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Classification of Leukemia Disease in Peripheral Blood Cell Images Using Convolutional Neural Network

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ABSTRACT

Classification is widely used in medical images to categorize patients and non-patients. However, conventional classification requires a complex procedure, including some rigid steps such as pre-processing, segmentation, feature extraction, detection, and classification. In this paper, we propose a novel convolutional neural network (CNN), called LeukemiaNet, to specifically classify two different types of leukemia, including acute lymphoblastic leukemia (ALL) and acute myeloid leukemia (AML), and non-cancerous patients. To extend the limited dataset, a PCA color augmentation process is utilized before images are input into the LeukemiaNet. This augmentation method enhances the accuracy of our proposed CNN architecture from 96.9% to 97.2% for distinguishing ALL, AML, and normal cell images.

Key words: Acute Leukemia, Convolutional Neural Network, Data Augmentation, Deep Learning, Image Classification

1. INTRODUCTION

Leukemia, a kind of cancer found in blood and bone marrow, is a dangerous cancer-causing 24,500 deaths in the United States in 2017 [1]. About 62,130 new cases of leukemia have been detected in 2017, leading a large number of patients required to be diagnosed. Clinically and pathologically, leukemia is subdivided into four main groups, acute myelogenous leukemia (AML), acute lymphoblastic leukemia (ALL), chronic lymphocytic leukemia (CLL), and chronic myeloid leukemia (CML). Among these, ALL and AML are known as the most dangerous types. Thus, the early detection and timely treatment of ALL and AML is essential to substantially prevent the rapid development of cancerous cells. According to the Cancer Treatment Centers of America [2], the acute types of leukemia (AML and ALL) can be classified based on the type of cell involved and how the cells look like under a microscope. For instances, the normal white blood cell, colored purple in Fig. 1 (a), has the similar size to that of surrounding red blood cells, while the leukemia blood cell has an

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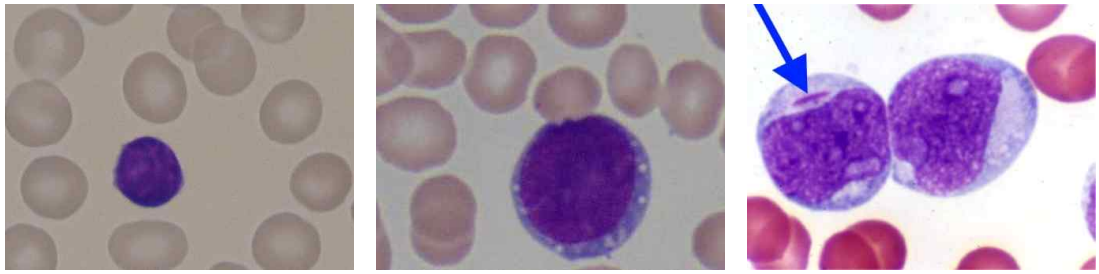


(a) (b) (c)

Fig. 1. (a) Healthy white blood cell from non-leukemia patients, (b) ALL image, (c) AML image (the blue arrow indicates an Auer rod).

average size of two times bigger than that of red blood cells, as shown in Fig. 1 (b) and (c). This is a good feature to distinguish normal cell images from ALL and AML images. In most ALL cells, the nucleus occupies nearly 80-90% of the whole cell, whereas the nucleus area in an AML cell is about 50-60%. In addition, the surface of an ALL cell is smooth, but the cytoplasm area of an AML cell has some Auer rods which are short purple stripes illustrated in Fig. 1 (c).

There are three main methods for diagnosing leukemia, including a physical exam, blood tests, and a bone marrow examination. Leukemia can be detected during routine blood tests before the patient has symptoms. If the patient has signs or symptoms, a physical exam may be required to check for any swollen or enlarged lymph nodes of the neck, axillary, and inguinal. A variety of blood tests might be performed to measure the number of white blood cells, red blood cells, and platelets. Since leukemia causes a large number of abnormal white blood cells, resulting in a low number of red blood cells and platelets, a blood count exam can detect those changes and leukemia is hence identified. Another method used in detecting leukemia is bone marrow examination. In this technique, a tissue sample taken from human hipbone or other large bones is used to detect cancer markers, called "Flow cytometry", and genetic markers. These aforementioned diagnosis methods must be strictly implemented by doctors in the laboratory environment with dedicated and specialized devices. Moreover, the results of these complex examinations are much dependent on skills and experiences of specialists.

Most of the research related to leukemia classification only focus on distinguishing between normal cell and ALL images based on the ALL-IDB1 dataset. In this paper, we present a methodology utilizing a specific CNN architecture, called LeukemiaNet, to classify ALL, AML, and normal cell images. This proposed method shows a comparably precise technique of leukemia diagnosis, compared to three above-mentioned complex examinations. In addition, this technique is totally independent of technician experience, which is one of the main challenges of those conventional examinations. An experiment is performed to evaluate the accuracy of the proposed CNN architecture. The result proves that LeukemiaNet can reach an accuracy of 97.2% when classifying ALL and AML. As a result, this work introduces a promising solution to an early clinical leukemia diagnosis system in detecting leukemia and categorization of leukemia.

The rest of this paper is organized as follows. Section 2 presents related works on applying image processing and conventional machine learning methods such as neural networks to detect leukemia. In section 3, we introduce state-of-the-art image augmentation methods and PCA color augmentation method of increasing the number of

images. A novel convolutional neural network, called LeukemiaNet, including 5 layers is also proposed in this section. Section 4 shows the experiment result and discussion. Finally, conclusions and future works are given in section 5.

2. RELATED WORKS

Usually, images in the used dataset are in JPG format. They are captured with a digital camera via an optical laboratory microscope. There is a need for enhancing the quality of images by using diverse image processing techniques, as mentioned in [3].

Because leukemia is a type of cancer found on white blood cells, most previous works try to segment white blood cells rather than red blood cell and platelets, which are included in a blood cell images. In the cell segmentation phase, various methods such as thresholding, clustering, region growing, and color segmentation are used. The feature extraction step usually follows the segmentation step. In most of the cases, the author extracts features including energy, contrast, shape feature, color feature. These features are then used as the input to the next step to detect leukemia disease. In the classification stage, most researchers conducted conventional machine learning methods such as support vector machine (SVM), neural networks for classification.

In [4], the authors converted original blood cell images from RGB into CIE L*a*b, then used K-means for cell clustering. They extracted five textural features, four Gray Level Co-occurrence Matrix (GLCM) and one fractal feature (Hausdorff Dimension) for the first neural network classifier to distinguish between normal and abnormal cell images. For the second neural network to classify ALL and AML images, geometrical features, including cell area, cytoplasm area, nucleus-to-cytoplasm area ratio and nucleus-to-cell area ratio were used. The authors used a neural network architecture for categorizing normal and abnormal cell images, then, ALL and AML images were classified from abnormal cell images using the same architecture. Because of the lack of dataset, the authors only focused on the first step to classify ALL images from normal cell images. The accuracy when classifying ALL and AML images was reported to reach 97.7%, but was only validated on the small dataset of 49 ALL images and 10 AML images.

In [5], the authors converted RGB images into grayscale images before applying median filtering to remove noise in grayscale images. In segmentation stage, K-mean clustering was used to extract the nuclei of the leukocytes. A local directional pattern (LDP) was used in this paper for white blood cell feature extraction stage. In addition, the author used a support vector machine (SVM) to classify cancer and non-cancer cell images. The overall accuracy was 98% when the suggested method was performed over 90 images obtained from the American Society of Hematology. Besides the advantage of using LDP operator for feature extraction, [5] showed a limitation that it only used AML images samples to build their model and focused on distinguishing between AML images and non-leukemia images.

In [6], they proposed a HIS color space for the segmentation step and used some morphological operators such as dilation, closing, median filter to remove unwanted noise in images. Especially, the authors extracted three kinds of features, including geometrical features (area, length, and compactness features), color features (Hue, Saturation, and Intensity), and textural features. In the classification stage, the author conducted an experiment on three methods for comparison, including Multilayer Perceptron (MLPs), Support Vector Machine (SVM) and Hyper Rectangular Composite Neural Network (HRC-NNs). They figured out that the trained MLP yielded the highest performance. However, the proposed system of [6] didn't classify

leukemia subtype cells.

Research in [7] is not only used MLPs and SVM but also use Dempster-Shafer method for classifying normal and abnormal lymphocytic cells with 80 input features comprising texture, color, and shape-based information using bootstrap validation, the authors show that the Dempster-Shafer achieves the highest accuracy of 96.72% when distinguishing ALL and normal cells.

All aforementioned classification techniques for the detection of leukemia make use of traditional machine learning methods such as SVMs and neural network. These classification models need a high number of significant and accurate features (such as pixel values, shape, texture, and color) for classification. The performance of most of the machine learning algorithms depend on how accurately the features are extracted; therefore, the selection of features must be carefully made and is one of the most difficult and time-consuming steps.

This challenge leads to the motivation of this work, in which the complexity of featuring is targeted to be reduced while the accuracy remains high. With a deep learning framework such as CNN, not only classification can be performed with high accuracy, but the necessity of feature engineering is also reduced because a deep learning framework can create new features by itself. Hence, in recent years, CNN is applied in a wide range of reality work such as face detection [8], forest insects' classification [9].

For leukemia detection, the task is to identify which are the abnormal white blood cells in an image accompanied by multiple blood cells, including the red blood cells, the normal white blood cells, and the platelets. In machine learning approach, we would follow two steps which comprise of white blood cell detection and leukemia cell recognition using object recognition algorithm like SVM. On the contrary, in CNN approach, CNN architecture can do the process end-to-end, without the need of dividing into two steps, just input an original cell image, and CNN model will label this image is patient with leukemia or non-patient.

Taking advantage of deep learning methods, in this work, the authors proposed using CNN to classify ALL, AML, and normal cell images. The details of our proposed method are introduced in the next part.

3. PROPOSED METHODOLOGY

A sufficient dataset of leukemia images is a challenge for our proposed method due to the privacy of such images. Therefore, we perform two types of data augmentation to train accurate and robust CNN architecture. The first data augmentation is conventional methods, in which available samples are transformed into new samples using some traditional affine transformation methods such as shear image, rotation, reflection, translation, histogram equalization and so on. The second one is PCA color augmentation, as mentioned in [10].

3.1 Pre-processing images

3.1.1 Conventional image augmentation methods

In this paper, to increase the number of images in the original dataset, we augment the dataset by applying following transformation methods.

Conversion of RGB images to grayscale images

All RGB images in the dataset are converted to grayscale intensity images by discarding the saturation and hue in the original images while the luminance remains.

Blurring

A Gaussian filter is applied not only in the original RGB images but also in grayscale images with a scalar value for sigma generated randomly between [4, 8].

Histogram equalization [11]

Histogram equalization is used to enhance the contrast of a grayscale image. The image after being applied histogram equalization has the higher contrast, as shown in Fig. 2(e).

Reflection

The image is symmetrically taken along the x-axis and the y-axis. Fig. 2 (f) depicts a reflection image of the image in Fig. 2 (a) along the x-axis.

Rotation

The image is rotated counterclockwise or clockwise some angle which is generated randomly between. The image rotates clockwise if the angle has a negative value. The rotated image makes the output image large enough to contain the entire rotated image. Therefore, we have to resize the output image to the same size as the original image.

Translation

We conduct horizontal and vertical translation for images with the displacement value randomly chosen with a uniform distribution of between 25 and 50.

Shearing images [12]

A simple vertical and horizontal shear transformation is applied to images with the value of distortion is chosen randomly between [0.3, 1], as illustrated in Fig. 2 (h) and (i).

3.1.2 PCA color augmentation

This method was first proposed by Alex Krizhevsky to increase the size of the dataset. [10] The main concept of this method is altering the intensities of RGB channels in an image. PCA reduces the number of dimensions in the data by finding patterns in the data.

There are 6 steps for performing PCA color augmentation which are summarized as below:

1. Each pixel of an image is composed of three vectors of red (R), green (G) and blue (B). PCA is then computed on these data points. Each channel of an image is converted to a vector $x=\begin{bmatrix}x_1\\x_2\\x_3\end{bmatrix}$

2. Compute the means for 3 dimensions of each image m_i with i: 1,2, 3:

$$m_i = \frac{1}{n}\sum_{k=1}^{n} x_k$$
$$n: size\ of\ image \quad (1)$$
$$m_i: mean\ of\ each\ channel\ of\ an\ image$$

2. Compute the covariance matrix. The covariance matrix has a size of 3×3 because the data is 3 dimensional

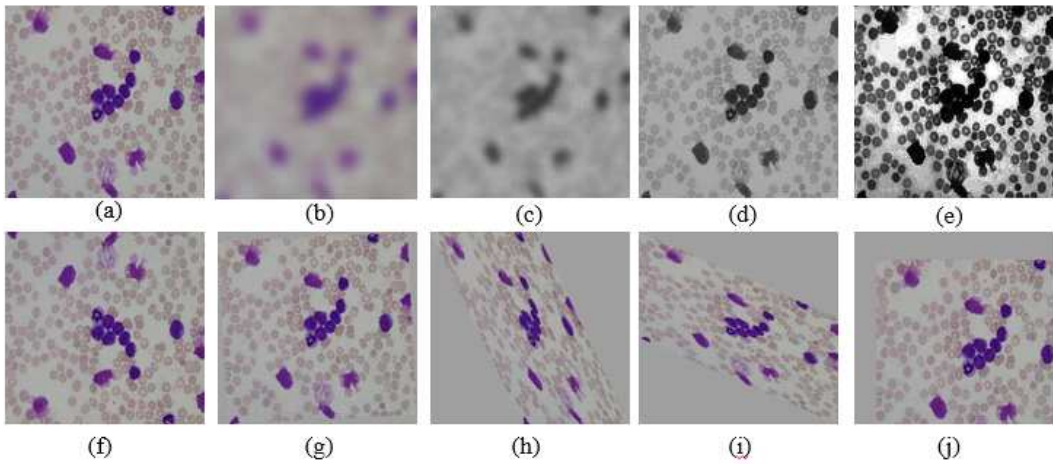
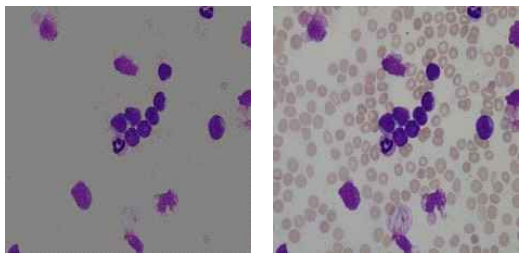


Fig. 2. Conventional data augmentation, (a) An original ALL image, (b) A blurring ALL image, (c) A blurring grayscale image, (d) A grayscale image, (e) Histogram equalization, (f) Reflection image through x-axis, (g) Rotated image, (h) Shearing image along x-axis, (i) A shearing image along y-axis, and (j) Image translation.



(a) (b)

Fig. 3. PCA color augmentation, (a) The original ALL image, and (b) ALL image after being applied PCA color augmentation.

$$S = \sum_{k=1}^{n}(x_k - m)(x_k - m)^T \quad (2)$$

4. Compute the eigenvector (e_1, e_2, e_3) and corresponding eigenvalues (λ_1, λ_2, λ_3)

5. Sort the eigenvectors from the highest to lowest and discard the lower eigenvalues. Choose k eigenvectors with the largest eigenvalues from a dxk dimensional matrix W. In W, every column represents an eigenvector.

6. Take the transpose of the vector and multiply it to the transposed original dataset, after that, take the transpose of the result. We need to add multiples of found principal components with magnitudes proportional to the corresponding eigenvalues times a random variable drawn from a Gaussian distribution with mean zero and standard deviation of 0.1.

PCA color augmentation changes those values based on which values are the most popular in the image. For instance, the image in Fig. 3 (a) has heavy purple abnormal cells and minimal another color values. Therefore, after PCA color augmentation is applied, Fig. 3 (b) has their purple values altered the most, highlighting the abnormal white blood cells and blurring normal blood cells in the image.

3.2 The proposed CNN architecture

The utilization of deep learning helps image recognition to reduce the error rate. This encourages the great innovation of image classification. In this paper, we propose a CNN architecture called LeukemiaNet. The experiment results described in the next section show that of with LeukemiaNet, a good accuracy is obtained when classifying Leukemia disease.

In Fig. 4, the input layer is in the dimension of [227x227x3] which corresponds to the height, width and the channel size of images. In this case, the channel size of the image is 3, corresponding to RGB values. In the convolutional layer, the filter is used for scanning along the input images. For instance, the first convolutional layer has the filter with a size of [4x4] and the number of neurons that connect to the same region of the input is 10 (the number of filters). We also utilize batch normalization after each convolutional layer to speed up network training and decrease the sensitivity to network initialization. The batch normalization is followed by a ReLu layer. Max pooling layer is

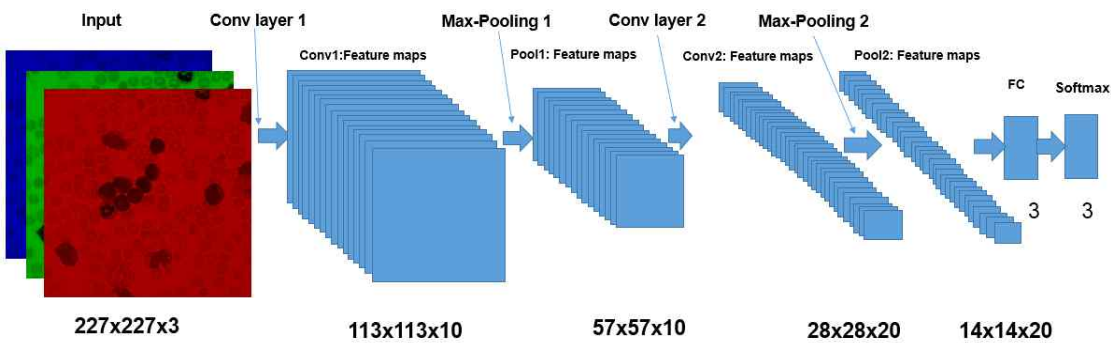


Fig. 4. The proposed CNN architecture to classify three classes.

used in our CNN architecture to reduce the spatial size of the feature map by returning the maximum values of the region decided by the pooling size. For example, the common pooling size is [2x2]. The fully connected layer (FC) follows the second convolutional layer to combine all the features of the previous layers to identify the patterns. In our experiment, the output size of the FC layer is 3, corresponding to 3 classes needed to be classified, including AML, ALL, and normal cell image, respectively.

After the last fully connected layer, we stack a softmax layer to normalize the output of the FC layer. The final layer of our CNN architecture is the classification layer. It uses the classification probabilities returned by the softmax activation function to assign the input to one of the classes and compute the loss.

4. EXPERIMENTAL RESULT AND DISCUSSION

Our experiment was conducted on Matlab with NVIDIA GeForce GTX 1080 Ti. We implemented two experiments on different datasets to evaluate the robustness of augmentation strategies and the effectiveness of our proposed CNN architecture. All of the experiments were run for 30 epochs at the learning rate of 0.001 with the input size image of [228x227x3].

4.1 Dataset

In this paper, the dataset includes 49 ALL images and 59 normal cell images from the ALL-IDB1 database, among which 33 AML images are collected from the Internet. Because of insufficient data, the CNN architecture cannot learn many rich features. To improve the accuracy of our proposed CNN architecture, we extend the original dataset by applying some data augmentation methods such as blurring using Gaussian filter, histogram equalization, converting images to grayscale image, shearing image, image reflection, image translation, etc. [13]. The advantage of using data diversification demonstrates that our CNN architecture can handle a diversity of images collected from different research groups with different quality (noisy images, tilted images, etc.).

4.2 Metrics to evaluate the performance of LeukemiaNet

In this paper, different performance metrics are utilized to evaluate the desired effects of LeukemiaNet architecture.

A. Confusion matrix

A confusion matrix figures out a detailed itemization of accurate and inaccurate classifications for each class, as illustrated in Fig. 5.

True positives (TP) is the case when the output class of an image and the target class are true. For instance, that occurs when a person is diagnosed with ALL and the LeukemiaNet classifies his case as ALL. In Fig. 5 (a), TP of ALL, AML, and the normal class correspond with 158 images, 101 images, and 175 images.

On the contrary, true negatives (TN) is a case when the target class of the image is false and the output class is also false. The total number of TN for the ALL class, the AML class, and the normal class in Fig. 5 (a) is 278 images, 339 images, and 265 images, respectively.

False positives (FP), for example, is defined as the case when LeukemiaNet model predicts a non-cancerous person as a patient who has ALL. In Fig. 5 (a), the total number of FP for the ALL class is 8, for the AML class is 0, and for the normal class is 6.

False negatives (FN) is a case when the target class of the image is true and the output class is false. For example, a person having ALL and the LeukemiaNet classifies this case as a non-cancerous person or AML patient. The total number of FN for the ALL class, the AML class, and the normal class are 4 images, 8 images, and 2 images,

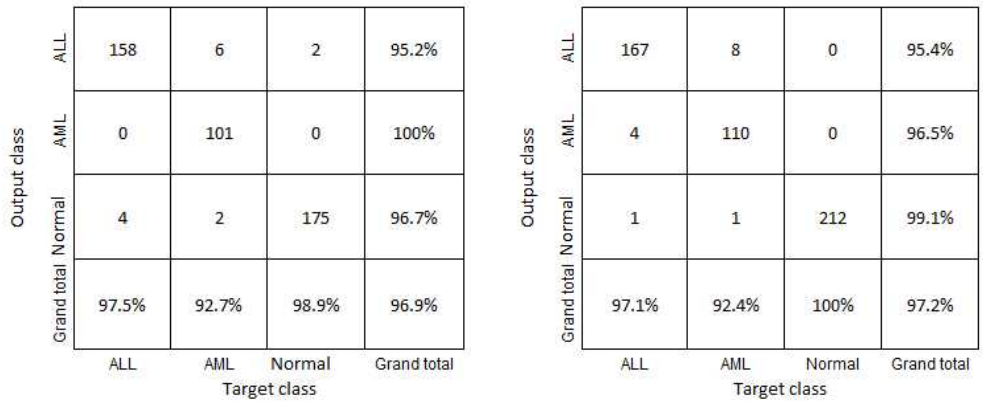


Fig. 5. The confusion matrix of our proposed CNN architecture on different datasets, (a) The original dataset and conventional augmented dataset; (b) The original dataset, conventional augmented dataset, and PCA color augmentation.

respectively.

B. Accuracy

Accuracy is a good metric to evaluate Leukemia Net because the number of images in classes is approximately balanced. Accuracy is calculated by dividing the sum of correct classifications by the total number of images.

$$Accuracy = \frac{TP+TN}{TP+FP+FN+TN} \quad (3)$$

C. Precision

Precision is a measurement metric that figures out what proportion of images that LeukemiaNet predicted belong to a class, actually belong to this class.

$$Precision = \frac{TP}{TP+FP} \quad (4)$$

Using Equation (4), the precision of three classes in Fig. 5 (a) is 95.2%, 100%, and 96.7%, corresponding to ALL, AML, and normal class. Similarly, the precision of ALL class, AML class, and the normal class in Fig. 5 (b) is 95.4%, 96.5%, and 99.1%, respectively.

D. Recall (sensitivity)

Recall corresponds to the true-positive rate of the interested class.

$$Recall = Sensitivity = \frac{TP}{TP+FN} \quad (5)$$

The sensitivity of three classes in Fig. 5 (a) and (b) is shown in Table 1.

E. Specificity

Specificity corresponds to the true-negative rate of the considered class.

$$Specificity = \frac{TN}{TN+FP} \quad (6)$$

4.3 Experiment results

Two experiments were conducted, one of which was based on the dataset extended using conventional data augmentation methods, whilst the other utilized the dataset extended using traditional data augmentation methods combined with the PCA color augmentation method to test the effectiveness of various augmentation methods. Table 1 shows the comparison of performance metrics of these two experiments.

The experiment on the dataset includes original and extended images using traditional data augmentation methods, notated as “Dataset 1”. We conducted LeukemiaNet on the dataset including 1,492 images in total after augmented by traditional augmentation methods. We used 1,228 images (373

Table 1. Performance metrics when training LeukemiaNet architecture on different datasets.

		Dataset 1	Dataset 2
True positive (TP)	ALL	158	167
	AML	101	110
	Normal	175	212
True negative (TN)	ALL	278	323
	AML	339	380
	Normal	265	289
False positive (FP)	ALL	8	8
	AML	0	4
	Normal	6	2
False negative (FN)	ALL	4	5
	AML	8	9
	Normal	2	0
Accuracy		96.9%	97.2%
Precision	ALL	95.2%	95.4%
	AML	100%	96.5%
	Normal	96.7%	99.1%
Recall (sensitivity)	ALL	97.5%	97.1%
	AML	92.7%	92.4%
	Normal	98.9%	100%
Specificity	ALL	97.2%	97.6%
	AML	100%	99%
	Normal	97.8%	99.3%

ALL images, 262 AML images, 409 normal cell images) for the training phase. There are 448 images (166 ALL images, 101 AML images, 181 normal cell images) for the testing phase. Therefore, the accuracy of this dataset reached 96.9%, as listed in Table 1.

The experiment on the dataset which was extended using traditional data augmentation methods combined with the PCA color augmentation method, notated as "Dataset 2". The LeukemiaNet above was run on the dataset which has a total of 1,676 images were replicated by traditional methods combined with the PCA color augmentation method. The accuracy obtained from this experiment is better than that from the first one, which is 97.2%, and 96.9%.

The comparison of Table 1 proves that LeukemiaNet performs remarkably better on the dataset, including images was extended by traditional methods combined with PCA color augmentation methods. The strategies combining traditional augmentation techniques with PCA color augmentation methods can significantly reduce the error rate of our proposed CNN architecture. Fig. 5 shows that PCA color augmentation can help Leukemia Net prevent overfitting.

For the purpose of evaluation, we also compare our method with existing state-of-the-art works, as shown in Table 2. In most recent works, leukemia classification is mainly based on computer vision techniques. The vast majority of these consist of several steps: image pre-processing, clustering, morphological filtering, segmentation, feature selection or extraction, classification, and evaluation. For the classification phase, most authors adopted conventional machine learning methodologies such as multilayer perceptron (MLP), and support vector machine (SVM). Consequently, feature ex-

Table 2. Comparison of the accuracy between recent works and our proposed methodology

Work	Classify methods	Classified objects	Number of images	Accuracy
Screening of bone marrow slide images for leukemia using multilayer perceptron (MLP) (2011) [14]	Multilayer perceptron (MLP) network and the Levenberg Marquardt (LM) training algorithm	142 normal bone Marrow and 858 abnormal bone Marrow samples	1000	94.5%
Leucocyte classification for leukaemia detection using image processing techniques (2014) [15]	Support vector machine (SVM) with a Gaussian radial basis kernel	245 of 267 total leucocytes of 33 ALL images	33	93%
Recognition of acute lymphoblastic leukemia cells in microscopic images using k-means clustering and support vector machine classifier (2015) [16]	Support vector machine (SVM)	21 peripheral blood smear and bone marrow slides of 14 patients with ALL and 7 normal people	21	97%
Proposed methodology (LeukemiaNet)	Convolutional Neural Network (CNN)	ALL, AML, and normal cell images	1676	97.2%

traction is such the most important steps affected the error rate of the classification phase. Besides, all related works conduct on a small and homogenous dataset. In this paper to overcome previously weakness of related works, a CNN architecture called LeukemiaNet was conducted. LeukemiaNet can extract high-level features and perform classification at the same time. Hence, this architecture is not only skipped most time-consuming pre-processing steps, but also it can handle the variety of leukemia image from diverse research institutes.

Table 2 shows that there are no studies classify ALL, AML, and normal cell images, like the one proposed in this work. Almost all of these works focus on classifying non-cancer and cancer patients. We remind that the accuracy rate after using LeukemiaNet is outperformer than conventional methods shown in Table 2.

5. CONCLUSION

In this work, two data augmentation strategies to extend dataset to prevent overfitting and memorize the exact details of the training images were implemented. While traditional augmentation methods are easy to apply and not consume time, the other techniques to extend dataset show a promising solution to help to reduce the error rate of CNN architecture. Besides, we proposed LeukemiaNet convolutional neural network architecture to detect effectively ALL, AML images from normal cell images with high accuracy. The proposed CNN architecture was experimented on two separate datasets, one with data extended using traditional methods only and the other with extended data using a combination of traditional and PCA color augmentation methods, to confirm that our network can deal with the variation of images. The accuracy and efficiency of LeukemiaNet architecture was also validated, in need reliable dataset of leukemia image. In future work, we would like to apply this proposed method in a huge dataset including four types of Leukemia (AML, ALL, Chronic lymphocytic leukemia - CLL and Chronic myelogenous leukemia - CML).

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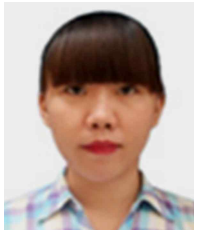

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