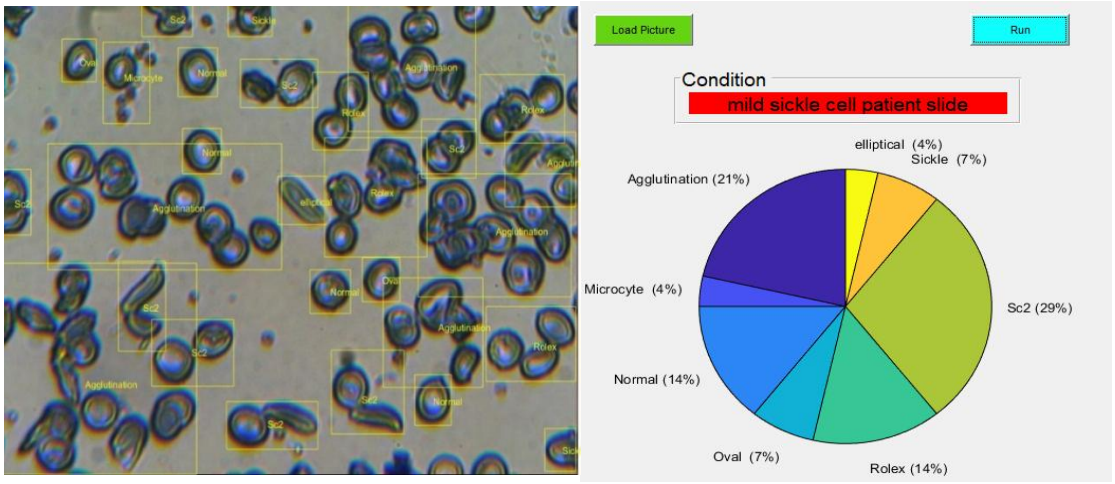

Figure 4: AlexNet prediction classification and patient condition

Table 3: Sickle Cell Severity Level Detection Comparison

S/N	Parameters	SVM (%)	AlexNet Model (%)
1	Accuracy	93	95.1
2	Sensitivity	67	89.2
3	Specificity	98.2	99.1
4	Precision	87.5	98.5

CONCLUSION

The study achieved 182 patients, with more than 11,000 single blotch images and AlexNet model performs better than SVM model in both image and severity level detections. It was concluded that AlexNet model outperform SVM model on sickle cell anemia severity predictions and recommended AlexNet model.

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