WHITE BLOOD CELL RECOGNITION FOR BIOMARKER MODEL USING IMPROVED CONVOLUTIONAL NEURAL NETWORK (CNN)

SYADIA NABILAH BINTI MOHD SAFUAN

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ABSTRACT

White Blood Cell (WBC) is one of important elements in protecting human's immunity system. WBC composed of two main elements namely cytoplasm and nucleus, with almost the same in color contrast, and hence make it hard to be detected and analyzed. Manual WBC analysis is less efficient, therefore a Computer Aided Diagnosis (CAD) based on Deep Learning (DL) model become subject of interest nowadays. However, with vast amount of WBCs data and various DL architectures available, tuning an optimal DL model is a daunting task. In this project, a diagnostic algorithm for WBCs' DL analysis is proposed by combining transfer learning approach with fine tuning (FT) approach and tested on Kaggle dataset (9957 images). Initially, a transfer learning analysis are conducted using six well known Convolutional Neural Network (CNN) structure which are Alexnet, Googlenet, Densenet, Mobilenet, Resnet and VGG. Next, the CNN model that yield high accuracy with less prone to overfitting is selected for the FT process. Finally, the optimal FT model will undergo series of performance testing using two public WBCs dataset which are LISC and IDB-2. From series of experiments, it can be concluded that the pre-trained AlexNet model gave highest performance with 98.79% training accuracy and 99.10% testing accuracy compare to other models. When implementing the layer refinement analysis, it shows that AlexNet model with 4-layer FT and RMSProp optimizer, significantly improved the performance with 100% accuracy in training and 100% accuracy in testing. Eventually, the FT-ALexNet model tested on LISC database demonstrate 95.52% performance for the true-positive samples, and on IDB-2 100% performance for the true-negative samples. Proposed method (FT-Alexnet) which compares and applies two-stage optimization technique works well with several WBC datasets and able to improve 2.22% from the existing work.

ABSTRAK

Sel Darah Putih (SDP) adalah salah satu elemen penting dalam melindungi sistem imunisasi badan. SDP terdiri daripada dua elemen penting iaitu *cytoplasm* dan *nucleus*, dengan kontras warna yang hampir sama dan menjadikan ia sukar untuk dikesan dan dianalisis. Analisis SDP secara manual adalah kurang efisyen, oleh itu, Diagnosis Berbantu Komputer berasaskan model Pembelajaran Dalam (PD) menjadi tarikan pada masa kini. Namun, dengan jumlah data SDP yang meluas dan pelbagai rekabentuk PD yang boleh didapati, memperbaiki PD yang optimal adalah tugas yang sukar. Di dalam projek ini, algorithma yang diagnostic untuk analisis PD SDP dicadangkan dengan menggabungkan kaedah Pemindahan Pembelajaran (PP) dengan Penalaan Halus (PH) dan diuji ke atas pengkalan data *Kaggle* (9957 gambar). Pada mulanya, analisis PP dijalankan menggunakan 6 struktur Rangkaian Neural Berlingkaran (RNB) yang terkenal iaitu Alexnet, Googlenet, Densenet, Mobilenet, Resnet dan VGG. Kemudian, model RNB yang memberikan ketepatan tinggi dengan kurang *overfitting* akan dipilih untuk proses PH. Akhir sekali, model PH yang optimal akan melalui beberapa siri ujian prestasi menggunakan dua pengkalan data SDP awam iaitu LISC dan IDB-2. Daripada beberapa siri eksperimentasi, ia boleh dikatakan bahawa model Alexnet membuahkan hasil ketepatan yang tertinggi, iaitu 98.79% untuk latihan dan 99.10% untuk pengujian dibandingkan dengan model lain. Apabila melaksanakan analisis pembaikan lapisan, hasil menunjukkan bahawa model Alexnet dengan 4-lapisan PH dan pengoptimum RMSProp, meningkatkan prestasi secara ketara dengan mendapat 100% ketepatan untuk latihan dan 100% ketepatan untuk pengujian. Pada akhirnya, model PH-Alexnet diuji menggunakan pengkalan data LISC dan memperoleh prestasi 95.52% untuk sampel positif-sebenar dan bagi IDB-2, prestasi 100% untuk sampel negatif-sebenar. Kaedah yang dicadangkan (PH-Alexnet) yang membandingkan dan menggunakan teknik pengoptimuman dua peringkat berfungsi dengan baik dengan beberapa set data WBC dan dapat meningkatkan 2.22% daripada kerja sedia ada.

CONTENTS

LIST OF TABLES

LIST OF FIGURES

LIST OF APPENDICES

CHAPTER 1

INTRODUCTION

1.1 Project background

There are three major components in human body which are red blood cell, white blood cell and the platelets as shown in Figure 1.1. Every cell has its own function. To illustrate, RBC helps to transport oxygen from the lung to each part of the body [1] and WBC fights diseases, viruses and bacteria [2]. White blood cell is reported to be closely related to human body immunity. Immune system is important to help the body fights bacteria, viruses and any other elements that will give a bad effect to our body system. Since the community environment is surrounded by different kinds of people every day and also exposed to the possibility of getting viruses, a strong antibody system is crucial and an analysis of WBC can greatly help to determine such condition. Number of WBC also explains the patient's diseases.

The normal WBC count is in the range of 4500-10,000 (µl) while the abnormal count is beyond that range. A patient with low WBC count can potentially be diagnosed with diseases such as HIV and Lymphoma while high WBC count can trigger diseases such as Anemia, Leukemia and tissue damage. Basically, if a patient complains about their continuous sickness, the first test that will be performed by a doctor is the blood test since it will definitely explain a lot about the patient's health condition. Necessary steps can therefore be taken to prevent serious illness.

Apart from that, WBC analysis can also contribute to the information on cancer therapy effectiveness. If a patient is getting better, it means that the therapy works but if the condition is worsening, then the therapy has to be stopped. Other than that, by analyzing the WBC in the body, the level of a person's immunity

system can be determined. Doctors can take further actions regarding the diseases and prevent the viruses from spreading all over the body.

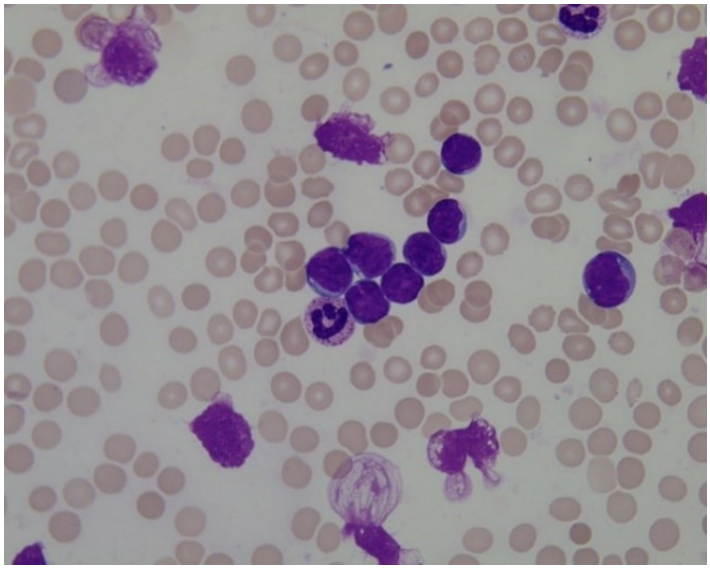


Figure 1.1: Sample of blood smear image

White blood cell analysis includes white blood cell detection and count is crucial to identify the patient health condition. One of the diseases that can be related to white blood cell analysis is Leukaemia disease. Leukaemia is one of the top causes of death in the world in recent time [3]. This is due to the uncontrollable growth of the unneeded cells in the body. When the old and damaged cells continue to survive whereas they do not need to be in a human body anymore, the continuous growth will become tumours and can affect the surrounding cells by damaging the immune system, tissues and other cells that protect human body from any infection [4].

There are five types of WBC in the blood smear image which are Basophil, Eosinophil, Lymphocyte, Monocyte and Neutrophil as shown in Figure 1.2. There are two categories of WBC which are granulocytes and agranulocytes. Granulocytes consists of Basophil, Eosinophil and Neutrophil while agranulocytes consists of Lymphocyte and Monocyte. The cell shape, texture and structure are slightly different from one another.

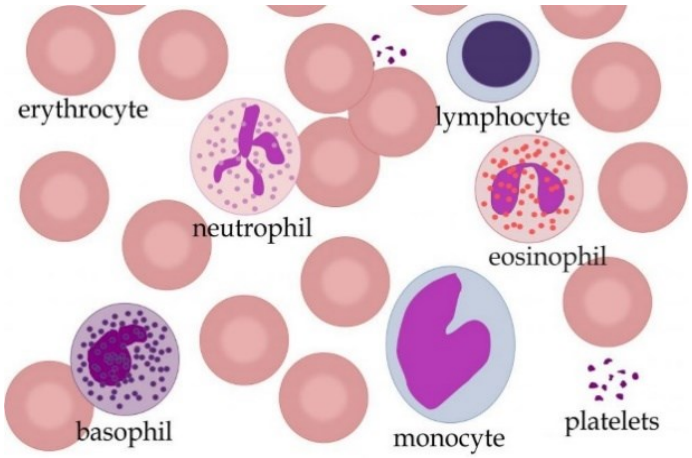


Figure 1.2: Illustration of five types of WBC in a blood smear image [5]

It is very important to detect the disease as soon as possible and an early treatment can be taken on the patient. Detection of WBC starts with the blood analysis which is done by the pathologists. If the WBC count is abnormal, further action such as bone marrow biopsy will be taken to study the morphological differences [6]. Hematologist will study the blood cell slide under the light microscope to find abnormalities in its nucleus and cytoplasm of the cells. In manual practice of WBC identification, as the blood sample increases, pathologists take longer time to come out with the result. It is a time consuming process and depending on the pathologists' skills which may yield inaccurate result.

Traditional ways of detecting and counting WBC is done manually by the pathologist [7, 8]. However, this manual practice creates problem as it yields inaccurate results and entirely depends on a pathologists skills and experiences [9]. Different pathologists might achieve different kinds of results which will create confusion. Other than that, as the sample increases, the workload that the pathologist is carrying will proportionally increase [10]. Since there are thousands of cells lie in the blood smear, it will make it more challenging for the pathologists to analyze it manually. Inevitably, the whole manual practice process is time consuming and sometimes requires a day for the results to come out. Other than that, microscopic images consist of non-uniform illumination and variations of color shades which will harden the pathologist's work [11].

One of the methods to identify and calculate the number of WBC in blood smear image automatically is by using computer vision. Under this framework, images acquired from an electronic camera will be processed and analyzed just

exactly like human perception system. Such system is widely used in industries especially among biologists for forensic studies and biometrics [11]. Even though computer vision cannot exactly replicate the human visual, it makes data analyzing faster and it is not time consuming. Furthermore, it is less complex and inexpensive solution. There are processes of computer aided such as segmentation, noise filtering, features extraction and classification. Most used classifiers which are SVM, ANN and FF-NN are often used to classify WBC.

Recently, a computer aided system using Convolutional Neural Network (CNN) become subject of interest to automatically analyze the WBCs variants. The biggest advantage of using such structure is its ability to learn the object's features, no complex classifier design needed and its performance is high [12]. Other than that, it is widely used in medical field due to its ability to achieve impressive performance [13]. Deep learning also can be defined as a class of machine learning techniques that exploit many layers of non-linear information processing for supervised or unsupervised feature extraction and transformation for pattern analysis and classification [14]. CNN process an input data by its multiple layers which consists of four key features: local connections, shared weights, pooling and the use of many layers [15]. Deep learning in medical benefit is exploit nowadays. There are many research and applications using deep learning that can be found previously such as image classification for Malaria diagnosis which use the AlexNet pre-trained model [16]. Other than that, AlexNet of CNN is also used for fire detection and it achieved stable accuracy as reported in [17]. CNN architecture that consists of 5 layers of convolutional, pooling and fully connected layer is proposed to detect the subtype of WBC [18]. Face and non-face image classification is reported in [19] to shows an outstanding performance. Other than that, there are also research on ALL identification which compares the result of machine learning and CNN and CNN showed the best performance result [20]. Some works combine CNN with Recursive Neural Network (RNN) to classify types of WBC [21]. Lastly, the most related work to ours is as reported in [22] which used AlexNet pre-trained model to identify lymphoblast and detect ALL.

In this project, the CNN based model was used as a basis to analyze the white blood cell (WBC) in blood smeared images. A comprehensive hyper-parameters tuning were conducted using state-of-the art CNN architecture and the performance were assess using three different databases which contain of 10459 samples of blood

smear images. In medical field, it is very crucial to have a good performance system that is able to do the analysis as good as the experts do. Apart from that, the developed system must provide faster response, less time consuming, easy to tune and economical for implementation.

1.2 Problem statement

Previous studies concentrated on WBC detection or classification. It can be seen that there were several problems in identifying the cells investigated in the works. The two major issues mentioned in [23] were:

1. Manual method

   One of the current methods of WBC identification and detection is by analysing the blood smear image manually. This practice is highly dependent on the pathologists' skills and it may yield inaccurate results. Furthermore, it takes longer time for the results to come out. As the samples increase, it will be more difficult for the pathologists to analyse it manually.

2. Cellavision

   Cellavision is a commercialized product that automatically counts the blood cell. However, this product is not widely available. The unit is also very costly and cannot be afforded by some developing countries.

It was also mentioned in [24] that the quality of captured images might be affected as there were variations of microscope exposure or its lighting condition while capturing the image.

Other than that, in terms of methods and techniques, most of the papers reviewed were not able to cater the various abnormal conditions problems. Furthermore, these methods are limited to normal cases and unable to identify the abnormality of WBCs. The previous methods and techniques are lacking in the terms of identifying abnormal RBC, WBC and Platelet [11].

Nowadays, the industrial sector has introduced a hematology counter which promises accuracy and fast result. However, this machine is costly [25] and unaffordable by some developing countries to be placed in their hospitals. Other than that, machine learning consists of complicated process of segmentation, feature

extraction and classification [26]. It is also challenging as the classification result is highly dependent on the selection of features. A system that is able to identify various type of WBCs is needed and will be a great help to the medical experts [11].

Other than that, rigorous algorithm or detail model analysis from layer to layer is not implement to improve the performance [27]. Some of the CNN models that been tested on Kaggle dataset showed various performance outcome ranging from 86.04% to the highest of 97.78% [21] [28] [29] [30]. Most of the previous work consider the tuning process by dynamically altered the dense layer only. In here, the work considers refinement process of the tuning by considering the convolutional layer of the pre-trained models. Apart from that, the develop model also tested with other two public datasets (LISC and IDB-2) to generalized the model performance with the unseen WBC condition.

WBC detection and classification using Convolutional Neural Network (CNN) is introduced in previous works. However, most of the cases contains small datasets and insufficient number of images [31]. Furthermore, not sufficient amount of training data and uneven class balance within the datasets is often mentioned as one of the challenges in CNN [32]. Therefore, performance assessment using various datasets is needed.

1.3 Objective of project

The objectives of this project are:

I. To classify White Blood Cell (WBC) regions in the blood sample images by analyzing Convolutional Neural Network (CNN) pre-trained models.
II. To improve the model performance using two-stage optimization technique.
III. To validate performance of the improvised model using various datasets.

1.4 Scope of project

This project required a production of WBC detection and classification by developing an algorithm and it is a computer based. The scopes of study of this project were: -

1.4.1 Type of cell identification

This project focused on the algorithm development for WBC classification only. It focused on WBC identification only based on its features extraction. It was not applicable for any other elements in the blood smeared images. WBC detection was done by processing the image using the software and coding that has been developed.

1.4.2 Database

There are three sets of database involved which are Kaggle, ALL-IDB2 and LISC. The system did not involve the process of getting the blood smear images. Kaggle database consists of 4 classes of Eosinophil, Lymphocyte, Monocyte and Neutrophil which contains of 2497, 2483, 2478 and 2499 samples respectively. Total samples in the database is 9957. IDB-2 database on the other hand, consists of 2 classes of data which are Lymphoblast and Non-Lymphoblast. Each class contains 130 images, therefore total images in this database is 260 images. Lastly, LISC database which consist of 5 types of WBC. The samples of Basophil are 53, Eosinophil are 39, Neutrophil are 50, Lymphocyte are 52 and Monocyte are 48 which gives the total of 242 samples in the database.

1.5 Contribution of the work

This project is about a development of biomarker model for WBC classification which is based on the improved CNN. One of the contributions is this project analyzes pre-trained models of CNN to provide the best model to be improved for WBC classification. Other than that, a diagnostic algorithm for WBC deep learning analysis is made by implementing two stages optimization techniques which includes optimization method and fine tuning method. The first stage is the optimization method where three optimizers are compared and the best optimizer is chosen. The second stage is the fine tuning process which several layers of the model is frozen to ensure that the learned weight is not updated while training. Most of the previous works emphasis on the combination of CNN with conventional classifiers such as LR

and QDA. This project emphasis on the combination of optimization method with layers tuning on the model to improve the classification performance.

Lastly, the final contribution is the optimal model is assessed using various WBC datasets to ensure the model is suitable for different types of WBC data. The improved model is also tested on various datasets which are Kaggle, IDB-2 and LISC using two types of assessments. The first assessment is the blind testing where the model is trained using Kaggle dataset and tested on IDB-2 and LISC. Second assessment is where the model is trained and tested using same model. It is done to ensure the effectiveness of the model and to prove that this model is capable to classify WBC correctly.

CHAPTER 2

LITERATURE REVIEW

2.1 Introduction

Basically, this chapter discusses about WBC types classification using deep learning which is CNN. The comparison between conventional method and CNN is as depicted in Figure 2.1 below. There are few steps of conventional method is discussed in Section 2.2.1 and CNN models is Section 2.2.2. Several pre-trained models which are Alexnet, Googlenet, VGG-16, Mobilenet, Resnet and Densenet is mentioned to differentiate its architecture and working system. Other than that, this chapter also explains the previous works of WBC classification using CNN and their advantages and disadvantages. Next, in Section 2.4 there are few works that uses CNN on the same dataset as this project which is Kaggle dataset. Matlab R2020a is the platform used with deep network designer toolbox.

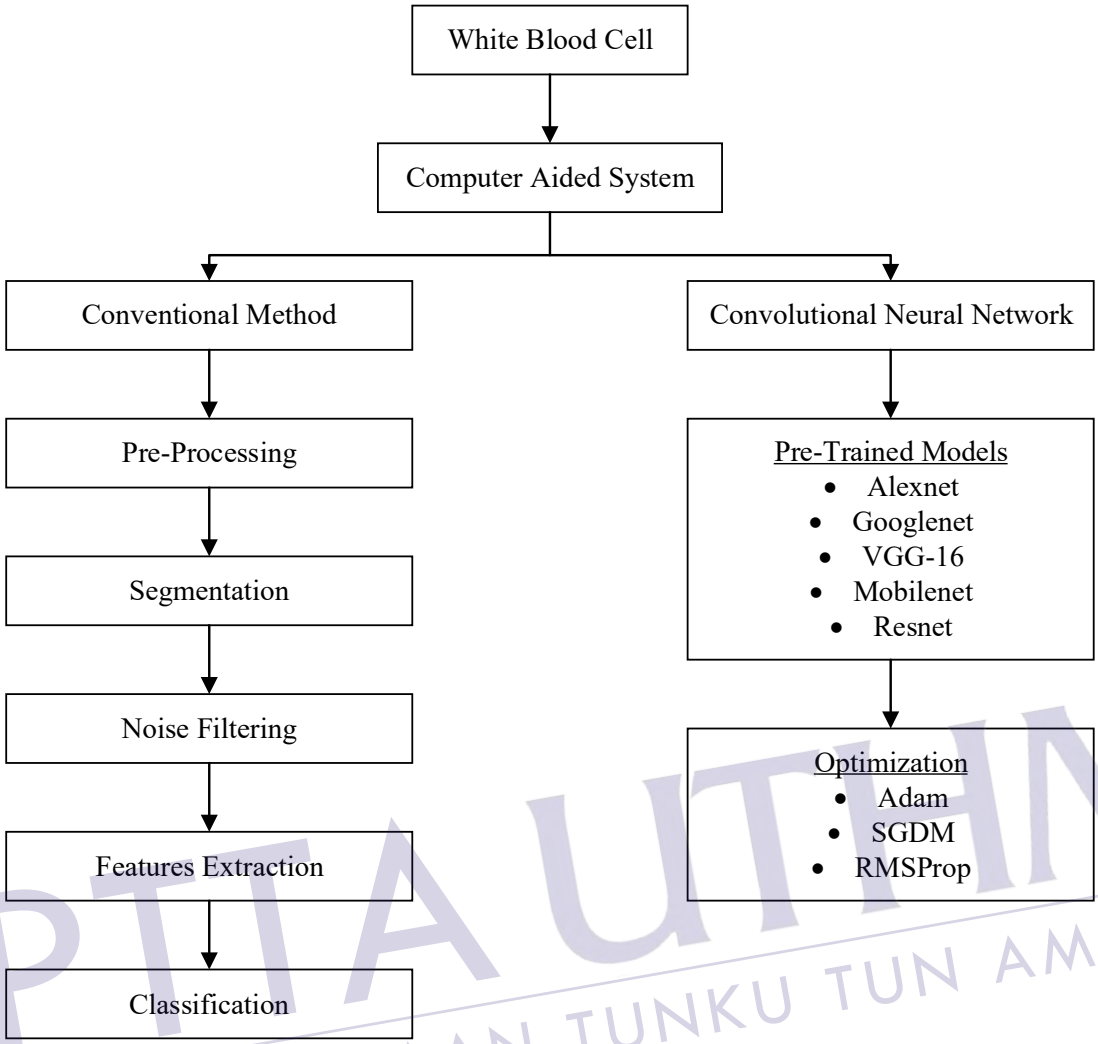


Figure 2.1: Tree diagram of CAS method

There are three major components in the blood of human body which are red blood cell, white blood cell and platelets [33]. White blood cell is closely related to cancer disease. However, a patient's health condition can also be determined by counting the number of white blood cell. The blood cell identification and detection will give information about the patient's blood to the haematologist or medical experts [34]. White blood cell count helps to determine the presence of disease in the patient's body. It is important to keep white blood cell count in track as it can help to allow doctors to take further action to prevent and reduce the risk of complication. In current practice, identification and counting of the blood cell is done manually. The blood sample is processed in a laboratory by using haematology analyzer [33, 35] in which the blood sample is placed under the light microscope and analyzed by the pathologists. This work focuses on the five types of WBC which are Lymphocytes, Monocytes, Neutrophils, Eosinophils and Basophils. These cells are differentiated by

its shape, number of lobes in the nucleus and the area of its cytoplasm. The differences can be seen in Figure 2.2 below.

Table 2.1 explains the differences of all WBC types for its nucleus and cytoplasm. It varies it terms of its size, component in the nucleus, size of the nucleus and color specifications of its cytoplasm.

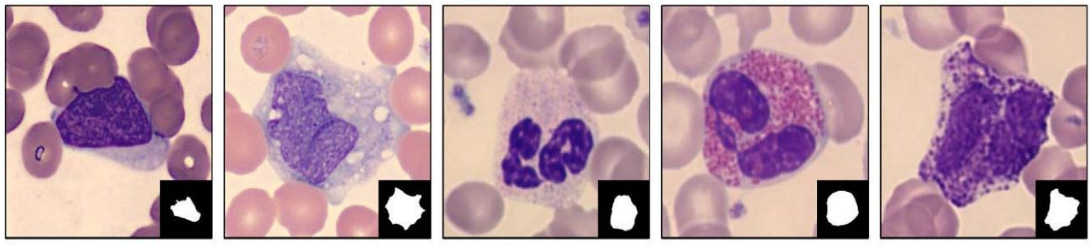


Figure 2.2: 5 types of WBC (a) Lymphocyte (b) Monocyte (c) Neutrophil (d) Eosinophil (e) Basophil [36]

Table 2.1: Basophil, Eosinophil, Lymphocyte, Monocyte and Neutrophil Specifications [37]

WBCs (~% in blood)	Nucleus	Cytoplasm	Size(□m)	Clinical significance
Neutrophils (60%)	Divided into 2 to 5 segments and stains dark purple (multi-lobe nucleus).	Pale pink to tan with fine pink-purple granules.	12-16	Dark purple color nucleus and very light color of cytoplasm.
Eosinophils (3%)	Blue coloured and is divided into 2 segments.	Full of pale pink to tan with large orange and red granules.	14-16	Two segments of nucleus and redish color of cytoplasm.
Basophils (1%)	Contains 2 lobes that stains purple and is difficult to see.	Pale pink-tan but contains large purple/blue-black granules obscure nucleus.	14-16	The color of nucleus and cytoplasm is almost the same.
Monocytes (6%)	Singular nucleus, kidney shaped or bean shaped.	Stains a blue grey colour with 'ground glass' cytoplasm with tiny granules.	14-20	Only one individual nucleus and its cytoplasm is light purple color.
Lymphocytes (30%)	Large, round or oval, dark staining nucleus.	Little to no cytoplasm with pale blue in colour.	8-15	The size of nucleus is almost the same with the cytoplasm.

2.2 Current technology of computer aided system (CAS)

2.2.1 Conventional method

One of today technologies that leads the world for a better improvement is the computer vision system for image processing. One of the efficient and cost effective WBC counting processes is based on Computer Aided System (CAS) concept in which the system can be tuned to work as good as human eyes and sometimes even better [38]. Many researchers have investigated and identified the use of image processing to implement new things that give benefits to the industry. Some examples of current practices that use image processing are detection of diseases on cotton leaves, automatic red blood cell and white blood cell counting. Basically, the methods that are used in the image processing include image enhancement, image extraction, colour correction, image segmentation, feature extraction, classification and region counting. In the CAS framework, the processes can be divided into two main parts which are WBC identification and lymphoblast classification. Prior to processing WBC, the CAS must be able to localize and segment the respective WBC region accurately. However, such task is challenging due to the complexity of WBC shape that consists of cytoplasm and nucleus region in which nucleus resides inside the cytoplasm with the same colour type but different level of intensity.

2.2.1.1 Pre-processing

The first pre-processing step is the colour conversion process which is applied by changing or enhancing the original colour image. This process is needed as the original image might contain noises and unwanted region. In order to focus on the region of interest, the noises must be filtered or lessened. There are many suggestions for this process. One of them is as suggested by [39] which the RGB colour image was converted to Lab colour space to reduce the colour dimension from three to two. Other than that, there was a work that converted the RGB or original image to grey level image [40] for background elimination purposes. In [17], the original image was enhanced by mapping the intensity value before converting it to greyscale image. Other than that, image enhancement was done by using histogram

equalization to increase the colour contrast [41]. Image enhancement can be done by converting the original image to HSV colour space and separating V (Value) channel [42]. Table 2.2 lists out various methods for image pre-processing and shows images before which are the original images and after the process. Most of the techniques enhance the color intensity of the original image which will also enhance the RBC and other particles in the blood image along with the WBC region. In [42], original image is transformed to greyscale image before it is enhanced to improve the image quality. As reported in [43], the number of references that used colour conversion for pre-processing purposes was the highest compared to other methods.

Table 2.2**:** References for pre-processing techniques [43]

Authors	Pre-processing techniques	Advantage/Disadvantage
Pradipta Maji, et al. [44]	color conversion technique	This paper presents a new image retrieval scheme using visually significant point features
J. M. Sharif, et al. [45]	average filtering	The resulted RBC segmentation is passing through marker controlled watershed algorithm which handles overlapping cells
Mostafa Mohamad, et al. [46]	contrast stretching and histogram equalization, Gram-Schmidt orthogonalization	This technique is relying on enhancing the color of the target object, nucleus, and filtering the image
Urmila Airsang, et al. [47]	color conversion	The accuracy of a system depends upon the standard of input image
Siti Madihah Mazalan, et al. [48]	color conversion and binary conversion	The completed project is able to obtain quick and accurate blood cell segmentation of both red and white blood cells
Su Mao-jun, et al. [49]	median filtering	The method can de-noise and segment blood cell image perfectly, well eliminate disturbed objects, and is able to segment specific isolated cell from its background
S. K. Karim, et al. [50]	color conversion	It can segment the ROI very well
Biplab Kanti Das, et al. [51]	Gaussian filter	The proposed work designed to obtain effective and more accurate result than other conventional edge detection techniques

Table 2.2: continue)

Authors	Pre-processing techniques	Advantage/Disadvantage
J. Theerapattanakul, et al. [52]	binary conversion	This paper proposes a segmentation scheme that utilizes a benefit of active contour
Heildi Berge, et al. [53]	color conversion and median filtering	Boundary curvature calculations and Delaunay triangulation is done for red blood cell clump splitting
Ngoc-Tung Nguyen, et al. [54]	color conversion and binarisation	With results from average cell size, central points with their boundary-covering degree, over-lapping cells in the image can be split correctly and rapidly
Mohendra Roy, et al. [55]	histogram equalization and binarisation	The shadow images of the Red Blood Cells(RBCs) are well detected and specified by the algorithm
Krishna Kumar Jha, et al. [56]	median filtering	This paper provides way to recognize types of different kind of WBC in its normal and abnormal form
Fabio Scotti [57]	contrast enhancement and gaussian low pass filtering	The paper presents how to suitably enhance the microscope image by robustly identify white cells permitting to better extract their features for subsequent automatic diagnosis of diseases
Ji Ge, et al. [58]	color conversion and binarisation for preprocessing the blood cell images	The throughput is improved by approximately 90 times compared to manual reading by technologists
Stephan Rupp, et al. [59]	color conversion and binarisation	A fast lookup of the counting area is performed enabling a fully automated analysis of blood smears for medical diagnosis

2.2.1.2 Segmentation

Pruning out the region of interest called segmentation is a tough process depending on the image itself. Segmentation is reported as a very important task as the accuracy of WBC or lymphoblast classification is highly dependent on this process [60]. This

process can be divided into five main categories that are threshold-based methods, learning-based methods, active-contour-based methods, metaheuristic-based methods and saliency-based methods [2]. All these categories can be used for segmentation purposes based on different kinds of image type. This section focuses on the threshold-based methods as for uniform type of image like blood image, a threshold-based is reported to be the best and have reliable performance with high running speed [2]. It is also reported in [43] that threshold method for segmentation has the highest number of references compared to other techniques as shown in Table 2.3. Thresholding is one of the simplest and less complex methods and it is used widely in cell segmentation.

Table 2.3**:** References for segmentation techniques [43]

Authors	Segmentation techniques
Pradipta Maji et al. [44]	Mathematical morphology that process image based on shapes and size of structuring element
J. M. Sharif et al [45]	Mathematical morphology that process image based on shapes and size of structuring element
S. Karim et al. [50]	Mathematical morphology that process image based on shapes and size of structuring element
Krishna Kumar Jha et al. [56]	Mathematical morphology that process image based on shapes and size of structuring element
Chunni Dai and Jingao Liu [61]	Feature matching technique that include features of index, location, intensity, symmetry
Mostafa Mohamed et al. [46]	Thresholding technique
Biplab Kanti Das et al. [51]	Thresholding technique
J. Plodpai et al. [52]	Thresholding technique
Timo Schlarb et al. [62]	Thresholding technique
Mohendra Roy et al. [55]	Thresholding technique
Fabio Scotti [57]	Thresholding technique
Mostafa Mohamed A. Mohamed and Behrouz Far [46]	Gram-Schmidt Orthogonalization
Urmila Airsang, et al. [63]	Contour feature-point tagging technique
Siti Madihah Mazalan et al. [48]	Circular hough transform
Li-hui Zou et al. [64]	Circular hough transform
Su Mau-jun et al. [49]	Pulse-Coupled Neural Network(PCNN)
Ms. S. S. Adagale and Ms. S. S. Pawar [65]	Pulse-Coupled Neural Network(PCNN)

One of the methods is Otsu thresholding and it is applied on the green channel of RGB to segment the RBC region as in [66]. Otsu thresholding also can be done on Y colour band of CMYK to segment the cell region [38] and the result images of Otsu thresholding are as depicted in Figure 2.3. Other than that, [67] proposed histogram thresholding to find the optimal values of threshold to segment the region of WBC. While in [68], K-mean clustering is applied for initial segmentation of the cell nucleus. As for the work reported in [40], the RGB image was converted to CMYK to take only the Y colour component as the region of interest had more contrast in it and threshold the image. To prune out the clumped region, work in [69] proposed the watershed seed region growing method and applied a threshold value of 90 for the internal marker. There are so many works that used watershed segmentation not only for cell segmentation purposes but to other image as well. It was also applied to identify lung cancer cell by setting the marker location to be regional minima which helped to emphasize the image information [70]. Some works used S and V colour component of HSV together with Zack thresholding as applied in [71] to identify the parasites and RBC [72], greyscale image was threshold to binaries the image.

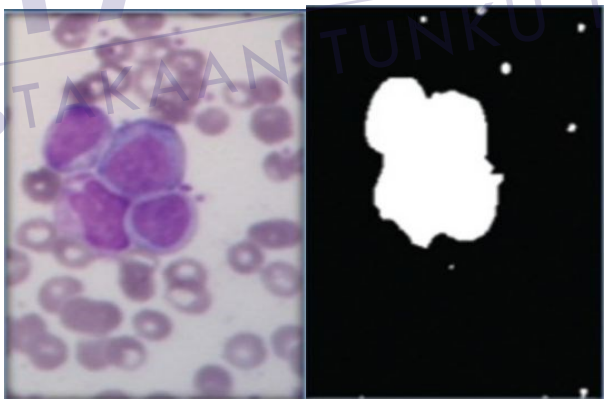
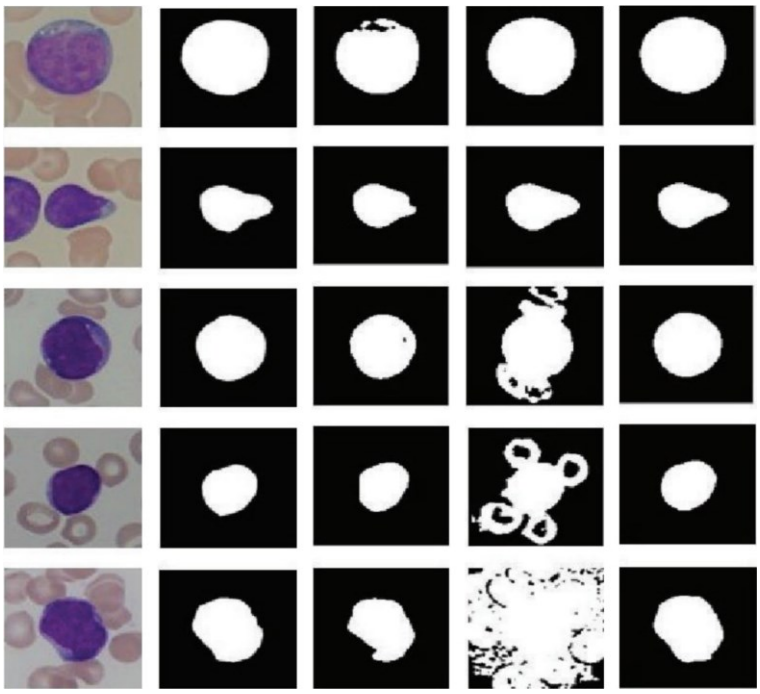


Figure 2.3: Original image (left) and cell segmentation result (right) [73]



(a) (b) (c) (d) (e)

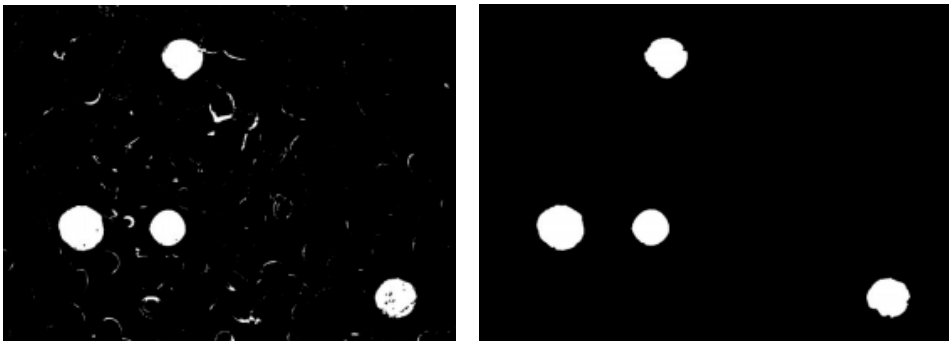
Figure 2.4: (a) Original image (b) Manual segmentation (ground truth) (c) RGB colour space based single-threshold method (d) HSV colour space based single-threshold method (e) Proposed method [74]

All the stated segmentation methods are single thresholding. There is also dual thresholding approach as suggested by [74]. In this work, dual thresholding was applied by combining two thresholds which were contrast stretching images and H colour component from HSV colour analysis. The authors stated that this dual thresholding was to improve the conventional method which was the single thresholding. The comparison is shown in Figure 2.4.

2.2.1.3 Noise filtering

The noises and unwanted regions that exist as a result of segmentation process need to be gotten rid of as it will affect the cell's segmentation accuracy. These are eliminated by using several image filtering methods. As projected by [2], noises in the segmented image is eliminated by applying an open operation to remove small dots and small particles were removed by using connected component labelling. Morphological operations such as dilation, erosion, opening, closing and reconstruction are applied on a binary image to distinguish unwanted region in the

image [75, 76]. Dilation operation is applied before image filling to fill in the internal holes [77] and the sample result is as shown in Figure 2.5.



(a) (b)

Figure 2.5: (a) Segmented image (b) Image after denoising [77]

2.2.1.4 Features extraction

Features extraction is a very important step before proceeding to the classification process. Some of the WBC region in the images are clumped and overlapped to each other. This is a challenge of the feature extraction process. Feature extraction is the process of extracting and obtaining data from object of interest. The classification process cannot be done directly if there is no train data. This is where the feature extraction is applied. There are many types of features extraction that can be taken based on the application and type of object that need to be classified. However, most of researchers used almost the same features for cell classification. Three main features extraction are focused on in [78] as depicted in Figure 2.6.

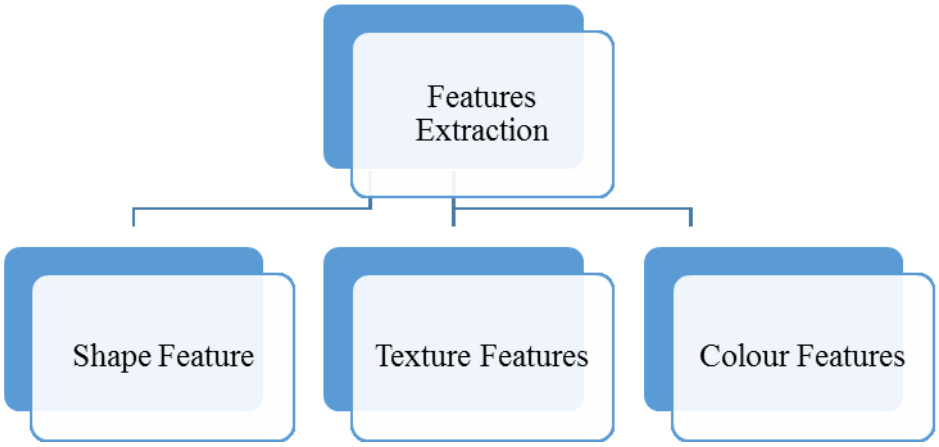


Figure 2.6: WBC's features analysis

Some researchers used shape features [77, 79]. Mohapatra, S., et al presented fractal dimension, contour signature, shape features, colour features and texture features to classify the lymphoblast cell from other cell particles in the blood sample [39]. Shape feature contains features such as area, perimeter, compactness, solidity, eccentricity, elongation and form factor [68]. On the other hand, texture features which are based on grey level image consist of homogeneity, energy, correlation and entropy. Grey Level Co-occurrence Matrices (GLCM) is also used to calculate the textural characteristics [79]. Some works proposed shape features, ratio between the cell and nucleus area, rectangularity and circularity on the binary image [80]. Colour or intensity feature extraction is important as it gives information about colour abnormalities of cells. Mean, variance standard deviation, and entropy is considered for colour feature extraction [79]. Table 2.4 tabulates the compilation of previous works in feature extraction of WBC or to be precise, lymphoblast.

Table 2.4**:** Previous works method in feature extraction

REFERENCES	FEATURES EXTRACTION			ACCURACY (%)
	SHAPE	TEXTURE	COLOUR	
S. Mohapatra and D. Patra [81]	√	√	√	95.00
L. Putzu and C. Di Ruberto [82]	√	√	√	92.00
F. Scotti [83]	√	√		99.98
M. D. Joshi, et al. [84]	√			93.00
M. Moradi Amin, et al. [85]	√	√		98.00

2.2.1.5 Classification

Classification process is the most crucial part in the system as the accuracy of the whole system performance is highly dependent on the accuracy of the classified cell. Classifiers such as Neural Network (NN) and Support Vector Machine (SVM) are widely used in this process. [80] compared three classifiers which are the nearest neighbour classifiers (kNN), feed-forward neural network (FF-NN) and linear Bayes Normal classifier. It was found that FF-NN showed mean error of 0.0133 which was lower than the other two classifiers. However, the execution time was higher. Two classifiers which were Artificial Neural Network (ANN) and Support Vector Machine (SVM) were compared to each other [86]. ANN classifier had more fluctuation in the overall accuracy while SVM was more stable. SVM also was superior compared to ANN. Another work used SVM as well and they achieved

classification accuracy of 93% [39] and 95% [68]. It is also can be seen in Table 2.5 that for WBC classification purposes, most of the works used SVM machine learning as a classifier.

Table 2.5**:** Comparative study on WBC classification

References	**Classification**		**Advantage**	**Disadvantage**
	SVM	**Neural Network**		
M. Habibzadeh , et al. [78]	√		This work achieved a satisfactory result	High number of features that needed to be extracted
N. Patel and A. Mishra [87]	√		Segmentation of the lymphocytes and myelocytes is done	The accuracy achieved is not higher than 95%
L. Putzu, et al. [88]	√		The system provides excellent performances allowing an early diagnostic suspicion	No experts validation regarding the result obtained
J. Rawat, et al. [42]	√		Better result is achieved when the GLCM texture-shape feature of the nucleus - cytoplasm region is combined	The result need to be improved as it only achieved 89.8%
M. Sajjad, et al. [89]	√		Validate the effectiveness and efficiency of the proposed system in contrast to state-of-the-art schemes	Prone to errors and time consuming
Q. Wang, et al. [90]	√		The proposed method use both spectral and spatial information for segmentation	Complex and lengthy method as the work combines two features
M. Z. Othman, et al. [91]		√	Lower number of feature extraction but higher classification accuracy	Insufficient amount of data
S. Manik, et al. [92]		√	Decreases the execution time of segmentation and classification	Finding Intensity maxima and then classified on the basis of various features extracted from segmented images is a complex task

2.2.2 Convolutional Neural Network (CNN) Architecture

Artificial Neural Network (ANN) with multilayers is called deep learning or deep neural network. One of the most efficient deep neural network is Convolutional Neural Network (CNN). It is a special structure of artificial neural network that has been used widely as it is indeed a powerful tool for various applications such as object and image detection, voice and video recognitions. Based on this condition, it allows CNN to be both translation and rotation invariant due to the architecture of the model [93]. CNN is also proven to have excellent performance in machine learning problems.

Nowadays, this technology is very much needed in the medical field as it requires efficient and reliable technique to diagnose life-threatening diseases [94]. It also helps to diagnose and analyze faster so the early prevention can be made. Traditional method that has been used before in medical field is time consuming and highly dependent on the experts' skills which can yield inaccurate result. CNN can be a great help to assist the experts in analyzing and detecting several diseases.

However, localization of object is not very accurate and requires a lot of computation operation [95]. It also includes the most exhausting process which is feature extraction. The feature extraction work can greatly impact classification process and the final result. Alternatively, deep learning provides an effective way to extract features of raw data automatically and the most effective deep learning method is CNN [96]. In CNN, hand-crafted feature extraction is not needed. The differences between CNN compared to other methods are CNN architectures do not necessarily require segmentation, far more data hungry and more computationally expensive as it requires Graphical Processing Units (GPU) for model training [97]. There are some beneficial aspects of CNN including it reduces number of parameter in ANN, it solves complex tasks and it also should not have features which are spatially dependent [98]. It is also said to achieve very amazing result as it has an excellent performance dealing with image data, such as largest image classification data set, computer vision and in Natural Language Processing (NLP) [98]. However, the efficiency and performance of deep learning schemes is depending on the size of the training dataset [99].

CNN architecture consists of several important components of convolution layers, pooling layers and fully connected layers. CNN model is built by stacking the blocks of these mentioned layers [100]. The convolution layer contains a set number of filters to obtain the feature maps of input images, while pooling layer is the down-sampling layer to reduce the feature dimensions of the input and lastly, fully connected layer computes the class score and act as a classifier [96]. More explanations of convolution layer, pooling layer and fully connected layer can be found in Table 2.6 below.

Table 2.6**:** Explanations of layers in CNN [101]

Layer	**Explanation**
Convolution	✓ The aim is to learn feature representations of the inputs. ✓ Consists of several feature maps. ✓ Each neuron of the same feature map is used to extract local characteristics of different positions in the former layer. ✓ Input feature maps are convolved with a learned kernel and the result are passed into a nonlinear activation function. ✓ Typical activation functions: - a) Sigmoid b) Tanh c) Rectified Linear Unit (ReLU)
Pooling	✓ Equivalent to fuzzy filtering ✓ It can reduce the dimensions of the feature maps and increase the robustness of feature extraction. ✓ The size of feature map in pooling layer is determined according to the moving step of kernels. ✓ Typical pooling operations :- a) Average pooling b) Max pooling
Fully Connected	✓ Classifier of CNN ✓ Take all neurons in the previous layer and connect them to every single neuron of current layer. ✓ Softmax regression is commonly used because it generates a well-performed probability distribution of the outputs.

2.2.2.1 AlexNet

AlexNet is the pre-trained model that won first place at the Imagenet Large-Scale Visual Recognition Challenge 2012 (ILSVRC-2012) [102]. It has 8 layers in total which consist of 5 convolutional layers and 3 fully connected layers. as shown in Figure 2.7.

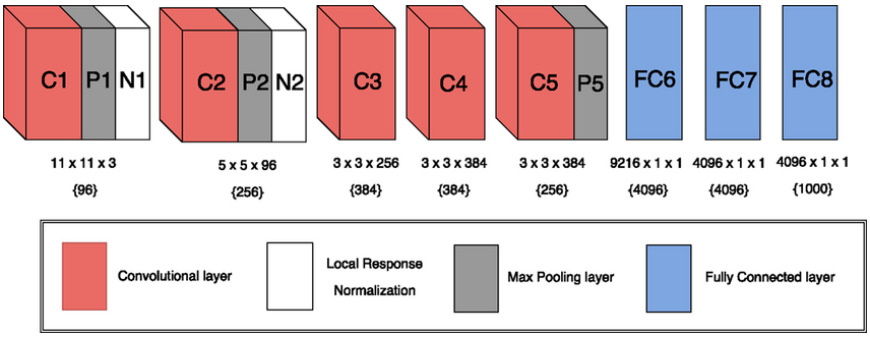


Figure 2.7: AlexNet Architecture

The input dimension of the data source must be fixed to 227×227 which indicates the height and width of the image [103]. It is mainly to reduce the computational cost of the framework. Dropout of 0.5 is applied to the sixth and seventh layer to overcome the overfitting problem and reduce the training time for each epoch [104]. Number of kernels and filter size of convolutional layers in AlexNet is as depicted in Table 2.7.

Table 2.7**:** Convolutional layers in AlexNet [105]

Layer	Number of kernels	Filter size
1	96	11×11
2	256	5×5
3	384	3×3
4	384	3×3
5	384	3×3

Feature maps are generated from each convolutional layer which feature extraction phenomena are performed in these layers [105]. These feature maps are connected to the fully connected layers so the classification probabilities can be made after performing softmax activation. Features of fully connected layers are more expressive that the features of convolutional layer [106]. In AlexNet, it can make up to 1000 classes of data in the final output classification layer. Rectified Linear Unit (ReLU) is often used as non-linearity function in AlexNet, misclassification and leakage will occur for high-brighting and low-brighting objects [106].

2.2.2.2 GoogleNet

GoogleNet is developed by Google and won ImageNet Large Scale Visual Recognition Challenge (ILSVRC) in 2014. It replaced the expensive fully connected layers at the end of the model with a simple global average-pooling layer which result to the reduction the number of parameters used in the model [107]. Thus, the model made it a faster in the training phase, lighter in size and higher in performance compared to VGGNet and AlexNet [107]. Figure 2.8 shows the comparison of top-5 test error between CNN models in the ImageNet competition. It can be seen that GoogleNet produced the lowest test prediction error compared to other CNN's model.

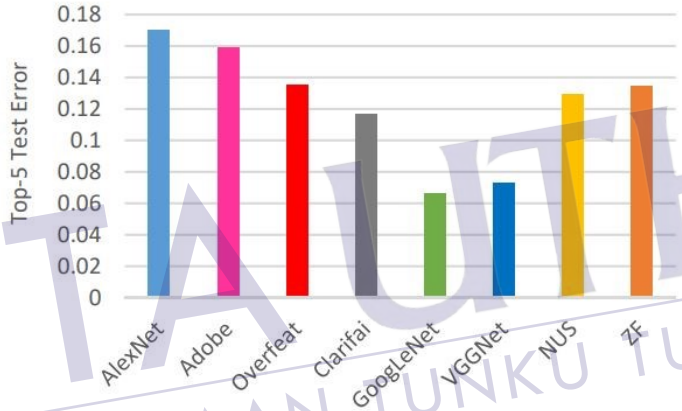


Figure 2.8: Comparison of top-5 test error for CNN's models [108]

GoogleNet input source must be fixed to 227×227 image dimension. Its architecture is developed of 22 layers which consists of 9 inception layers and another 13 layers are made up from convolutional layer, local response normalization, max pooling layer and fully connected layer as shown in Figure 2.9.

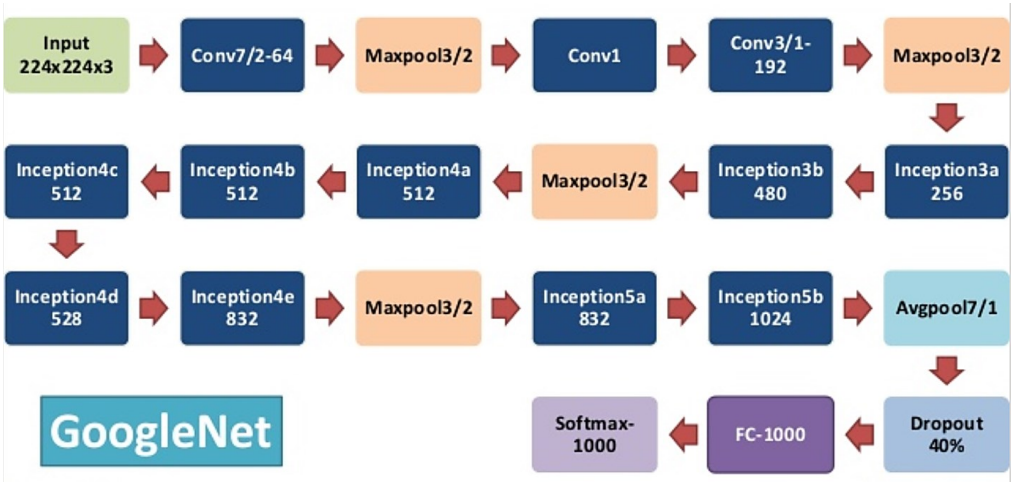


Figure 2.9: GoogleNet Architecture

Inception module which can be seen in Figure 2.10, are embedded to increase the network depth and width by processing data through several convolutions simultaneously which helps to shorten the network's training time and also increase the utilization of computing resources [109].

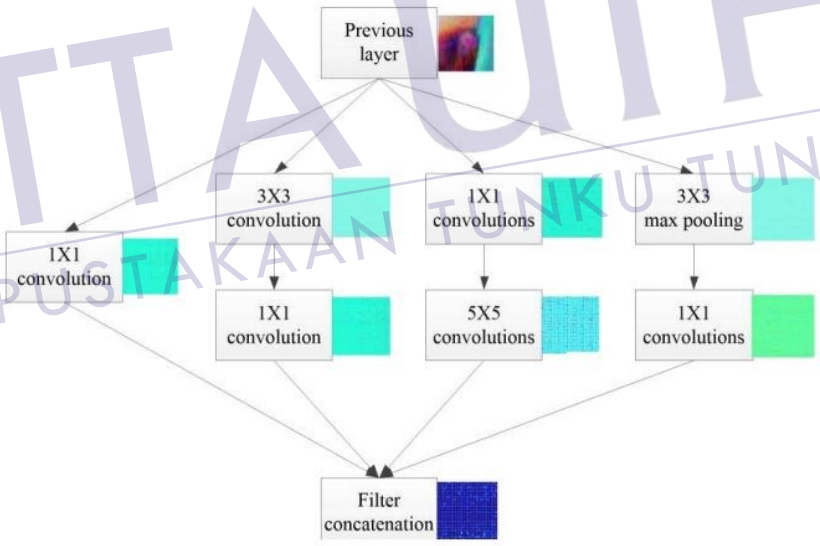


Figure 2.10: Illustration of inception module [109]

Basically, GoogleNet is the inception modules, which has the multiscale convolutional kernels used to convolve the data in parallel different size [110]. As it is an inception module, it is meant to have different sizes of convolution for the same input and stacking all the outputs [111]. The two most popular GoogleNet architecture are Inception-v1 and Inception-v3. There are several differences of these two models which has been tabulated in Table 2.8.

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APPENDIX A

LIST OF PUBLICATIONS

1. Syadia Nabilah Mohd Safuan, Mohd Razali Md Tomari, Wan Nurshazwani Wan Zakaria, Nurmiza Othman, *Lymphoblast cell morphology identification to detect Acute Lymphoblastic Leukemia (ALL) using various color segmentation.* In *Journal of Physics: Conference Series*. 2020. IOP Publishing. (Scopus)
2. Syadia Nabilah Mohd Safuan, Mohd Razali Md Tomari, Wan Nurshazwani Wan Zakaria, Mohd Norzali Hj Mohd, Nor Surayahani Suriani, *Investigation of White Blood Cell Biomaker Model For Acute Lymphoblastic Leukemia Detection Based On Convolutional Neural Network*. Bulletin of Electrical Engineering and Informatics, 2020. 9(2): p. 611-618. (Scopus)
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