



Detection and Classification of Leukocytes in Leukemia using YOLOv2 with CNN

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Authors' contributions

This work was carried out in collaboration between both authors. Both authors read and approved the final manuscript.

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ABSTRACT

The development of machine learning systems that used for diagnosis of chronic diseases is challenging mainly due to lack of data and difficulty of diagnosing. This paper compared between two proposed systems for computer-aided diagnosis (CAD) to detect and classify three types of white blood cells which are fundamental of an acute leukemia diagnosis. Both systems depend on the You Only Look Once (YOLOv2) algorithm based on Convolutional Neural Network (CNN). The first system detects and classifies leukocytes at the same time called computer-aided diagnosis with one model (CADM1). The second system separates detection and classification by using two models called computer-aided diagnosis with two models (CADM2). The main purpose of the paper is proving the high performance and accuracy by fragmentation of the main task into sub-tasks through comparing between CADM1 and CADM2. Also, the paper proved that can be depending only on deep learning without any traditional segmentation and preprocessing on the microscopic image. The (CADM1) achieved average precision for detection and classification class1=56%, class2=69% and class3 72% while (CADM2) achieved average precision up to 94% for detect leukocytes and accuracy 92.4% for classification. The result of the second system is very suitable for diagnosis leukocytes in leukemia.

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1. INTRODUCTION

Nowadays, Machine Learning (ML) used in every area of computational work where algorithms are designed, and performance is increased [1]. In the last years, learning from unbalanced data sets has become a critical problematic in machine learning and is frequently found in several applications such as computer security [2], biomedicine [3,4]. The blood consists of three types of components: red blood cells (RBC), white blood cells (WBC) and platelets. Microscopic test of blood smears plays a critical part to analyze numerous blood illnesses. The human immune system depends on the WBC [5–7]. The white blood cells are divided into four types called Monocytes, Eosinophil, Lymphocytes, and Neutrophils (there is another type called basophils). The total WBCs number and the number of each type give important information about human health status. Furthermore, many diseases such as leukemia can diagnosis based on WBCs [8–11]. According to the type of infected cells and severity level, leukemia was divide into four main types: Acute Myeloid Leukemia (AML), Acute Lymphoblastic Leukemia (ALL), Chronic Myeloid Leukemia (CML) and Chronic Lymphocytic Leukemia (CLL) [12]. On other hand, leukemia diagnosing may be through physical exam tests such as lymph nodes is large, the person appears pale, the spleen may be larger from normal size, bleeding, fever, infection...etc. The other method for diagnosing leukemia is a blood test method which showing the abnormal appearance of WBCs such as changing the shape of cells or the number of cells is increasing or decreasing. In spite of that, diagnosing leukemia needs specialists with the experience to be able to distinguish between WBCs types and also is time-consuming. Besides, the blood smears preparation needs the specialist to have high skills to be able to distinguish between WBC types and prepare an accurate report to contain statistics about blood cells which helps the doctor to diagnosis leukemia.

In recent years, artificially intelligent systems were used for diagnosing many diseases. However, detection and classification of white blood cells in microscope images by deep learning without pre-processing or traditional segmentation is a challenge due to lack of data, data noise, and data from different sources [13]. Traditionally, researchers were used shallow

machine learning to extract features map of digital images and then used as input of prediction algorithms. The main shallow machine learning methods used in leukocyte detection and classification are Artificial Neural Networks (ANNs), Support Vector Machine (SVM), Naive Bayes Classifier, and Multi-Layer Perceptron (MLP). On another side, many studies used image pre-processing, traditional segmentation, feature engineering, and manual object extraction to obtain high performance of detection and classification. Moreover, the diagnosis by the computer system is a great challenge; deep learning assists to build Computer-Aided System (CAD) system to do that.

This paper proposed two systems to localize and classify three types of white blood cells directly from microscope images of acute leukemia patients based on the modified You Only Look Once (YOLOv2) algorithm and Convolutional Neural Network (CNN) and compare between them. The systems were trained on generated datasets specially created for this purpose. The data were labeled and created ground truth by specialists. The data took from private hospital due to that; there is a severe lack of training data and just three types of white blood cells. For lack of data, the paper used the data augmentation technique.

This paper is structured as follows: Section (2) theatrical and related works that contributed to this field in recent years. Section (3) the proposed systems architecture and with data acquisition. Section (4) discussing the results for both systems and evaluation. Finally, Section (5) is a conclusion and mentioning important points.

2. THEORICAL AND RELATED WORK

Both systems are used CNN which refers to Convolutional Neural Network and YOLOv2 which refers to You Only Look Once, both of them a case of Deep Learning neural networks and the CNN consists of a set of layers. Each layer consists of computational elements called neurons and each of them connected to previous neurons. The main difference between ANN and convolutional neural network in the convolution operation, in CNN layer learn the local small area of two dimensions while ANN layer learns global input space [14,15]. See Fig. 1 the common architecture of CNN [16].

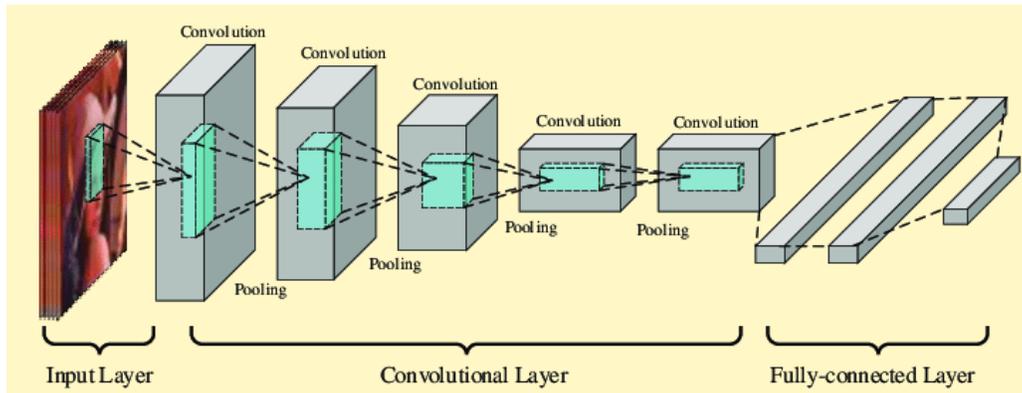


Fig. 1. Main layers of CNN architecture

Source: [16]

However, there are three main layers used in CNN, convolutional layers, pooling layers and fully connected layers. In addition, there are other optional layers that can be used in CNN such as batch normalization and dropout layer. However, the Convolution, pooling and fully connected layers are the most mainly used in CNN architecture [17–20].

The convolutional layer is used to extract the feature map by applying a kernel over the entire input image. Also, the convolutional layer is considered the core of the CNN, which consists of a set of learnable parameters called kernels (or filters) [21]. The kernel is a small piece of the receptive field that slides over the entire image [22]. During the forward pass process, each kernel is convoluted through the image from top-left to bottom-right. The production of this process is computed by the dot product between the kernel and the same area of the input image [23,24]. During this processing, the network learns the kernel which activates when it detects special features in some position in the image. Moreover, the output of each above process is called a feature map. Each moving of the kernel for one pixel is known as a stride, and the stride is larger than one, and its benefit is to down-sample the feature map [25,26]. Often, after the process of extracting the feature map, the output passes through the batch normalization layer, which normalizes the gradients propagating and activations. This layer makes the training of the network easier for an optimization problem. After that, it is followed by the activation function, which is a crucial component in the network due to it determining the output and its accuracy. There are many activation functions such as Sigmoid Function, Hyperbolic Tangent Function (Tanh), Rectified Linear Unit

(ReLU) Function and Softmax Function, all these functions try to decrease the computational cost.

Next step, the extracted feature map passes through the pooling layer, which is used to down-sample the input patch by summarizing to obtain a single value. The patch size should be larger than 2 in vertical and horizontal. There are two main pooling layers: max pooling, which outputs the maximum value of the input, and average pooling, which outputs the mean value of the input [27,28].

Finally, fully connected, which is typically placed at the end of the network, consists of neurons and an activation function, which provide the classification decision [29].

On another side, the term YOLO, which means the model needs one stage to detect all objects in the input image at one time, while other detection systems need more than one time or more than one stage to detect all objects in the image. For these reasons, YOLO is a very fast model. The first step of YOLO is dividing the input image into $K \times K$ grid cells, then checking each grid cell if the center of the object falls into it or not. If the center of an object falls into a cell, the cell will be responsible for detecting the object [30]. YOLO provides object classification and localization in each grid cell for one object. There are many versions of YOLO (YOLOv1, YOLOv2, YOLOv3). The first version has a limitation; it can only detect 49 objects in each image, detect one object for each grid cell, and detect more than one object if it is located in more than one cell. All these limitations were solved in the version 2 of YOLO, which focused basically on improving

localization, average precision and accuracy of classification for better performance. Also, YOLOv2 use batch normalization which improves better accuracy and high resolution [25]. In addition, YOLOv2 used Anchor Boxes which allows detecting more than one object in the same grid cell. Any detection system needs to the pre-trained network which used for extract feature map, the YOLO also used pre-trained network such as (Alexnet, ResNet 50, VGG16), see Fig. 2 the YOLOv2 architecture [31]. Both systems are used the custom pre-trained network which that will explain in the next section [32].

Nowadays, machine learning (ML) used in every area of computational work due to the rapid advancement of computer technology [33,34]. Recently, machine learning was used in many fields such as military, industry, learning and health. Many researchers use the classical methods for extraction of feature map from medical images, while others used machine learning to analyze the medical images based on some algorithms for feature extraction, localization and classification. In general, dealing with images means feature extraction which is used either for localization or classification or both of them together.

In [35] the author proposed system to classify the ALL lymphoblast cells into normal and abnormal. The system was consisting of two steps; the first step was separates white blood cells from other blood cells and then extracts the lymphocytes. The system used Gray Level Co-occurrence Matrix (GLCM) to detect the hematological disorders and then classified extracted feature map by Support SVM. The author in [36] focused on segmentation of cells by traditional approaches to separate the red blood cells. The automatic system was computed threshold of image and used a canny filter to extracts edge by morphological operations. In [37] the author used the Gram-Schmidt method and parametric deformable models to separate nucleus and cytoplasm. Also, the author used a new pre-processing approach to segment white blood cells by Hue Saturation Intensity (HSI). The author in [38] also used traditional methods to extract the objects in images and deep learning for classification. Firstly, the original images converted into binary images to separate foreground (objects) from the background and then used threshold as the value of the intensity of object and background. In addition, the object is filtered by area which separated the object

from the background. The obtained binary image used as a mask for the original images. However, this method consumes time and hand working which is different from our system that tries to use only deep learning without pre-processing.

Some other research combine between traditional and machine learning, in [39] proposed an algorithm using feature weight adaptive K-means clustering to separate white blood cells. Firstly, the initial clustering center used based on histogram distribution on the images and decomposed the color space. Secondly, combined the K-mean clustering and color space decomposition was used for image segmentation. And then white blood cells were separated based on the watershed algorithm. Finally, classified the white blood cells using a convolutional neural network. In [40] the author proposed a CAD which basically depends on image processing and machine learning to extract ALL cells and classify extracted cells into subtypes. The image converted into HSV (Hue, Saturation, Values) as preprocessing and then chose S component to be processed for specified color to obtain lymphoblast cells, due to this channel has more information. Next step applied threshold to find maximum value and then subtracted random values for robust segmentation. Moreover, hole filling filter was used for blasts segmentation and then the image converted into RBG color. Finally, the segmented images were classified using convolutional neural network. The papers [41] also focused on the traditional segmentation of white blood cells, where it used investigated various approach such as Thresholding, CMYK, HSV with Otsu Thresholding, CCL and CHT. Mainly, the work was based on preprocessing. In this paper [42] introduced method combined between Thresholding, k-means clustering and also used watershed algorithms which consist of three phases: firstly, white blood cells was separated. Secondly, nuclei were extracted from cell and finally, segmentation of overlapping cells and nuclei. However, there were other approaches which used different methods such as GP-based decision tree for classifying thalassemia cells. The paper [43] compared between the traditional and deep learning to segmentation of red blood cells and classification of them. Where the author used SVM for segmentation and extracting features and deep neural network for classification of the extracted features. The author proofed that SVM is better inaccuracy when used the same data.

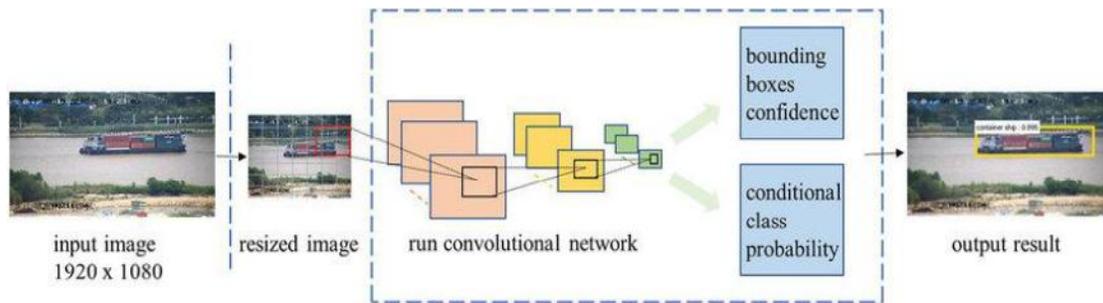


Fig. 2. The common architecture of YOLOv2

Source: [32]

Some other researchers tried to using deep learning, this author [44] used a convolutional neural network with previous preprocessing of images to classify white blood cells into its types. All previous studies that mentioned above used different approaches for segmentation and classification. The pre-processing was the based phase which were different from the approach that addressed our problem, where this work only used deep learning for segmentation (White blood cells detection) and classification (Convolutional neural network). In [45] the author used the deep convolutional neural network to extract the features to classify the red blood cells in sickle cell Anemia. The system consisted of four stages: extracting patch of hierarchical red blood cells, patch normalization of size invariant, classify the red blood cells based on deep CNN and calculated the red blood cells. In [46] the author detects white blood cells in ALL by using region-based convolutional neural network (RCNN), this network consisted of two sub-networks pertained network AlexNet and Region proposal networks (RPN). In [47] the work was different from the traditional methods which used to detects objects in the images. The author tried to using deep learning to extract the object in the images, the faster region convolutional neural network (Faster R-CNN) was used to detected and classified the malaria Images. In addition, preprocessing was applied. The author in [48] used a convolutional neural network to classified the entire image into normal or abnormal without using extraction of white blood cells. The network consisted of 7 layers, the first five layers used for extract features and the last two layers for classifying the image. The author in [49] applied a new approach which depended on semantic segmentation, in this method all pixel is classified based framework along with VGG16 as pre-trained that used to extract features, detection and classification.

3. THE ARCHITECTURE OF PROPOSED SYSTEMS

This study developed CNN as a pre-trained network to extract feature map which uses in YOLOv2 Framework for detect white blood cells; the proposed CNN in our systems as pre-trained experimentally determined the suitable architecture of CNN as a pre-trained network for the addressed problem which focused on two concepts [50,51]. The first concept is the size of a network with a small or large number of convolutional kernels and the second concepts are increasing or decreasing subsequent layers [13,26]. Experimentally, the network with a small and increasing number of feature map improve better performance [52,53]. The proposed CNN architecture is detailed in Table 1.

The CNN that used in both systems as a pre-trained network consists of six convolutional layers (layers 1, 3, 5, 6, 8 and 10) and five max-pooling layers and the end of the network two fully connected layers. Each of convolutional layers followed by batch-normalization layers and rectified linear unit (ReLU) as activation function [9]. The first convolutional layer consists of 8 kernels with size 3x3, stride one and padding same which mean the output size of the convolutional layer is the same size as the input image. The second convolutional layer is defined 16 feature map with size 128x128, the third convolutional layer defines 32 feature map with size 64x64, the fourth convolutional layer defines 64 feature map with size 64x64, the fifth convolutional layer defines 64 feature map with size 32x32 and the last convolutional neural network defines 128 feature map with size 16x16 [29].

The reduction in the size of the feature maps is obtained by max-pooling layers (layers 2, 4, 7, 9

and 11); max-pooling kernel size 2x2 uses for all layers with a stride of 2 followed the convolutional layers [54]. After the features map generation, the classification process is completed by two layers of fully connected (layers 12 and 13) the first layer of fully connected consist of 100 neurons and following by a ReLU activation function; also, the network used a dropout mechanism with probability 0.5 to reduce overfeeding [55]. The second layer of fully connected consists of 2 neurons which is the output of the network, the softmax activation function used for the final [18,56].

3.1 Computer-Aided Diagnosis with One Model (CADM1)

The CADM1 system consists of one model which receives the input image with size 256x256x3 as a first step and then divides input images into KxK grid cells. Fig. 3 is the architecture of CADM1. Each cell checked if contain an object or not bypassing the input image in six convolutional layers in pre-trained CNN (explained above) to extract the features map, the size of the feature map will be 16x16x128. After that, the extracted features map from the sixth convolutional layer pass via two YOLOv2 Convolutional layers each layer followed by batch-normalization layers and rectified linear unit (ReLU) and after this layer, there are three other layers: yolov2 class convolutional, yolov2 transform and the yolov2 output layer these layers responsible of reshaping the output of the network.

In addition, YOLOv2 used an anchor box which is a set of boxes with a certain height and width which use to capture the object with different scale and ratio in the image. These boxes

typically estimated from a training dataset based on object sizes. The anchor box slides on the entire image to predict the probability and other attributes such as background and intersection over union (IoU). When the dataset contains objects of different size, it can use several anchor boxes, in our experiment 9 anchors are used which achieved better precision and the number of class 3 which is the type of white blood cells in our dataset. Finally, the output of the last layer reshaped into 16x16x72 which means the input image divided into 16X16 grid cells and the depth represent the number of anchors and each anchor box have eight elements ($P_c, X_c, Y_c, W, H, C_1, C_2, C_3$): P_c will be equal one if the grid cell contains an object and zero otherwise, X_c and Y_c are the centers of object bound box, W and H are width and height of bound box respectively. In addition, C_1, C_2 and C_3 are classes of WBC and finally used loss function mean-squared-error between predictions (the one with highest IoU) and ground truth to calculate the loss.

3.2 Computer-Aided Diagnosis with Two Models (CADM2)

The CADM2 consists of two models as shown in Fig. 4. The first model is the same model in CADM1 but the difference in a class number. This model is only used for the detection of white blood cells as one object. For this reason, the class number was chosen 1. The first model in CADM2 only extracts white blood cells of different size and without classification. The extracted white blood cells will pass as a new input image into the second model with size 64x64x3. The second model in CADM2 is CNN that using for classification extracted white blood cells by the first model, see Table 2.

Table 1. Proposed CNN as pre-trained in both systems

Layer	Layer Type	Layer Output	Kernel Size	Stride
1	Convolution	256 x 256 x 8	3x3	1
2	Max Pooling	128 x 128 x 8	2 x 2	2
3	Convolution	128 x 128 x 16	3x3	1
4	Max Pooling	64 x 64 x 16	2 x 2	2
5	Convolution	64 x 64 x 32	3x3	1
6	Convolution	64 x 64 x 64	3x3	1
7	Max Pooling	32 x 32 x 64	2 x 2	2
8	Convolution	32 x 32 x 64	3x3	1
9	Max Pooling	16 x 16 x 64	2 x 2	2
10	Convolution	16 x 16 x 128	3x3	1
11	Max Pooling	8 x 8 x 128	2 x 2	2
12	Fully Connected	100	-	-
13	Fully Connected	2	-	-

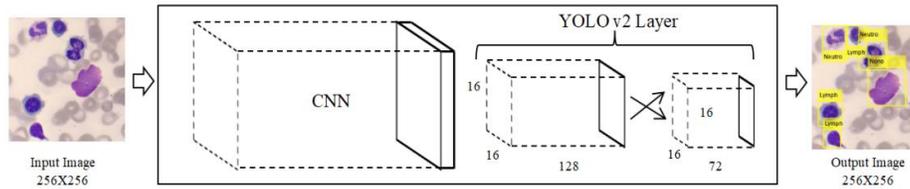


Fig. 3. The architecture of CADM1

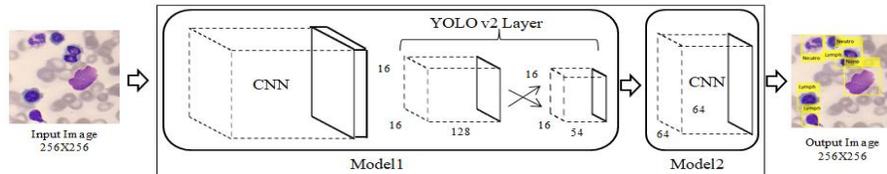


Fig. 4. The architecture of CADM2

Table 2. The details of the CNN (model2) architecture in CADM2

Layer	Layer Type	Layer Output	Kernel Size	Stride
1	Convolution	64 x 64 x 32	3x3	1
2	Max Pooling	x 32 x 3232	2 x 2	2
3	Convolution	32 x 32 x 16	3x3	1
4	Max Pooling	16 x 16 x 16	2 x 2	2
5	Convolution	16 x 16 x 8	3x3	1
6	Max Pooling	8 x 8 x 8	2 x 2	2
7	Fully Connected	65	-	-
8	Fully Connected	3	-	-

The CNN is very simple which consists of 8 layers; three layers are convolutional layers (layers 1, 3 and 5) and each layer followed by batch-normalization and ReLU activation functions. The first convolutional layer defines 32 feature maps with size 64x64, the second convolutional layer defines 16 feature maps with size 32x32, and the last convolutional layer defines 8 feature maps with size 16x16. The kernels size of each convolutional layer is 3x3 with stride one and padding is the same which mean the input size and the output is the same size for each layer. The reduction of size obtained by max-pooling layers (layer 2, 4 and 6) with kernel 2x2 and stride by 2. The last two layers (layer 7 and 8) are fully connected, the first one consist of 65 neurons followed by ReLU activation functions. The second fully connected consist of 3 neurons which implemented classification by softmax activation function that provides multi-classification.

3.3 Data Acquisition and Augmentation

The data were acquired from blood smears of 15 leukemia patient archive in the VIN Hospital lab. The samples took from different ages, adults and children. Each patient had at least 7 smears or

more and then all smears were converted into 360 images in high resolution via Olympus CX22 light microscope with lens 100X by adding oil on smears pane, the images were taken by a camera with resolution 12Mb. After that, each image was dividing into non-overlapping patches with size 256x256 to obtaining 2700 patches. The number of white blood cells for each type were different (Monocytes= 4117 cells, Lymphocyte=1093 cells and Neutrophils =1092 cells). Due to the inequality of type of white blood cells, a dataset consisting of 1870 was generated. The 1500 images took for training which the types of white blood cells were close in number and 370 images for the test dataset (80% training dataset and 20% test dataset). Therefore, the number of each type of cells became (Monocytes= 1095 cells, Lymphocyte=1014 cells and Neutrophils =1019 cells) which represent (Class1, Class2 and Class3) respectively.

Due to the lack of data and difficulty obtaining more smears of leukemia patients, this paper used the augmentation approach that used in [17]. Since our input images for both systems is 1500 image and randomly rotated (0 - 90), randomly reflecting in horizontal and vertical axis

are used. In addition, color jitter with random values is used which is another data augmented method used in object detection [50]. Each cell in the dataset labeled and created its ground truth manually by some specialists using Matlab toolbox which called Image Labeler. The tool is very simple to create ground truth with high performance; also, it allows the user many options to choose a dataset and some algorithms to create ground truth automatically. In addition, three type of labeling shape (Rectangle, Line and Pixel Label). In our experiment, a rectangle shape is chosen to create a bound box for each cell manually.

4. RESULTS AND DISCUSSION (SYSTEM EVALUATION)

Both systems implemented using Matlab R2020a version 9.8 and Deep Learning Toolbox with Computer Vision Toolbox, Image Processing Toolbox and Image Labeler. The system's code executed on a personal PC (Laptop) with Intel processor core i7 generation 8 and RAM 8 GB. The first CADM1 is consisting of a pre-training CNN and YOLOv2 algorithm which use for recognition WBC which means detection and classification at the same time. The model trained on dataset consists of 1500 images with size 256x256 and test dataset 370 images without any pre-processing.

The CADM1 code executed with mini-patch size 32 during 100 epochs, each epoch tacked about 2 minutes and the performance for training achieves higher level. The model used Adam optimizer for training which proved high accuracy from another optimizer [33]. The initial learns rate $\alpha = 0.01$, Learn Rate, schedule is setting to piecewise and learn rate drop period = 50. The evaluation of the model is measured by the average precision (AP) and mean average precision (mAP) value. The results of the system for each type of WBC as following (Class1=56, Class2=69 and Class3 =72) which mean mAP is 65.6%. The CADM2 consists of two models; the first model is YOLOv2 algorithm which used for detection WBC. The first model in CADM2 is such as the model in CADM1 with different in output; the number of class in the first model in CADM2 is one while the numbers of class in CADM1 was three. The dataset used for training it such that used for CADM1, the images size 256x256 used as input in a model in CADM2 to extract white blood cells. The average precision of the first model in CADM2 achieved 94.1%, also without any pre-processing. After that the

extracted cells by the first model used as input images in the second model with size 64x64. The model2 consist of CNN which trained on dataset consists of three class, this dataset extracted from 1500 as cells and the number of images for each class as the following (Class1 =1095, Class2 = 1014, Class3 = 1019) the dataset divides by ratio 80% for training data and rest of the data for testing. The network trained on data without pre-processing by Adam optimizer with mini-patch size 64 and the initial learn rate $\alpha = 0.01$. The CNN achieved the best performance at 100 epochs, each epoch tacked about half minutes. The global accuracy of CNN (model2) achieved 92.4% which is very suitable to distinguish among types of WBC that helps to diagnosis Leukemia types. Fig. 5 shows the confusion matrix of CNN in the model2 on the test dataset.

Each class of test dataset consists of 202 images, 180 images are correctly classified for class1 and class2 (True Positive), while 22 images are classified as other class for class1 and class2 (False Negative). then 200 images are correctly classified as class3 (True Positive) while only 2 images are classified as other class for class3 (False Negative).

Through our experiment, the CADM1 results were very poor and not enough for diagnosis of acute leukemia, due to using one model to identifying and classifying the white blood cells at the same time on images tacked directly from the microscope. The YOLOv2 model proved to extract the object in images but inefficient to distinguish among objects. Since YOLOv2 is very useful to only identify one type of object in images. In CADM2, the YOLOv2 model is used only for extract the white blood cells and by adding another model which only used for classification, the system achieved excellent results for classifying white blood cells which help specialists to diagnosis acute leukemia. Table 3 comparison between both systems.

The comparison between both systems is depending on some factors. The first factor is the time of training, it is clear that the total training time in CADM1 is less than the CADM2 and also the complexity of the CADM1 is simpler than the CADM2. According to these two factors, there is a simple difference between both systems. But depending on the accuracy factor, the difference is very high where the accuracy of CADM2 is very high comparing with CADM1 when the systems are used the same dataset without pre-processing.

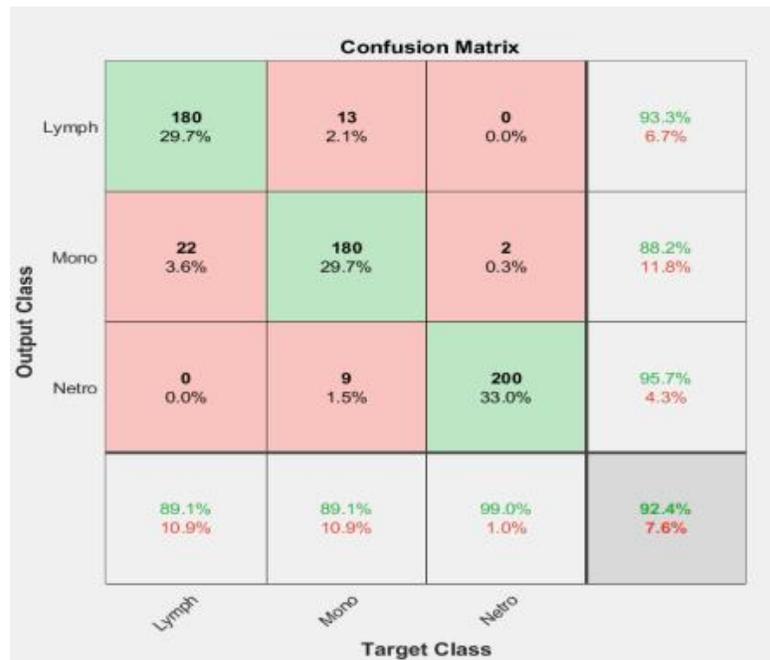


Fig. 5. Confusion matrix on test dataset for CNN in second model, CADM2

Table 3. Comparison between both systems

System	Total training time	Accuracy	Architecture complexity
CADM1	3 Hours and 44 Minutes	Class1=56% Class2=69% Class3 =72% mAP = 65.6%	Very simple with one model
CADM2	4 Hours and 44 Minutes	Detection =94.1% Classification=92.4%	Also simple but with two models

5. CONCLUSION AND MENTIONING IMPORTANT POINTS

Many systems are used for recognition, detection, and classification to analyze medical images depends on pre-processing which is the main step of any system that deals with the images. In another word, any system without pre-processing cannot achieve high performance. Our experiment compared two systems, basically, both systems depended on YOLOv2 framework and CNN and both systems used the same training optimization algorithm. The second system proves that can achieve high accuracy without any pre-processing when the main task is divided into sub-tasks. The results of the second system were very high compared with the first system due to processing each procedure individually. The system can achieve high performance when the system deals with images took directly from the microscope by processing

each problem with only one model. Also, the paper explained two important procedures, firstly, when one model is used for more than one problem, the model will be low performance. Secondly, it can achieve high performance without pre-processing by using more than one technic, such as detection and classification that used in our experiment.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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