



Diagnosis of B-ALL and classification of Blood Smear Images using Ensemble CNN models infused on Fuzzy Rank

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Abstract. A highly dangerous cancer, which needs invasive, costlier and time-consuming diagnostic tests are considered in this study. ALL diagnosis based on peripheral blood smear (PBS) images are taken for the implementation. There exist chances of misclassifying the cancer cases by the medical experts. Therefore, an appropriate diagnosing model was developed based on Deep learning algorithms to distinguish ALL subtypes. CNNs are the most prominent model to use in classifying bio-medical images with high percentage of accuracy. For this study, an ensemble model was built by having a publicly available ALL data set, which consists of 3256 PBS images. Three CNN architectures were used to classify the 4 class labels. The proposed model has been evaluated using a 5-fold cross-validation scheme. It achieves a classification accuracy of 99.23%.

Keywords: Convolutional Neural Network, Fuzzy Rank, acute lymphoblastic leukemia, classification

1. Introduction

Normal blood contains red blood cells, platelets and white blood cells. White blood cells are protecting our organs and fighting against viruses, illnesses, diseases and bacteria. Normal growth of cell is hampered by rapid growth in abnormal blood cells. There are three major types of blood cancers. They are Leukemia, Lymphoma and Multiple myeloma [1].

Leukemia is one of the most dangerous diseases that affects humans. Leukemia is a cancer of blood cell, starts in bone marrow. It forms in the blood-forming stem cells of the bone marrow, where body's blood cells are made. People affected with Leukemia, the bone marrow develops an excessive number of abnormal white cells. These are called Leukemia cells [2]. There are many types exist such as Acute Lymphoblastic Leukemia (ALL), Acute myeloidleukemia (AML), Chronic myeloid leukemia (CML), Chronic lymphocytic leukemia (CLL) [3].

Acute Leukaemia is a disease which affects both children and Adults. The detection of blast cell in peripheral blood is the basic initiative task of clinical pathologists. Depending on the type of leukemia, treatment can be given to the children and Adults. For many types of cancer, finding the stage is very important. The stage is based on the tumor size and the spread levels in our body [4]. Acute Lymphocytic Leukemia

(ALL) cancer does not form tumors, it affects of the bone marrow in our body by creating too many white blood cells. It begins to occupy the space inside of our bone marrow. As a result it affects our body organs (kidney, liver, spleen etc.) and tissues won't be able to get the oxygen required to function properly.

"Acute" means that the leukemia can progress quickly, and if not treated, would probably be fatal within a few months. "Lymphocytic" means it develops from early forms of lymphocytes, a type of white blood cell [5]. In many countries, the diagnosis of leukemia needs different levels of diagnostic methods and equipment, performed by using bone marrow samples through an invasive method. The procedure for diagnosis of leukemia is a time consuming and also not affordable overhead. Very skilled knowledgeable experts needed to classify normal and cancer cell from a slide under the microscope. It can become error prone.

Therefore there is a necessity to develop an automated computer aided diagnostic method for the accurate detection. Deep learning is a method based on Artificial Neural Networks. Deep learning is known to give better functioning than conventional Machine learning algorithms in bio medical Image classification. Deep learning models requires large amount of data to train the model for classification. It is often not possible to get huge amount of data in medical domain, Transfer learning is the best solution to this problem [6].

For this study, the model was built by having a publicly available ALL data set, contains 3256 peripheral blood smear (PBS) images from 89 suspected ALL patients, including 64 patients with the diagnosis of ALL subtypes and 25 healthy patients with a benign diagnosis (hematogone). Hematogone (Immature B-cell precursors) found in the bone marrow and in blood, don't need complicated treatments. It improves on its own. Sometimes these are mistaken as cancerous B cell for its similarity [7]. The Blood smear images for crow were taken to dragonize cancer cells in crow.[13].

Other than ALL diagnosis, its subtype detection will help the patients to choose the therapeutic and chemotherapy methods. The proposed computer aided diagnosis system (CAD) applies ensemble learning method using standard Convolutional Neural Network architecture like DenseNet-169, Xception and Inception V3, where decision scores from different base classifiers are combined to predict the final class label for an input image. We map the decision score into two non-linear function namely tanh function and decaying function to define the ranks to the predicted class probabilities. The products of the ranks from each classifier are added to find the final rank.

2. Review of Literature

Here are the relevant works done to detect and classify Leukemia using blood cell images. Leukemia is a dangerous cancer of the blood. It has to detect earlier. The study discussed on a deep Neural Network for ALL segmentation and classification using the dataset of SN-AM and ALL-IDB. Segmentation was done using a UNet with InceptionV2 model. Preprocessing were done to reduce overfitting. The validation accuracy of ResNet-50, VGG-19 and improved CNN (i-Net) are 92.2%, 92.3% and 99.18% [5].

The proposed model helps to detect Acute lymphoblastic leukemia and define its subtypes from hematogone cases. It implements color-thresholding-based segmentation and ten different CNN architecture used for feature extraction. The better accuracy, sensitivity and specificity was obtained is 99.85%, 99.52% and 99.89% using DenseNet201. The proposed dataset is taken from kaggle [7].

The proposed Methodology implements apache spark BigDL library using CNN architecture GoogleNet deep transfer learning to detect four types of Leukemia from the microscopic images of human blood cell. The dataset consists of a total 1200 images of 5 classes. It gives 97.33% accuracy in training and 94.78% in validation. The BigDL model performed well with more effective and accurate than the keras model [2].

The paper is defining a technique for automatic detection and classification of acute Myeloid Leukemia (AML) in blood cell. The K means algorithms are applied for segmentation and for classification used KNN and SVM algorithm. They used Blood microscopic images for testing and classifier performance was analyzed [3].

This paper exhibits the proposed model trained on preprocess image and best features are extracted. Train the model with Optimized Dense Convolutional neural network framework to predict the type of cancer present in the given image. The accuracy was evaluated to 97.2% [1].

The paper implements ensemble-based classification model using three standard Convolutional Neural Network architectures to classify cytology Images. The model generates ranks of the classifier using two non-linear functions. The model was evaluated using dataset SIPaKmeD Pap Smear and Mendeley Liquid Based Cytology (LBC) dataset using cross validation scheme. For the Pap smear dataset, after using k-fold cross validation, 95.43% of classification accuracy was achieved. And also 99.23% of accuracy was attained on Mendeley LBC dataset. [6] In the study [12] CNN with Grid Search optimization used to detected the brain tumor and the study achieved accuracy of 90.25%.

The paper proposed a ML approach to predict the diagnosis of acute leukaemia using PB image. The dataset contains a set of 442 smears from 206 patients. Mathematical morphology and colour clustering were used to segment cell images. The feature selection was achieved with linear discriminant analysis. The classification accuracy for the six groups of cell types and individual smear was 85.8% and 94% respectively.[14] The study explains the clustering portions to detect ROI in an effective manner.[15] The study detects the intima media thickness of the carotid artery which used to detect the thickness of tumor.

3. Proposed Methodology

Publicly available dataset of ALL diagnosis PBSimages and its subtype classifications namely early ALL, Pre B ALL and Pro B ALL classes were taken for implementation. The data set consist of 3256 PBS images of 89 patients suspected of ALL was taken forthis work. Fuzzy based Ensemble model was proposedfor the diagnosis and classification of PBS images of patients suspected of ALL.

Table .1.Training and testing dataset used for this study

Type	Subtype	SamplesCount	PatientsCount	Size ofImage
Benign	Hematogones	504	25	1024 × 768
Malignant	Early pre-B ALL	985	20	
	Pre-B ALL	963	21	
	Pro-B ALL	804	23	
		3256	89	

Images in the dataset were divided into two classes as benign and malignant are listed in Table I. Benign class images consist of hematogones whichbe similar to ALL cases highly. Chemotherapy is required for this hematopoietic precursor cell as it is benign. And this type of cancers is usually recovered by its own. The latter types of cancers are theALL group with three subtypes of malignant lymphoblasts: early pre B, pre B, and proB ALL.

3.1 Implementation

This section gives an overview of the base learners that is used in this work.To this basic models, some customizations are applied and additionally the confidence scores of the methods are evaluated using the proposed fuzzy rank based fusion. In this ensemble method, the confidencescores generated from each base learners are utilized. The signified mapped values are one that abidance or closeness to 1 and the next one implies the deviation from 1. In this study, three base learners used and evaluated the customized CNN models on bio-medical image dataset.

Next, two different functions are used to calculate the non-linear fuzzy ranks. Concavities of these functions are different in nature. By adding these two ranks, by this functions, used to calculate a fused score. This fused score is used for quantify the classification accuracy. If the deviation is lesser thenit shows that better confidence towards a particular class. The class that have least fused score value is considered as the predicted class label for the given input image.

Inception v3. This architecture was developedby Szegedy et al.[8]which had many prominent features and have parallel convolutions involved in the structure. Xception. Chollet et al [9] developed this architecture which was inspired from the Inception v3architecture. As similar to Inception V3 model, thisXception model

also contains the same number of model parameters. The Xception architecture used the model parameters more efficiently than Inception v3. Noticeable difference between these two models were, in the Xception model pointwise convolutions and depthwise separable convolutions lie at the two extremes of a discrete spectrum, where as, in the inception v3 these convolutions exists in the middle. Xception model provides a boost in the classification performance comparative to Inception model. The computation cost of these models are same.

DenseNet-169. Huang et al [10] proposed this architecture which is computationally efficient than the other models. In this model, each layer is a concatenation of the feature maps in the present layer and all in the layers preceding to it. This DenseNet model is very much compact as it accommodates less number of channels in the convolutional layers, therefore the number of trainable parameters are decreased. And also the feature representation is enhanced by combining the feature maps from previous layers.

Table .2. Hyperparameters and its value used in the study

Hyperparameter	Value
Optimizer	RMSProp
Loss function	Categorical cross entropy
Learning rate	2.00E-05
Batch Size	32
Dropout rate	20%
Number of epochs	20

As the next level, some customized layers were added to the pre-trained models for better results and accuracy. A fully connected layer of 1028, 1024 and 256 nodes were added in DenseNet-169, Inception v3, and Xception models respectively. Rectified Linear Unit (ReLU) activation function is used for gradient problem and to make the model to learn faster. To handle the overfitting problem, Dropout layer of 20% was included.

Accuracy of the model may be effected when calculate the confidence scores using the high number of hidden units which were mentioned for the three base learners. The number of hidden nodes included in this architecture are 128, 64, and 32 nodes for DenseNet-169, Inception v3 and Xception respectively, in order to boost the performance. Finally, implemented class number specific output units. The hyperparameters used for training the CNN models were set based on experimental work mentioned by Manna et al.[6] and shown in Table II. As the model weights are optimized for image classification, so 20 epochs are used for fine-tuning the dataset. Also 99.23% of accuracy was reached for 20 epochs itself. Proposed ensemble method architecture is shown in Fig 1.

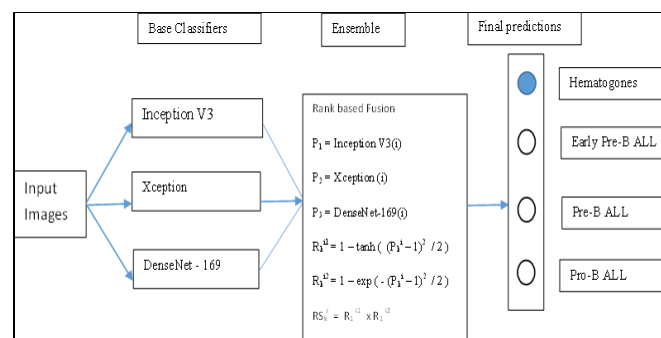


Fig 1. Proposed fuzzy rank-based ensemble of CNN models architecture used for classification of ALL blood smear images

3.2 Proposed Ensemble Method

In recent years, ensemble learning becomes popular because it is an alternative method to evaluate decision scores from multiple classifiers. In an ensemble method, the decision scores generated by individual classifiers were combined to predict the final class label for an input image.

The aim of an ensemble method was to capture the most prominent features from all the essential classifier models and combine them to predict the output more accurately than the independent classifiers. By adding the bias to the base learners, the difference in the prediction errors occurred in the base classifiers were reduced in the ensemble model.

The proposed method was developed by combining the strategies of three base CNN classifiers, such as DenseNet – 169, Inception V3 and Xception to create an ensemble model and to obtain the decision scores. In the current work, fuzzy ranking-based approach were used. The probability scores are generated by using exponentially decaying function and the tanh function. These two functions were used to assign the ranks to the class probabilities evaluated by the base classifiers.

Using the two non-linear functions, the ranks were calculated and multiplied. The above multiplication process is repeated for the three base learners. Rank products from each classifier are added to get the fused score. Among the evaluated fused score, the minimum fused score is considered as the predicated class label for the given input data image. The two non-linear functions are of different concavities and the generated results are complementary to each other. Fusion requires merging the multiple ranks related with an individual base learners and a new rank was determined which was used to establish the final predicated class label.

The main objective of using two non-linear functions was to generate ranks. This rank score exhibits the difference between expected final result and actual result. The lower value of the product is considered as a lesser deviation and it was a best result. Therefore, the class with lowest value of the sum of products of ranks is finalized as the predicted class label for the given input image data.

The exponentially decaying function and the tanh function had opposite concavity in the range [0, 1]. Higher confidence score results in a larger value of rank generated by one of the function and a smaller value in the other function were multiplied. The minimized product value is considered for the further process. The sum of products gives a lower value, when the predicted rank score is high. The mathematical explanation of this process is explained in the next section.

3.3 Mathematical Formula

The mathematical formulation used in the proposed system to generate the rank score is explained in this section [6]. Let the base learner gives the confidence scores for X number of classes are $(P_1^i, P_2^i, P_3^i, \dots, P_X^i)$, here $i = 1, 2, 3$. Initially, aggregate each base learners confidence scores. The probabilities are represented as $(P_1^i, P_2^i, P_3^i, \dots, P_X^i)$ in Eq. (1).

$$\sum_{k=1}^C P_k^i = 1, \forall i = 1, 2, 3. \quad (1)$$

The fuzzy ranks $(R_1^{i_1}, R_2^{i_1}, R_3^{i_1}, \dots, R_X^{i_1})$ and $(R_1^{i_2}, R_2^{i_2}, R_3^{i_2}, \dots, R_X^{i_2})$ were generated by using two non-linear functions.. The fuzzy ranks are calculated by Eqs. (2) and (3).

$$R_k^{i_1} = 1 - \tanh\left(\frac{(P_k^i - 1)^2}{2}\right) \quad (2)$$

$$R_k^{i_2} = 1 - \exp\left(\frac{(P_k^i - 1)^2}{2}\right) \quad (3)$$

The calculated non-linear rankings for the functions will be [0, 1] as $P_k^i \in [0, 1]$ [6].

Image classification is done by Eq.(2). The amount of reward increases, when x approaches 1, i.e. the value of Eq. (2) increases. Contrarily for Eq. (3), while calculate deviation from 1, i.e., the deviation will be more, when x approaches 0. The fused rank scores were represented by $(RS_1^i, RS_2^i, RS_3^i, \dots, RS_X^i)$, where RS_k^i is mentioned in Eq. (4).

$$RS_k^i = R_1^{i_1} \times R_1^{i_2} \quad (4)$$

The exponentially decaying function, $\exp\left(-\frac{(x-1)^2}{2}\right)$ is concave downward in its domain of definition $[0, 1]$. Because of the negative of this function the curve will be concave upward. The output rank score will shift towards 1, due to its negative gradient in $[0, 1]$. [6]

The tanh function, $\tanh\left(\frac{(x-1)^2}{2}\right)$ is concave upward in its domain of definition $[0, 1]$. The curve is concave downwards as the negative of this function is concern. The output rank score will shift towards 0, due to its positive gradient in $[0, 1]$. [6]

The rank score is calculated by the product of deviation for a specific confidence score derived from a base learner and reward. A Lesser rank score represents lesser deviation calculated from the confidence score. At last, the Fused scores are calculated based on the rank scores.

This RS_k^i is defined by the product of fuzzy ranks, which is calculated by the non-linear functions of exp and tanh. It indicates how the confidence level is towards a particular class. The fused score tuple is (FS1, FS2, FS3, ..., FSX), where FS_k is given by Eq. (5).

$$FS_k = \sum_{i=1}^I RS_k^i, \forall k = 1, 2, \dots, X \quad (5)$$

The Final score relevant to each class is considered as the fused score. Next, the least fused score class were found and considered it as the final examined by Eq. (6).

$$class(I) = \min_{\forall k} FS_k \quad (6)$$

4. Results & Discussions

The results obtained from the proposed ensemble method implemented on ALL blood smear image dataset is discussed in this section. In this study, the performance of the proposed ensemble model was compared with three existing methods (Densenet, Xception and Inception).

Dataset : To implement and evaluate the proposed fuzzy based ensemble model, in this research work images are taken from the publicly available ALL-IDB2 repository given in Table I. In Fig 2. Sample input images of all the four classes are displayed.

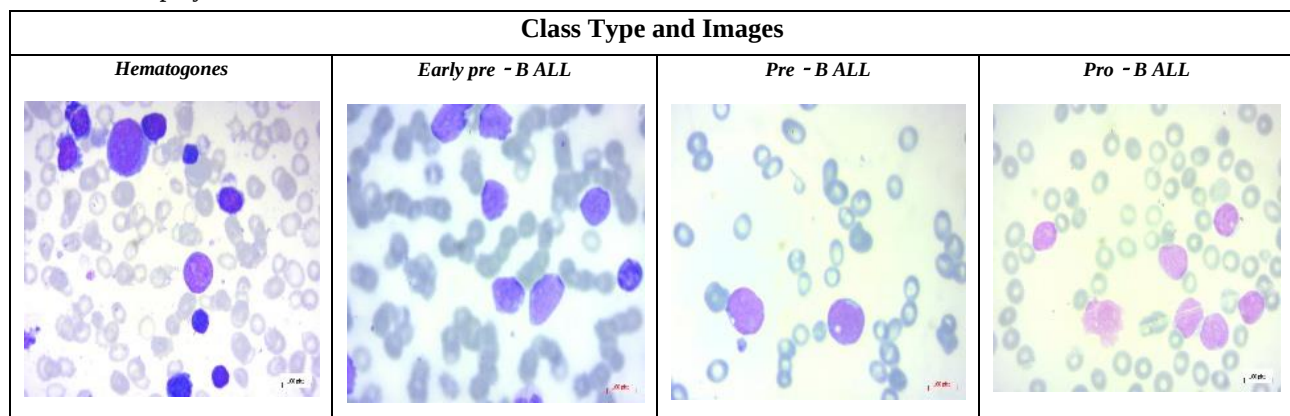


Fig.2. Input samples of Non-Segmented Images

The dataset is divided into two classes such as benign and malignant. The hematogones (benign) class images highly resembled ALL cases; whereas the latter type cancer cells was the ALL group with three subtypes of malignant lymphoblasts namely early pre-B, pre-B, and pro-B ALL. These images were taken from a Zeiss camera in a microscope with a $\times 100$ magnification and saved as JPG files.

All models was implemented in Python by using the Keras library, which is a highlevel library for the TensorFlow Machine Learning framework, and was trained on a system with 11th Gen Intel(R) Core(TM) i5-1135G7 @ 2.40GHz 2.42 GHz, 8 GB RAM.

Evaluation metrics: Four popular evaluations namely Accuracy, Precision, Recall and F1-Score were used to validate the performance of the proposed model.

The following parameters are required to calculate these evaluation indicators. True positive (TP): Number

of correct predictions of positive cases by the method; True negative (TN): Number of correct predictions of negative cases; False positive (FP): Number of incorrect predictions of positive cases and False negative (FN): Number of incorrect predictions of negative cases by the method.

However, accuracy is not always adequate to evaluate the performance of the model. Hence, there is a requirement to evaluate other performance metrics [11] to test the model. These measures are explained in below:

Accuracy: It is a parameter that evaluates the capability of a method by measuring a ratio of correctly predicted cases out of total number of cases. Mathematically, it is expressed as follows:

$$Accuracy = \frac{TN+TP}{TN+TP+FN+FP} \quad (7)$$

Precision: It is the ratio of correctly predicted positive cases to the total predicted positive cases. High precision relates to the low false positive rate. It is expressed as follows:

$$Precision = \frac{TP}{TP+FP} \quad (8)$$

Recall: It is the ratio of correctly predicted positive observations to the all observations in actual class.

$$Recall \text{ or } Sensitivity = \frac{TP}{TP+FN} \quad (9)$$

F1 score: Is one of the common measures to rate how successful a classifier is. It is the harmonic mean of two other metrics, namely: precision and recall. In a binary classification problem. F1 score is more sensitive to data distribution, it is a suitable measure for classification problems on imbalanced data sets.

$$F1 \text{ Score} = 2 \times \frac{Precision \times Recall}{Precision+Recall} \quad (10)$$

Table .3. Evaluation Metrics For Proposed Models UsingFive Fold Cross-Validation On The Test Data

Methods	Accuracy (%)	Class	Precision (%)	Recall (%)	F1-Score (%)
DenseNet - 169	92.78	Benign	86.60	84.00	85.28
		Early	87.50	92.39	89.88
		Pre	98.39	94.82	96.57
		Pro	96.88	96.27	96.57
Inception v3	98.46	Benign	95.92	94.00	94.95
		Early	97.00	98.48	97.73
		Pre	100	99.48	99.74
		Pro	100	100	100
Xception	96.62	Benign	94.85	92.00	930
		Early	94.00	95.43	941
		Pre	97.93	97.93	973
		Pro	99.38	99.38	99.38
Proposed Ensemble	99.23	Benign	97.89	93.00	95.38
		Early	95.12	98.98	97.01
		Pre	100	98.45	99.22
		Pro	100	100	100

Discussion. Table III shows the results obtained after 5-fold corss validation applied on the proposed ensemble CNN models. From the table III, we can conclude that the proposed CNN model accomplish high classification accuracy. It is much faster and better than the manual screening procedure, confirming the reliability of the automated approach.

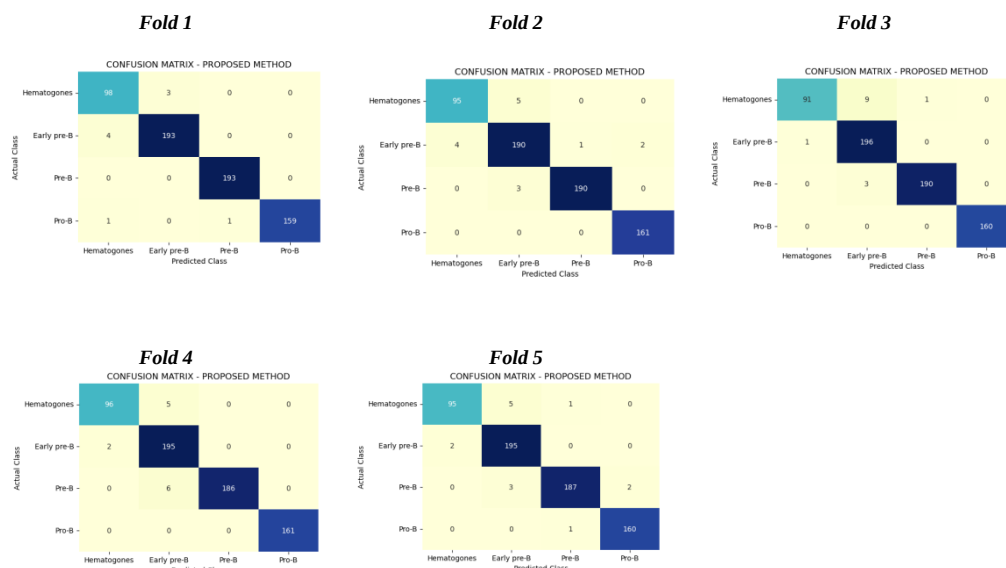


Fig.3. Confusion matrix of proposed method for five folds

The confusion matrices derived by the proposed framework on 5fold cross-validation on the ALL datasets used in this study are shown in Fig.3. To confirm the choice of the base learners, the execution was done using three base learners: Xception, Inception v3 and DenseNet-169. The results obtained are reported in Table III. The proposed combination of Inception v3, Xception and DenseNet-169 obtains the best result on the taken datasets and is significantly better than the individual performance obtained by the Inception v3, Xception and DenseNet-169. The performance of an ensemble was determined by the ability of the choosen base learners which generates corresponding information, than the individual performance of the base learners. The three classifiers used in this research are better suited for the ensemble than the individual performance of each classifiers. The accuracy result is shown in the Table III.

The proposed fuzzy based ensemble model can be used as a plug-and-play model to test new bio-medical images, which can be passed through the model to generate the predictions. The more accurate results generated by this proposed model will be helpful for the expert clinicians to make a quicker and appropriate decision. Hence, the proposed method is reliable for use in the bio-medical field.

Comparison of base learners. Table III shows the classification results obtained by the three classifiers and their ensemble using the proposed ensemble framework. For the taken ALL image dataset, the Inception v3 model performs better than the Xception and DenseNet-169 models. The accuracy generated by the Inception v3 was 98.46% which is highest and performs better than the other two in the dataset. The proposed fuzzy rank based ensemble method performs significantly better than all the three base classifiers. Clearly indicated that the classification performance of different CNN models was dependent upon the dataset which was taken for examination. Inception v3 accomplishes improved accuracy for single-cell images dataset, while Xception was best suited for the whole slide images dataset. The proposed ensemble method performs robustly based on the confidence score from all its base learners. Thus the ensemble model can be generalized better than a single CNN classifier with accuracy of 99.23%.

5. Conclusion and Future Work

Unlike other chronic diseases, Acute lymphoblastic leukaemia(ALL) has examined as a treatable blood disorder. With precise treatment and early diagnosis, patients survival was possible. Early diagnosis of this ALL subtypes leads to effective treatment of the disease. In this work, a deep neural network was used for classification of ALL using three base classifiers namely, DenseNet – 169, Inception V3 and Xception.

In this paper, a fuzzy rank based ensemble model was developed that classifies PBS images for ALL diagnosis using an ensemble of three standard CNN based classifiers. The proposed ensemble model generates ranks of the classifiers using two non-linear functions which support to calculate the confidence in predictions of the base learners. The proposed framework, when evaluating benchmark datasets for ALL blood smear

image classification, produces good results in terms of accuracy and sensitivity to the disease, thus quantifying the effectiveness of the ensemble model.

The fast detection tool developed can function like a plug-and-play model that involves little interference of the medical expertise to diagnosis the ALL subtypes, and hence suitable for incorporation in the bio-medical field. As a future work, more CNN classifiers can be included to examine the performance of all classifiers.

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