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RESEARCH ARTICLE

Automated Classification of Cells from Bone Marrow Cytology with Deep Learning

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ABSTRACT:
The manual classification of bone marrow (BM) cell morphology, a pivotal aspect of haematological diagnosis, is performed thousands of times daily due to the lack of comprehensive data sets and trained models. This process is often time-consuming and susceptible to human errors. The effectiveness of deep learning algorithms in biomedical applications is proven. The impact is undeniable and unquestionable as these techniques use extensive datasets encompassing diverse disease classes, meticulously annotated by medical professionals. This also eliminates any scope for error, shortens the diagnosis time and enhances the accuracy. Over time, deep learning techniques have improved further with new advancements. This research aims to evaluate the performance of several pretrained Convolutional Neural Network models to automate the classification of BM cells. More specifically, the models are compared by their ability to assist medical professionals in identifying the presence of 'hairy cells' in the bone marrow smear of a subject. The presence of hairy cells in the blood is indicative of the possibility of a person having Hairy Cell Leukemia. A custom CNN architecture, ConvNeXtSmall, ConvNeXtTiny, DenseNet121, EfficientNetB5, ResNet50, VGG16 and Xception were compared. ConvNeXtSmall has the highest validation accuracy of 0.85. DenseNet121 and ConvNeXtSmall have the highest F1 score of 0.81 while classifying Hairy Cells.

KEYWORDS: Bone marrow cell morphology, Deep Learning, Convolutional Neural Network (CNN), Hairy Cell Leukemia, Classification.

INTRODUCTION:
This research addresses the challenges of manual bone marrow cell classification in hematological disease diagnosis. It emphasizes the limitations of traditional methods and the need for precise BM cell classification, particularly for diseases like Hairy Cell Leukemia.

The evaluation of bone marrow cell morphologies is critical in the diagnosis of hematopoietic system disorders.[1,2] However, automating this process has proven to be complex and remains the responsibility of medical professionals, who conduct microscopic examinations and morphological classifications of BM cells. The process of physically evaluating specimens can be particularly challenging and laborious, especially when dealing with obscure BM smears.[3,4] Errors in manual cytological evaluations can occur due to their reliance on the knowledge and expertise of medical examiners, increasing the risk of inaccurate diagnoses.[5] Moreover, some pathology labs may lack personnel with the expertise required for this analysis.[6]

Current literature indicates that few automated techniques are available for identifying leukemia by analyzing and classifying white blood cells (WBCs) from blood smear images. Moreover, these techniques are only partially automated.[7] Previous research in automated cytomorphologic classification has mainly concentrated on analyzing normal cell types or

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peripheral blood smears. This restricts their use to the classification of bone marrow leukocytes for diagnosing hematological malignancies.[8-14]

AI, inspired by human brain operations, seeks to develop intelligent software systems for problem solving and decision making.[15] Alan Turing, a British mathematician, pioneered contemporary computer science and artificial intelligence by establishing the notion of intelligent behavior in computers through the 'Turing test'.[16] AI is utilized for a variety of medical purposes, including clinical diagnosis, image analysis, data interpretation, and waveform analysis.[17] AI's capacity to convert pictures into sequences has been used in cancer diagnosis, assisting with the interpretation of imaging studies and pathology slides.[18] Deep-learning techniques for BM cell classification have faced challenges, including limited sample numbers, few disease categories, and the private nature of related data.[19-22] CNN-based image classification is dependent on the presence of a significant volume of reliable, meticulously annotated image data, which is difficult to obtain from medical professionals.[23,24]

This study highlights the potential of CNNs to automate BM cell classification but notes the data and annotation challenges. It also discusses the significance of recent expert-annotated datasets and custom as well as pretrained CNN models. The specific focus on classifying different types of lymphocytes contributes to the improved diagnosis of HCL, a rare but significant hematological malignancy.

MATERIALS AND METHODS:

Dataset:

The dataset furnished by Matek et al. is an Expert-Annotated Dataset of Bone Marrow Cytology in Hematologic Malignancies.[25,26] It contains over 170,000 cells from 945 patients with various hematological disorders. We obtained the dataset from The Cancer Imaging Archive (TCIA), a publicly available resource for cancer research. The photographs of bone marrow cells were taken using a brightfield microscope with a magnification of 40x and oil immersion. The cells were stained with Pappenheim stain. The dataset was created in collaboration with the Munich Leukemia Laboratory (MLL), the Fraunhofer IIS, and the Helmholtz Munich.[25-27] For our study we have considered seven main classes of lymphocytes required for detection of Hairy Cell Leukemia. They are hairy cells (HAC), basophils (BAS), monocytes (MON), lymphocytes (LYT), eosinophils (EOS), segmented neutrophils (NGS) and band neutrophils (NGB). We have used 1000 images each for monocytes (MON), lymphocytes (LYT), eosinophils (EOS), segmented neutrophils (NGS) and band neutrophils (NGB). For hairy cells (HAC) and basophils (BAS) we have considered all available images in the dataset, i.e., 409 and 441 images respectively.

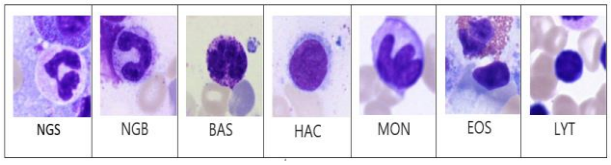

Figure 1: Bone marrow cell images from each of the 7 classes used

Image Preprocessing:

OpenCV library was used for image preprocessing. The images underwent the following pre-processing steps:

1. Image resizing using cv2.resize.
2. Image denoising using fast Nl Means Denoising Colored, a function used to remove noise from RGB images on the basis of non-local means (NLM) denoising.
3. Image sharpening using filter2D with a NumPy array of ([[-1,-1,-1], [-1,9,-1], [-1,-1,-1]]).

Data Augmentation:

Image augmentation is a commonly employed technique in machine learning and computer vision to enhance the variety of training data by implementing diverse transformations on pre-existing images. It's particularly useful in scenarios where the size of the available training dataset is limited.

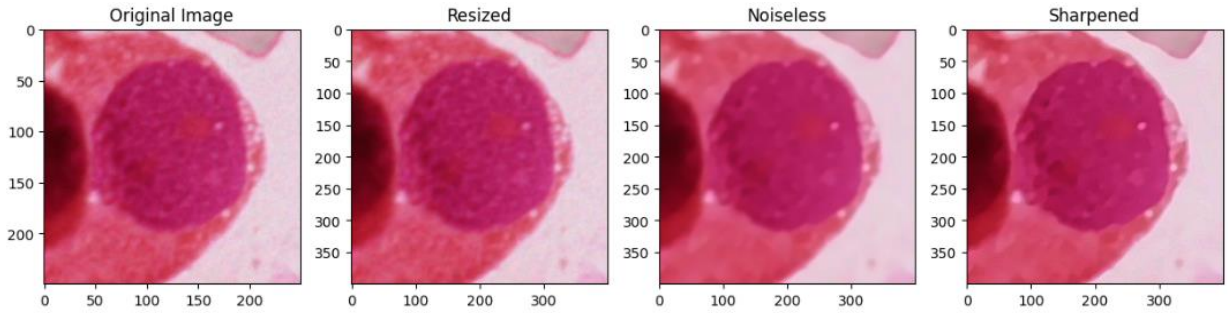

Figure 2: Bone marrow cell image post each step of preprocessing

Class imbalance is a prevalent challenge in machine learning, especially in classification tasks related to medical images, where certain classes exhibit significantly fewer instances than others. This imbalance may cause the model to forecast the majority class more often than the minority class, which might result in biased models and subpar performance.

Since our dataset has class imbalance with respect to the leukemic cells i.e., hairy cells, we adopted image augmentation in our project to prevent the minority class from being overshadowed.

We used the Keras library to augment our dataset. We randomly flipped, rotated, zoomed and changed the contrast and brightness of the dataset images.

Convolutional Neural Network:

Convolutional neural networks (CNNs) are a popular choice for image processing tasks because they excel at extracting features while maintaining the spatial relationships between pixels.[28] Typically, CNNs consist of multiple layers, with at least one convolution layer. Originally, CNNs employed a single convolution layer, but over time, researchers have refined their approach, focusing on the architecture of these layers.[29]

In a CNN classifier, each layer contains kernels with different weights. These kernels are responsible for extracting features from the input data, and the resulting feature maps are then passed to the next layer. This process is facilitated by backpropagation, where the network learns to adjust the weights based on the error between predicted and actual outputs.[30]

Additionally, CNNs can benefit from transfer learning, a technique where pre-trained models are adapted to new tasks.[31] In transfer learning, adjustments are typically made only to the last layer of the CNN, while the rest of the layers remain unchanged. This allows for efficient utilization of pre-existing knowledge while fine-tuning the model for specific tasks.

Creation of custom CNN Sequential model:

A custom CNN sequential model was created and trained, with the first layer being a rescaling layer that adjusts the pixel values to be in the range of 0 to 1. The following layer has a ReLU activation function and 16 filters in a 2D convolutional architecture. The subsequent layer is a 2D max-pooling layer. The next layer is a 2D convolutional layer that has 32 filters. Similarly, a 2D max-pooling layer follows with a 64-filters 2D convolutional layer. Again, this is followed by a 2D max-pooling layer. The dropout layer comes next, with a dropout rate of 0.5. The next layer is a flatten layer which converts a multi-dimensional input into a 1-dimensional vector as dense layers require 1-dimensional array as input for processing. Next, we have a dense layer with 128 neurons activated by ReLU function. Finally, there is a 7-neuron output layer with the softmax activation function.

Use of pretrained CNN architectures and transfer learning:

a) ConvNeXt:

In the past, Vision Transformers (ViTs) excelled in image classification but struggled with tasks like object detection and segmentation. Hierarchical Transformers, like Swin Transformers, blended convolutional neural network (ConvNet) concepts back into Transformers to improve their flexibility for various vision applications. The research by Liu et al.[32] investigated pure ConvNets for vision tasks and introduced ConvNeXt models, built entirely from standard ConvNet components. ConvNeXt models achieved impressive accuracy and scalability, reaching a top-1 accuracy of 87.8% on ImageNet and thus, surpassing Swin Transformers in ADE20K segmentation and COCO detection. Remarkably, these achievements were attained with a simple and efficient design.

We employed transfer learning using two ConvNeXt models: ConvNeXtSmall and ConvNeXtTiny. In both cases, we took the base model and removed its final layer. Then, we added a batch normalization layer, a dense layer with 256 neurons and ReLU activation, and a dropout layer. The final output layer has 7 neurons with a softmax activation function.

b) Dense Net:

Dense Convolutional Network, or DenseNet, deviates from traditional convolutional network structures by establishing a highly interconnected architecture featuring L(L+1)/2 direct connections among its L layers, in contrast to the one-to-one connections typically found in conventional networks.[33] In DenseNet, each layer not only receives inputs from all previous layers but also shares its outputs with all subsequent layers, offering a range of substantial advantages. These benefits encompass mitigating the vanishing-gradient challenge, improving the propagation of features throughout the network, encouraging the reuse of features, and notably reducing the overall parameter count. DenseNet thus introduces a potent and innovative approach in the realm of neural networks.

In our model, we have done transfer learning using DenseNet121. The first layer was a rescaling layer which normalized the pixel values between 0 and 1. DenseNet121 was our base model. We removed the top layer of the base model. Next, we added a batch normalization layer, a dense layer of 256 neurons having

ReLU activation function and a dropout layer. Our output layer has 7 neurons and softmax activation function.

c) EfficientNet:

The research by Mingxing Tan and Quoc V. Le[34] delves into the systematic process of scaling Convolutional Neural Networks (ConvNets) and underscores the importance of achieving a delicate equilibrium among network depth, width, and resolution to enhance performance. The authors introduce an innovative scaling technique that uniformly adjusts these dimensions through a compound coefficient, demonstrating its effectiveness in upscaling MobileNets and Res Net models. Additionally, they employ neural architecture exploration to create a novel baseline network, subsequently expanding it to produce a family of models, denoted as EfficientNets. These EfficientNets surpass previous ConvNets in both accuracy and efficiency, representing a substantial advancement in neural network design and scalability.

In our model, we have done transfer learning using EfficientNetB5. The first layer was a rescaling layer which normalized the pixel values between 0 and 1. EfficientNetB5 was our base model. We removed the top layer of the base model. Next, we added a batch normalization layer, a 256-neuron dense layer having ReLU activation function and a dropout layer. Our output layer has 7 neurons and softmax activation function.

d) ResNet:

The study by He et al.[35] addresses the complexity of training deeper neural networks by introducing a residual learning framework. The approach involves reinterpreting network layers as residual functions explicitly referring to the layer inputs, as opposed to learning functions devoid of such references. It is substantiated through extensive empirical evidence that these residual networks are more amenable to optimization and can attain higher accuracy when significantly increasing their depth, effectively mitigating the challenges associated with training deep neural networks.

In our model, we have done transfer learning using ResNet50. The first layer was a rescaling layer which normalized the pixel values between 0 and 1. ResNet50 was our base model. We removed the top layer of the base model. Next, we added a batch normalization layer, a dense layer of 256 neurons having ReLU activation function and a dropout layer. Our output layer has 7 neurons and softmax activation function.

e) VGG:

The VGG16 CNN architecture is well-known for its use in computer vision applications.[36] With 13 convolutional layers, 5 max pooling layers, and 3 fully connected layers, it has 16 weighted layers. VGG16 processes RGB channels of size 224x224x3. Its architecture is distinct from other CNNs since it employs 3x3 convolution filters with equal padding and unit stride. Furthermore, after every two convolutional layers, a 2x2 max pooling layer with 2 units stride is used. The first two convolutional layers each use 64 filters, followed by 128 filters in the next two, 256 filters in the next two, and 512 filters in the last three. 3 fully connected layers stack after the convolutional layers. The first two have 4096 channels each, which corresponds to the number of classes in the ImageNet dataset. There are 1000 channels in the third layer, and a probability distribution across these 1000 classes is output by the softmax layer, which is the final layer.

We used VGG16 to integrate transfer learning in our model. The first step involved rescaling the pixel values between 0 and 1 using a dedicated layer. VGG16 acted as our base model, and we removed its final layer. We then added a batch normalization layer, a dense layer with 256 ReLU-activated neurons, and a dropout layer. The final layer we added has 7 neurons activated by softmax function.

f) Xception:

Xception is a deep learning model that takes the principles of Inception to an extreme.[37] Xception is a deep learning model that extends the concepts of Inception. While Inception utilizes 1x1 convolutions to reduce the input dimensionality before applying various filters, Xception takes a different approach. It applies filters directly to each depth map and then compresses the input space using 1x1 convolutions across the depth. This methodology closely resembles depthwise separable convolution, a technique present in neural network design since at least 2014. A notable distinction between Xception and Inception lies in the application of non-linearities after the first operation. While both operations are followed by ReLU non-linearities in Inception, Xception opts not to introduce any non-linearity.

In our model, we have done transfer learning using Xception. The first layer was a rescaling layer which normalized the pixel values between 0 and 1. Xception was our base model. The top layer of the base model was removed. Next, we added a batch normalization layer, a dense layer of 256 neurons having ReLU activation function and a dropout layer. Our output layer has 7 neurons and softmax activation function.

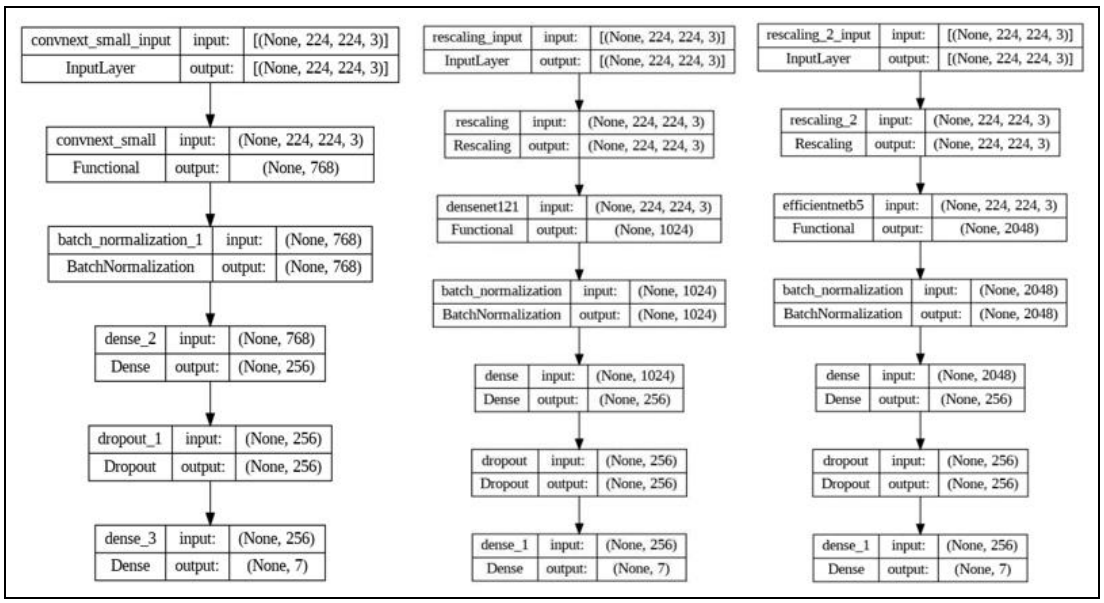

Figure 3: Block diagrams of transfer learning models using ConvNeXtSmall, DenseNet121 and EfficientNetB5 respectively

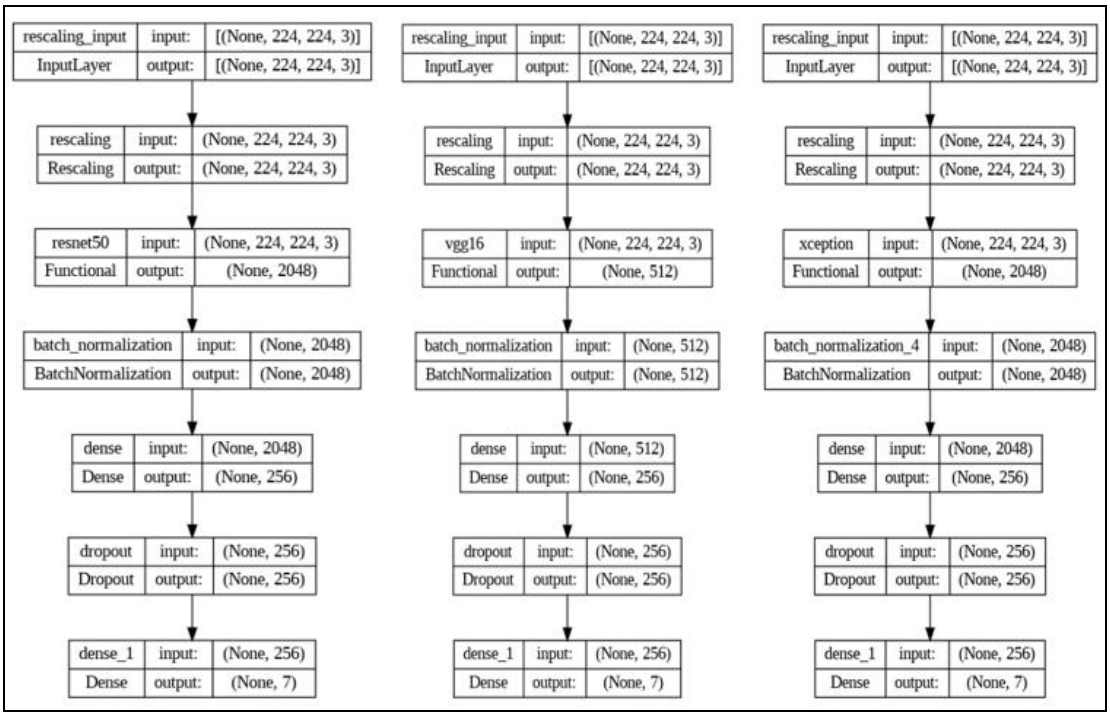

Figure 4: Block diagrams of transfer learning models using ResNet50, VGG16 and Xception respectively

RESULT:

We have used precision, recall, F1 score and accuracy to evaluate the performances of the various CNN models we have implemented for Bone Marrow cell classification with focus on Hairy Cell Leukemia.

On comparison of the training accuracy and validation accuracy of the various CNN models implemented, i.e. ConvNeXtSmall, DenseNet121, EfficientNetB5, ConvNeXtTiny, ResNet50, VGG16, Xception and Sequential model, ConvNeXtSmall has the highest validation accuracy of 0.85 (Table 1). On comparison of precision, recall and F1 score of HAC class for the above CNN models, DenseNet121 and ConvNeXtSmall have the highest F1 score of 0.81 while classifying Hairy Cells (Table 2). Thus, we can say that ConvNeXtSmall and DenseNet121 give the best results in classification of HAC which are useful indicators for detection of Hairy Cell Leukemia. Conv Next Small gives the best overall results with regards to classification of all the considered classes (Table 3).

Table 1: Comparison of Training Accuracy vs Validation Accuracy of all models implemented

Model	Training Accuracy	Validation Accuracy
Xception	0.99	0.79
ConvNeXtSmall	0.99	0.85
DenseNet121	0.90	0.82
EfficientNetB5	0.99	0.83
ConvNeXtTiny	0.99	0.81
ResNet50	0.99	0.76
VGG16	0.99	0.76
Sequential model	0.72	0.58

Table 2: Comparison of Precision, Recall and F1 score of HAC class of all models implemented

Model	Precision	Recall	F1- score
Xception	0.68	0.74	0.71
ConvNeXtSmall	0.86	0.76	0.81
DenseNet121	0.82	0.81	0.81
EfficientNetB5	0.81	0.76	0.78
ConvNeXtTiny	0.89	0.71	0.79
ResNet50	0.73	0.77	0.75
Model	**Precision**	**Recall**	**F1- score**
VGG16	0.77	0.73	0.75
Sequential model	0.6	0.56	0.58

Table 3: Comparison of Precision, Recall and F1 score of all classes of all models implemented

Cell Type	Evaluation Metric	Xception	Conv NeXt Small	Dense Net121	EfficientNetB5	ConvNeXtTiny	ResNet50	Vgg16	Sequential model
BAS	precision	0.81	0.87	0.88	0.84	0.75	0.78	0.7	0.44
	recall	0.57	0.69	0.75	0.7	0.69	0.56	0.5	0.16
	f1- score	0.67	0.77	0.81	0.76	0.72	0.66	0.58	0.24
EOS	precision	0.94	0.95	0.89	0.92	0.95	0.82	0.85	0.6
	recall	0.92	0.95	0.97	0.93	0.89	0.94	0.91	0.67
	f1- score	0.93	0.95	0.93	0.93	0.92	0.87	0.88	0.63
HAC	precision	0.68	0.86	0.82	0.81	0.89	0.73	0.77	0.6
	recall	0.74	0.76	0.81	0.76	0.71	0.77	0.73	0.56
	f1- score	0.71	0.81	0.81	0.78	0.79	0.75	0.75	0.58
LYT	precision	0.85	0.91	0.96	0.87	0.92	0.94	0.9	0.69
	recall	0.88	0.95	0.77	0.94	0.91	0.83	0.81	0.74
	f1- score	0.87	0.93	0.85	0.9	0.92	0.88	0.85	0.71
MON	precision	0.74	0.83	0.66	0.83	0.75	0.73	0.72	0.53
	recall	0.83	0.82	0.93	0.84	0.85	0.81	0.75	0.63
	f1- score	0.78	0.83	0.78	0.83	0.8	0.76	0.73	0.57
NGB	precision	0.73	0.76	0.75	0.76	0.67	0.57	0.61	0.51
	recall	0.65	0.78	0.76	0.73	0.77	0.86	0.76	0.41
	f1- score	0.69	0.77	0.75	0.75	0.71	0.69	0.67	0.45
NGS	precision	0.74	0.76	0.9	0.78	0.8	0.92	0.77	0.57
	recall	0.79	0.82	0.68	0.8	0.72	0.43	0.68	0.62
	f1- score	0.76	0.89	0.78	0.79	0.76	0.59	0.72	0.59

DISCUSSION:

Continuous refinement of the CNN model is essential to improve its accuracy and efficiency. In algorithmic prediction, we worry about overfitting and underfitting. Overfitting happens when a model looks really good, even if it's based on flawed data or methods. Underfitting is when a model doesn't catch the main trends in the data, so it doesn't predict well with new data. Both lead to wrong predictions.[38] The problem of overfitting and underfitting should be better tackled. Fine-tuning the architecture, optimizing hyperparameters, and enhancing the training process can lead to better performance. The dataset and model can be scaled to accept input images with multiple cells, and then we can automate the detection and classification of each cell type in the image. Combining image data with patient clinical information, such as medical histories and test results, can enhance the diagnostic capabilities of the system and provide a more holistic approach to disease detection. Developing user-friendly interfaces for medical professionals to interact with the automated system can make it more accessible and practical for clinical use. These tools could include visualization of BM cell classifications and explanations for the model's decisions. We can also investigate the potential for real-time diagnosis by reducing the time required for image processing and classification, which can be a valuable addition to the project.

CONCLUSION:

In this research we explored the use of various CNN models to automate the classification of cells from bone marrow cytology. We created a custom sequential CNN model and also used transfer learning with ConvNeXtSmall, DenseNet121, Efficient NetB5, ConvNeXtTiny, ResNet50, VGG16 and Xception models. The DenseNet121 and ConvNextSmall models gave the best results in classification of HAC cells which are useful indicators for detection of Hairy Cell Leukemia. ConvNeXtSmall gave the best overall results for classification of all the considered classes.

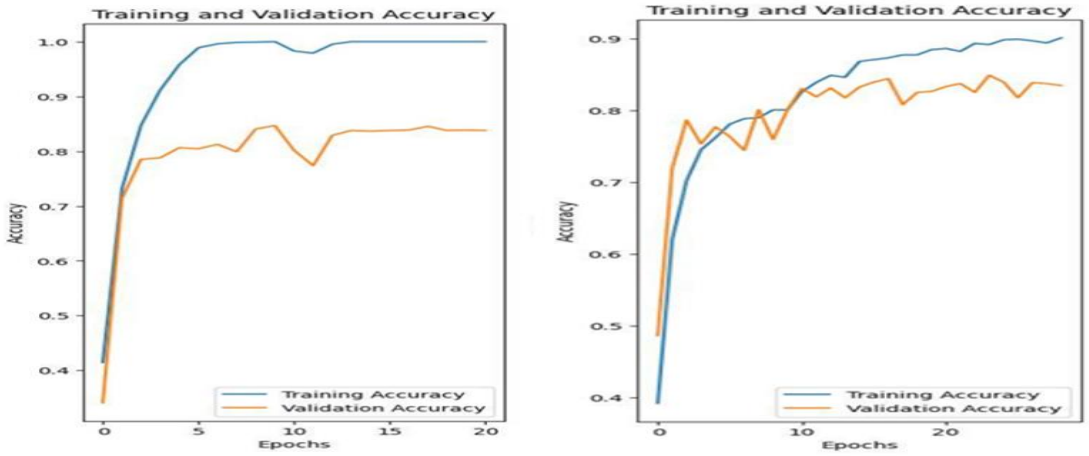

Figure 5: Training Accuracy Vs Validation Accuracy of ConvNeXtSmall and DenseNet121 respectively

Our findings underscore the transformative impact of deep learning on haematological diagnostics, offering substantial improvements in accuracy and efficiency over traditional manual methods. The integration of these models into clinical practice could significantly reduce diagnostic time and error rates, thereby enhancing patient prognosis.

CONFLICT OF INTEREST:

The authors state that there are no conflicts of interest in this work.

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