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WHITE BLOOD CELLS CLASSIFICATION FOR THE DIAGNOSIS OF BLOOD RELATED DISEASES USING NEURAL NETWORK TECHNIQUES

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Abstract
Quantitative analysis of white blood cells (WBC) or leukocytes is crucial in the diagnosis of various blood diseases including blood cancers like Leukemia and Myeloma. They are an integralconstituent of the immune system and the production of excess white blood cells is one of the initial steps in the defence mechanism by the human body against any disease. An abnormal WBC count or an increase in one type of white blood cells can be an indication of an infectious or inflammatory diseases. Hence, an analysis and identification of the different blood cells in a patient's blood is pivotal for an early diagnosis of diseases. The manual methods adopted for this purpose are time-consuming and vulnerable to errors. Automating this process involves careful feature extraction for an increased accuracy. In this research, Convolutional neural network (CNN) models are exploited for automatic feature extraction and the images are classified using traditional classifiers such as Linear discriminant analysis (LDA) and Logistic Regression (LR). The different hybrid models obtained by using VGG19, Inception V3 and DenseNet169 with the above mentioned classifiers are evaluated and analysed to find the most suitable approach for this application. DenseNet169 – LDA model was shown to have the best performance in classifying the white blood cell images into neutrophils, lymphocytes, monocytes and eosinophils.
Keywords: Image classification, white blood cells, convolutional neural networks, deep learning.

I. Introduction

Blood cells are classified into three broad types: Leukocytes (white blood cells), erythrocytes (red blood cells) and thrombocytes (platelets)[1]. These cells differ in their structure and functions in the body. In contrast to Red blood cells (RBC) which account for about 45% of the blood, the white blood cells account only for 1% of the total blood [2, 3, 4]. Nevertheless, their impact is significant and thus considered as a vital component of the blood. They are formed in the bone marrow and as part of the

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body's immune system they protect against foreign elements entering the body, particularly the microorganisms which are responsible for causing dreadful diseases.

The five types of white blood cells are basophils, eosinophils, neutrophils, lymphocytes and monocytes which can be further categorized into two groups, granulocytes and granulocytes. Granulocytes are white blood cells that have small visible granules whereas agranulocytes do not possess such granules when visualized under a microscope [5]. Granulocytes include basophils, eosinophils, neutrophils while lymphocytes and monocytes are agranulocytes. Neutrophils represent 40-60% of the total white blood cells in the body followed by lymphocytes (20-40%), monocytes (2-8%), eosinophils (1-4%) and basophils (0.5-1%) [3]. Each white blood cell has a specific functionality and indicates different condition of the patient's health. Thus identifying the different white blood cells is deemed important. Predominantly, precise identification leads to the chance of counting the different white blood cells to evaluate their presence in the correct or expected proportions. Additionally, after identification, different white blood cells can be isolated towards thorough examination for abnormalities.

The evaluation of white blood cells (leukocytes) is the prime step to identify various blood related diseases. The assessment of major subtypes of Leukocytes, namely-Monocytes, Eosinophils, Lymphocytes and Neutrophils proves to be helpful in the identification of various diseases including AIDS (Acquired Immune Deficiency Syndrome) and blood cancers, such as Lymphoma, Leukemia, and Myeloma. According to the Leukemia and Lymphoma society, at least person is diagnosed with a type of blood cancer every three minutes and approximately 186,400 people are expected to be diagnosed with either Leukemia, Lymphoma or Myeloma in 2021 in the United States. Blood cancers account for approximately 9.8% of the total cancer cases in US [6]. It is a known fact that blood cells consist of RBCs (red blood cells), WBCs (white blood cells) and platelets. Leukocyte in blood assumes a primary job in human immunity, thus named as the immune cell. Typically, haematologists consider shape data and granulated data in leukocytes to segregate WBCs platelets into non-granular cells: lymphocyte and monocyte and granular cells: eosinophil, neutrophil, basophil. The ratio of these types of cells in the blood is different for the healthy and infected bloods. Therefore, arises the necessity to introduce accurate, efficient, fast diagnostic systems to precisely determine the white blood cell count to uncover varied diseases. Doctors mostly utilize these primary data as the basis for judging the type and extent of effect of the disease. Thus, the study of WBC classification has prime importance and source for medical diagnosis especially for blood related diseases like myeloma, leukemia etc.

The conventional method of identification requires a laboratory set up wherein blood cells stained with special chemicals are examined under a microscope by a trained professional. However this method is quite tedious, intricate, and prone to error

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which can result in inaccurate classification of the white blood cells.Owing to their significance in medical analysis field, substantial research has been carried out in the classification and quantification of WBCs. The usual image classification system comprises several phases such as image pre-processing, segmentation, feature extraction and the classifier. The automated classification algorithms have gained importance as expert decision support systems that are ideal for various medical diagnostic applications such as radiology and detection of diseases. Over the years, different classifiers such as SVM, KNN, Naïve Bayes, Logistic regression(LR), Linear discriminant analyser (LDA), Random forest etc. have emerged, the most recent being convoluted neural networks (CNN). A number of neural networks have been developed for utilization in various fields. In this paper, CNN models are used for automatic feature extraction and combined with traditional classifiers for classification of white blood cells into their types.

This paper is organized as follows: Section II discusses the relevant work that has been carried out for image classification tasks. The dataset and the proposed approach are discussed in Section III of the paper. Section IV analyses the results obtained and compares the different hybrid models. Finally, section V gives the conclusion and explores possible future work scope.

II. Related work

Image classification has been an area of abundant research, with contributions from a huge number of researchesand scientists across the world.Medical image processing and classification have become one of the most researched uponareas especially with the advancement in machine and deep learning.

In 2018, Macawile et al [8], proposed a new segmentation method using HSV (Hue, Saturation, Value) saturation and blob analysis. Convolution neural networks such as AlexNet, GoogleNet and ResNet-101 were used for counting and classification with the AlexNet giving the best performance.

Liang *et al.*[9] proposed an Xception-LSTM model for classifying blood cell images proposed in the same year which was proved to be more accurate and efficient than many existing CNN models such as Inception and ResNet. The local features which are extracted from CNN and the features extracted from RNN are combined followed by the classification process. The pre-processed data is fed into the RNN model, the resultant features are extracted, saved while keeping the pre-trained CNN model frozen and the features from the CNN and RNN are merged. The weight parameters of RNN are updated at regular intervals, after which, all the network layers are released with the training data being used as an input to the RNN and CNN model. Corresponding element multiplication methods are performed to combine the features of the two models.

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Habibzadeh et al. [10] carried out similar work using Inception and ResNet architectures with emphasis on pre-processing. Different techniques such colour distortion, bounding box distortion and image flipping mirroring were incorporated with CNN architectures for feature extraction. The proposed model was shown to have excellent performance with an accuracy of 99.46%and 99.84% with ResNet 101 and ResNet V1 152 respectively.

Transfer learning approaches based on deep activation features along with fine-tuning of CNN models was proposed by Shahin, Ahmed Ismail, et al [11]. A new convolution architecture WBCsNet was built and used as pre-trained network to extract features. Their overall system achieved an average accuracy of 96.1% on three different publicly available white blood cell datasets. Traditional image processing approaches were compared with deep learning methods for classification by Hegde, Roopa B., et al [12]. Using hand-crafted features, an average accuracy of 99.8% was obtained. In addition, full training was shown to give better results when compared to transfer learning.

Jung, Changhun, et al. [13] proposed W-Net, a CNN based architecture to improve the accuracy further. It was evaluated on a real-world dataset which included real images of the five types of leukocytes. It achieved an accuracy of 97% and was proven to be superior to other architectures like ResNet.

Partially visible cells and overlapping cells are one of the major concerns while classifying. To overcome this problem, Kutlu et al.[14] proposed regional convolutional neural networks(R-CNN) as a strategy. A detector was used to classify the different cell types in an image simultaneously. AlexNet, VGG16, GoogLeNet, ResNEt50 architectures were used as basis of the R-CNN and were evaluated with full learning as well as transfer learning. ResNet architecture with full learning showed best performance when a combined dataset of BCCD and LISC was used.

Another challenge faced in developing classification models for leukocyte images is the inadequacy of data that covers the morphological variations. Generative adversarial networks (GAN) are employed for data augmentation in an attempt to solve this problem by Almezhghwi et al. [15] The images were classified using VGG16, ResNet and DenseNet using manullay extracted features. The authors also compare the models using randomly initialised weights and using weight pre-trained on CIFAR-100 dataset.

Noor, Anas Mohd, et al. [16] introduced speed up robust feature (SURF) to reduce the influence cell orientations, colour variations and quality of the image captured influences on classification accuracy. A scale and rotation invariance feature was proposed and classified using support vector machine (SVM) and artificial neural

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network (ANN). 10 SURF points was shown to have the best performance and concluded to be optimum for this application.

Çınar et al. [17] proposed a hybrid AlexNet-GoogleNet-SVM model builtfrom the pretrained GoogleNet and AlexNetarchitectures for the classification of WBCs. The proposed method was tested with Kaggle and LISC datasets and performed better than both AlexNet and GoogleNet models.

Deep learning using Canonical correlation analysis (CCA) was another notable idea proposed by Patil, A. M. et al [18] to resolve the issue of multiple cell overlap. CNN and LSTM were combined for the classification task and the training phase incorporates fine tuning and transfer learning. CCA extracted a range of overlapped features hence increasing the accuracy rate.

Data Set

The publicly available BCCD (Blood Cell count Detection) dataset has been exploited for the work [19]. It is a small-scale dataset for blood cell detection which is licensed by MIT and is available by Kaggle. The dataset consists of RGB images of size 320 x 240 x 3 pixels which are categorized and labelled with their cell type, namely, neutrophil, eosinophil, lymphocyte and monocyte. The images are in JPEG format which can be readily used for training and testing the models. Moreover, the BCCD dataset has more data points when compared to other publicly available datasets available for research in this field. It has to be noted that, the number of basophil images available in the dataset are very few and hence are excluded. Few sample images from the dataset are shown in Figure 1.

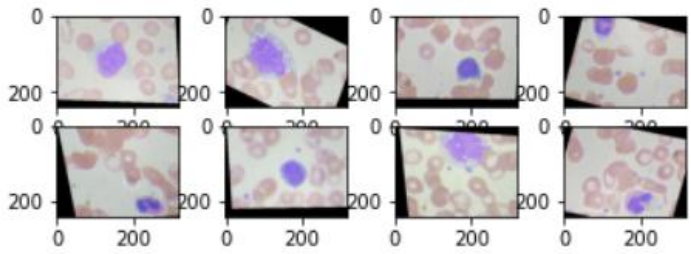

Figure 1: Sample images from the BCCD dataset

Data pre-processing

The unavailability of sufficient data for training is a major impediment to developing efficient classification models for any medical application. In addition, using

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unbalanced datasets for training often leads to poor results in classifying. It can make the model biased towards one type since it learns that a type is more common when significantly greater number of samples from training data belong to that type. This further leads to various problems such as overfitting of such class of data and accuracy paradox.

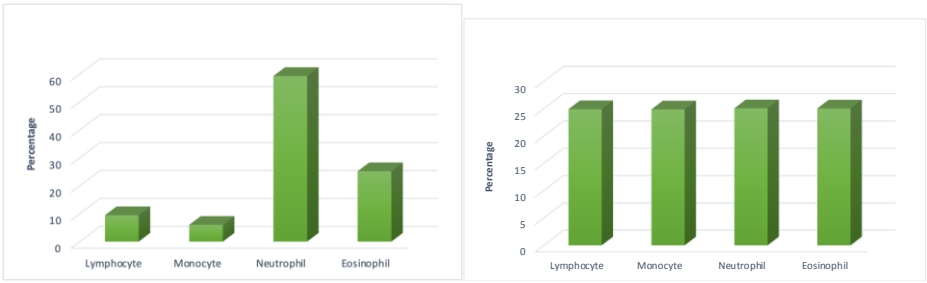

Figure 2: Proportion of different cells in the dataset before (left) and after (right) data augmentation

To overcome these problems, several data augmentation techniques are used to generate additional data. This includes image transformations such as horizontal flips, height and width shifts, shears and image rotations. This ensures sample equalization and hence helps improve the classification accuracy of the model. the proportion of each type of white blood cells before and after data augmentation is shown in figure 2. There are about 3120 images in each cell type after applying different augmentation techniques.Further, all the images were cropped to a size of 128*128 and the dataset was split in the ratio of 9:1 for training and testing respectively.

Proposed method

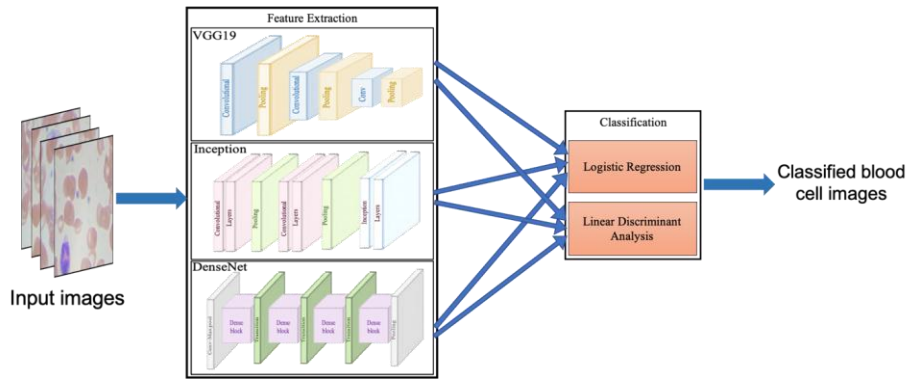

Fig 3: Model design

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The design of the proposed model is shown in Figure 3. After processing the input data, a CNN model is used to extract the features which are then fed into classifier for classification. The CNN models used for implementation of feature extraction are VGG19 [20], Inception V3 [21], DenseNet-169 [22]. The pre-trained weights from training over the ImageNet dataset are exploited instead of building the models from square one. Since the models need different weights for medical images, the layers are left unfrozen during training. This method has been proved to be productive [23]. In each model, the last fully connected layer is eliminated to reach the feature vector. Thus, a fixed feature extractor can be obtained for the new dataset [24]. The feature vector extracted from the chosen CNN model is then passed to the traditional classifier.

Linear classifiers LDA and Logistic regression were chosen for this work considering their relevance to our application. Using LDA for classification of large datasets, high accuracy levels have been achieved [25]. It is especially suitable because of its singular value decomposition solver. It has shown to be consistent and outperforms most traditional classifiers. In addition, it has a very simple and portable design which greatly contribute to its speed. It boosts the ratio of inter-class to intra-class variance by transforming features into a lower dimensional space [26, 27]. Though LDA has been criticized for its assumptions like multivariate normality, homogeneity of co-variance and multicollinearity, it has been proved that it relatively robust and allows slight violations [28, 29]. Logistic regression is another popular classifier adopted when the data is linearly separable. It is easy to implement and simple to interpret. It is widely used in the prediction of categorical variables and is more flexible than LDA. The different hybrid models obtained from combining the CNN models and classifier are analysed and evaluated exhaustively in the following sections.

Evaluation metrics

The different evaluation metrics used to evaluate the performance of the models were precision, sensitivity, specificity, accuracy and F1-score. These were calculated using the true positive (TP), false positive (FP), true negative (TP) and false negative (FN) values which collectively represent all the possible outcomes of prediction. TP and TN represent how correctly the model predicts the positive class and negative class respectively. Similarly, FP and FN are outcomes where the model incorrectly predicts the positive and negative classes as vice-versa.

Accuracy is defined as the ratio of the number of instances that were predicted correctly to the total number of instances tested. It is given by the equation in (1).

Precision is the positive prediction value i.e., probability that a sample predicted as positive is actually positive. It can be calculated using (2).

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Sensitivity *or True Positive rate* (also known as Recall) measures the ability of the model to correctly classify positive examples as positive. It is given by the ratio of TP to the sum of TP and FN as in (2).Specificity *or True Negative rate* measures the ability of the model to correctly classify negative examples as negative. It is given by the ratio of TN to the sum of TN and FP as in (3).

F1-score is given by the harmonic mean of Precision and recall of a model. It represents the test accuracy of the model and is given by (5).

$$Accuracy = \frac{TP+TN}{TP+TN+FP+FN} \quad (1)$$

$$Precision = \frac{TP}{TP+FP} \quad (2)$$

$$Sensitivity = \frac{TP}{TP+FN} \quad (3)$$

$$Specificity = \frac{TN}{FP+TN} \quad (4)$$

$$F1-Score = \frac{2TP}{2TP+FP+FN} \quad (5)$$

Receiver operating curve (ROC) is a plot of False positive vs True positive. It was observed that the ROC curves for the models in consideration were quite alike and not an ideal criterion for comparison. The AUC values of the curves were used as it would be a superior metric to analyze the performance of the models.

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Results and discussion:

The first observation is that the length of feature vector extracted varied depending on the CNN model used. The length of the feature vectors for VGG19, Inception V3 and DenseNet169 models is shown in figure 4.

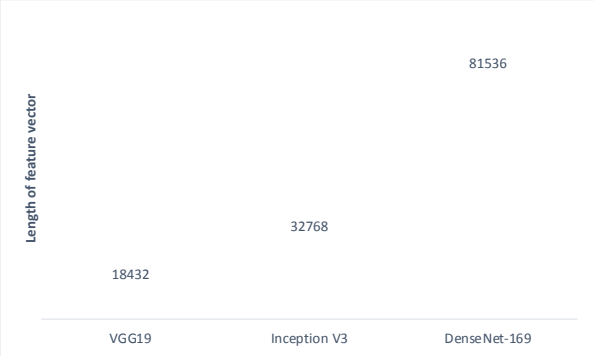

Fig 4: Length of feature vector when different CNN models are used

Table 1: Performance of the different hybrid models for White blood cell image classification

Model	Precision	Sensitivity	Specificity	Accuracy	F1-Score
VGG19 – LDA	0.75	0.76	0.75	0.76	0.76
Inception V3 – LDA	0.82	0.83	0.82	0.82	0.82
DenseNet169 - LDA	**0.96**	0.94	**0.96**	0.95	**0.95**
VGG19 - LR	0.94	0.93	0.94	0.93	0.93
Inception V3 – LR	0.91	0.93	0.91	0.92	0.92
DenseNet169 - LR	**0.96**	**0.95**	**0.96**	**0.96**	**0.95**

The Precision, sensitivity, specificity, accuracy (Rank-I) and F1-Score of the different hybrid models have been shown in Table 1. It is evident that models using LR for classification tend to perform better when compared to the respective models using LDA classifier. It can be seen that DenseNet169 - LR performs best among the six

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hybrid models. Though the sensitivity and accuracy values of DenseNet169 - LDA are slightly lower than the respective LR model, it can be observed that its performance is almost identical to that of DenseNet169-LR.

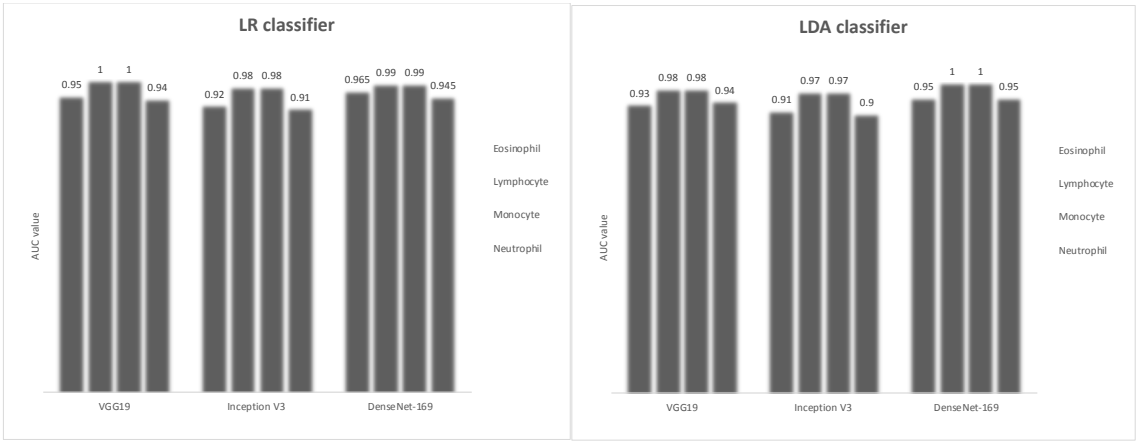

Fig 5:Plots showing the AUC values of the hybrid models with LR classifier (left) and LDA classifier (right)

For further analysis, the AUC values for the three CNN models when combined with LDA and Logistic regression for classifying is given in figure 5 and the average of AUC values over the four types of cells are given in table 2. From the plots in figure 5, it can be deduced that DenseNet169 models achieve the best performance with both LR and LDA classifiers. Another important observation is that lymphocyte and monocyte are always higher than the AUC values for eosinophil and neutrophil. In other words, classifying eosinophil and neutrophil images are more challenging than classifying lymphocyte and monocyte images correctly.

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Table 2: Comparison of the average AUC values computed over the 4 types of WBC cells in the dataset

Model	Average AUC value
VGG19 - LR	0.9725
Inception V3 - LR	0.9475
DenseNet169 - LR	0.9725
VGG19 - LDA	0.9575
Inception V3 - LDA	0.9375
DenseNet169 - LDA	**0.975**

AUC values help us visualize the ability of a classifier to distinguish between classes. The excellence of DenseNet169 – LDA hybrid model can once again be observed with its highest average AUC value of 0.975. It is closely followed by DenseNet169 – LR and VGG19 – LR with an average AUC value of 0.9725. The other models show moderate performance when evaluated based on average AUC values of their ROC curves.

Future work and conclusion

The primary focus of this paper is to classify white blood cells accurately which can help in the diagnosis of Leukemia and various other blood related diseases. Different CNN models were used for automatic feature extraction with LDA and Logistic regression classifiers. These different hybrid models were analysed using various evaluation metrics and DenseNet-169 with LDA was found to be the best fit for this application. In future, the model can be trained and tested with datasets that include multi-celled and overlapped cell images to make it ideal for using the model in medical diagnosis systems. The model can further be exploited for other similar classification problems such classifying blood cells into RBC, WBC and platelets.

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