KHALED ABDALLA ALMEZHGHWI

IMPROVED CLASSIFICATION OF WHITE BLOOD CELLS WITH GENERATIVE ADVERSARIAL NETWORK AND DEEP CONVOLUTIONAL NEURAL NETWORK

NEU 2020

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A THESIS SUBMITTED TO THE GRADUATE SCHOOL OF APPLIED SCIENCES OF NEAR EAST UNIVERSITY

By
KHALED ABDALLA ALMEZHGHWI

In Partial Fulfillment of the Requirements for the Degree of Doctor of Philosophy in Electrical and Electronics Engineering

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Approval of Director of Graduate School of

Applied Science

Prof. Dr. Nadire CAVUS

We certify this thesis is satisfactory for the award of the degree of Doctor of Philosophy in Electrical and Electronics Engineering

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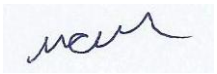

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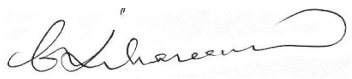

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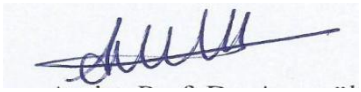

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I hereby declare that all information in this document has been obtained and presented in accordance with academic rules and ethical conduct. I also declare that, as required by these rules and conduct, I have fully cited and referenced all material and results that are original to this work.

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ACKNOWLEDGMENTS

Firstly, I would like to express my thanks to my supervisor Assist. Prof. Dr. Sertan Serte for the support of my Ph.D study. I want to appreciate my family particularly my wife for her immerse support throughout the period of this study. My sincere heart of gratitude goes to the entire instructors in the department and my supervisor, for the invaluable impact in my study.

To my Family…

ABSTRACT

Blood is composed of plasma, erythrocytes, leucocytes, and platelets also known as thrombocytes. However, this study focused on the automatic classification of leucocytes with the use of approaches involved with the augmentation of data and deep neural networks as an alternative for manual laboratory procedures by using Artificial Intelligence (AI). Several objectives were outlined for this study, which consist of an end-to-end equipped deep neural network for the automatic classification of leucocytes into their five different categories: neutrophils, eosinophils, basophils, lymphocytes and monocytes. The exploration of a host of deep neural network systems was conducted by using pre-equipped standards for enhancing the performance of classification. Dataset acquisition and simulation analysis prove that the suggested approach performs well directly with obtained images and performs better the than previous approaches, which require tedious image preparations stages and feature engineering. Moreover, a deep learning approach was used to analyze the LISC dataset. The results from this study revealed a high level of accuracy of 97.4%, 98.3%, 98.8%, 96.5% for ResNet-50 (Tran_aug3 + GAN_aug3), DenseNet-121 (Tran_aug3 + GAN_aug3), and DenseNet-169 (Tran_aug3 + GAN_aug3) respectively. However, the results of this study revealed that the proposed technique is very effective and more studies should be conducted using this technique.

Keywords: Artificial Intelligence (AI), Deep learning, ResNet, DenseNet, Blood.

Özet

Kan, trombosit olarak da bilinen plazma, eritrositler, lökositler ve plateletlerden oluşur. Bununla birlikte, bu çalışma Yapay Zeka (AI) kullanılarak manuel laboratuvar prosedürlerine alternatif olarak verilerin ve derin sinir ağlarının arttırılması ile ilgili yaklaşımların kullanılmasıyla lökositlerin otomatik olarak sınıflandırılmasına odaklanılmıştır. Bu çalışma için uçtan uca donanımlı derin sinir ağı kullanarak, lökositlerin nötrofiller, eozinofiller, bazofiller, lenfositler ve monositler olmak üzere beş farklı kategoride otomatik olarak sınıflandırılması için uçtan uca donanımlı bir derin sinir ağı içeren çeşitli hedefler belirlenmiştir. Sınıflandırma performansını artırmak için önceden donatılmış standartlar kullanılarak bir dizi derin sinir ağı sisteminin keşfi gerçekleştirilmiştir. Veri kümesi elde etme ve simülasyon analizi, önerilen yaklaşımın doğrudan elde edilen görüntülerle iyi performans gösterdiğini ve sıkıcı görüntü hazırlama aşamaları ve özellik mühendisliği gerektiren önceki yaklaşımlardan daha iyi performans gösterdiğini kanıtlamaktadır. Ayrıca, LISC veri kümesini analiz etmek için derin öğrenme yaklaşımı kullanılmıştır. Bu çalışmadan elde edilen sonuçlar, sırasıyla ResNet-50 (Tran_aug3 + GAN_aug3), DenseNet-121 (Tran_aug3 + GAN_aug3) ve DenseNet-169 (Tran_aug3 + GAN_aug3) için %97.4, %98.3, %98.8, %96.5'lik yüksek bir doğruluk düzeyi olduğunu ortaya koymuştur. Ancak bu çalışmadan elde edilen sonuçlar, önerilen tekniğin çok etkili olduğunu ve bu teknik kullanılarak daha fazla çalışma yapılması gerektiğini ortaya koymuştur.

Anahtar Kelimeler: Yapay Zeka (AI), Derin öğrenme, ResNet, DenseNet, Kan.

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LIST OF ABBREVIATIONS

CNN: Convolutional Neural Network

AI: Artificial Intelligence

ACC: Accuracy

GAN: Generative Adversarial Network

DNN: Deep Neural Network

SVM: Support Vector Machine

CHAPTER 1
INTRODUCTION

The optimal defence of the body against harmful foreign elements (bacteria and viruses) depends of the presence of functional white blood cells in the correct proportion. If the blood is deficient in healthy white blood cells or the different types are present in the wrong proportions, several harmful elements can easily invade the body causing various types of diseases for which the subject may require considerable medical care. As such, white blood cell type classification and subsequent defect inspection are important to ascertain the overall good health of subjects.

Traditionally, counting white blood cells is achieved in the laboratory using a staining process and manual examination under the microscope. This process is however tedious, and errors can occur due to fatigue on the part of the human examiner. The use of automated cell counting systems such as laser-dependent cytometers are commercially available, but are not morphologically nor image-dependent. Moreover, blood cells are destroyed in the course of analyses. An interestingly alternative is the non-destructive classification approach that relies on images of white blood cell types for learning the classification problem. However, a major problem for image-based automatic classification of white blood cells is the small size of data that is usually available for training. This problem worsens for deep neural networks, which are well known to be 'data-hungry'. As such, the following section summarizes the objectives of this thesis.

1.1 Objectives of Study

The main objectives of this thesis are as follows.

i. An end-to-end equipped deep neural network for the automatic classification of leucocytes into their five different categories: neutrophils, eosinophils, basophils, lymphocytes and monocytes.

ii. The exploration of a host of deep neural network systems with the use of pre-equipped standards for enhancing the performance of classification.
iii. Dataset acquisition and simulation analysis.
iv. To prove that the suggested approach performs well directly with obtained images and also performs better than previous approaches which require tedious image preparations stages and hand engineering of important features.

1.2 Significance of Study

The different kinds of leucocytes have different functions. Particularly, they depict different pathologic conditions of the patients. Therefore, it is necessary to enumerate and identify the number of the various leucocytes in a blood sample to ascertain whether they are present in their correct proportions. In addition, the various leucocytes after identification can be extracted for in-depth analysis for irregularities. This investigation of white blood cells quantitatively and qualitatively provide much information on the health status of the patient. For instance, this process makes it possible to investigate patients for health conditions like leukemia, immune system irregularities and cancers (Shafique et al., 2018).

Traditionally, identification is performed in a laboratory setting in which the obtained slides of blood cells are stained with special stains or reagents. These are then microscopically examined by specialists. Nonetheless, this procedure is time consuming and subjective to operation errors.

1.3 Overview on the Composition of Blood

Blood is the main body fluid composed of four constituents, which are: plasma, erythrocytes, leucocytes and platelets otherwise known as thrombocytes. Blood is split into main parts: plasma, which makes up about 55% of whole blood and the remaining 45% made of cells. The total contribution by mass of whole blood to the overall body mass is about 8%. The adult human possesses about five litres of blood. The vital functions of blood are the transportation of respiratory gases, notably oxygen and carbon dioxide to and from organs and tissues, the

transport of nutrients, the transport of antibodies to designated sites for fight against infections, transporting waste products of metabolism for detoxification in the liver and kidney, the regulation of human body temperature, the transport of hormones and more.

1.4 Blood Components

Plasma is the straw-colored liquid component of blood which is largely made up of water, about 90%, proteins, sugars, fats and salts such as sodium, potassium, chloride and calcium. Plasma is responsible for the transportation of blood cells and other constituents to all organs of the body. Blood cells such as erythrocytes, leucocytes, cell fragments like thrombocytes, constituents like nutrients, electrolytes, antibodies, vitamins, clotting factors and hormones are borne in plasma. Plasma void of its clotting factors is known as serum (Fathima et al., 2017).

Erythrocytes, otherwise known as red blood cells, they are the commonest of the three kinds of blood cells in the human body. Their main distinction is the absence of a nucleus from the mature cells (anucleate). This morphology renders them more flexible to be able to squeeze through cell-to-cell junctions through a process known as diapedesis. In addition, the absence of a nucleus gives more room for the continence of respiratory gases to and from tissues. This anucleated morphology gives them a biconcave disk shape with a flattened center. These cells bear a protein known as haemoglobin, which is primarily responsible for binding respiratory gases, either oxygen from the lungs as oxyhemoglobin or carbon dioxide as carbaminohemoglobin.

Figure 1.1: Red blood cell (Fathima et al., 2017)

This hemoglobin is also responsible for the red color of blood and is so because of the binding of iron to oxygen. This compound functions as a transport system for the transportation of oxygen from the lungs to body tissues. It also transports the generated carbondioxide from the body tissues as waste back to the lungs for expulsion from the system. The manufacture of erythrocytes is regulated by a hormone known as erythropoietin produced in the kidneys. The mean lifespan of an erythrocyte is 120 days (Fathima et al., 2017).

Leucocytes, also known as white blood cells, they are implicated with the human immune system as they protect the body from foreign invading infections. The manifestation of infection is readily observable from an increase in overall white blood cell count in circulation. They police the body searching for infectious agents.

White blood cells can be further divided into two categories based on the absence or presence of granules in the cells. These are either granulocytes (bearing granules) or agranulocytes (absence of granules). Granulocytes can be further split into three categories: neutrophils, eosinophils and basophils. Agranulocytes are divided into two kinds namely monocytes and lymphocytes.

Granulocytes: Neutrophils are responsible for the destruction of alien bodies particularly bacteria by phagocytosis. Eosinophils are responsible for fighting against infections due to parasitic worms by the release of toxins. The action of basophils is through the release of two chemicals namely histamine which produces allergic reactions and heparin which is an anti-coagulant.

Agranulocytes: The role of monocytes is in the process of phagocytosis as they form macrophages. These are the main white blood cells and are further divided into T lymphocytes and B lymphocytes. T lymphocytes are thymus dependent cells. Their function is through cell mediated immunity and act directly against infected cells and tumors. B lymphocytes are bursa dependent cells and are responsible for humoral immunity. They generate antibodies which target bacteria, viruses and other alien bodies. Lymphocytes are different from other leucocytes in their having the power of memory in the recognition of invading alien bodies.

As previously seen, whole blood comprises red blood cells, white blood cells as well as platelets. The absence of nucleus on red blood cells makes them inappropriate for chromosomal culture. With adequate conditions, white blood cells can be utilized for in vitro (culture) investigations. The objective of a white blood cell culture is the acquisition of an adequate proportion of metaphases to permit the analysis of chromosomes. The differentiated T lymphocytes circulating in peripheral blood do not undergo any further mitosis. As such, white blood cells are cultured in rich culture media (RPMI 1640 containing low thymidine) as well as bovine calf serum (which acts as a natural environment for growing cells). Large quantities of white blood cells enter mitosis is made possible with the use of a mitogen or microprotein known as phytohemaglutinin (PHA). The introduction of PHA results in changes in morphology like the production of RNA and DNA as well as the enlargement of nuclei. These cells are incubated for about three days so as to obtain the maximum mitotic index. At this point, the mitotic index is enhanced by the introduction of colchicine, a mitotic inhibitor. The addition of this into the culture media prohibits the production of mitotic spindle fibres thus suspending the process of mitosis at the metastatic phase. This leads to an accumulation of cells at the metastatic phase of mitosis. These cells are then harvested and exposed to a hypotonic solution of 0.56% KCl. This induces swelling such that the chromosomes are well dispersed and the cells are further exposed to Carnoy's fixative containing a mixture of methanol and acetic acid in a ratio of 3:1.

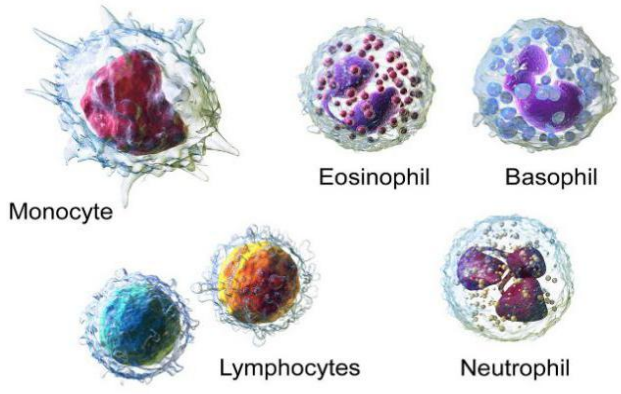

Figure 1.2: Leucocytes (Fathima et al., 2017)

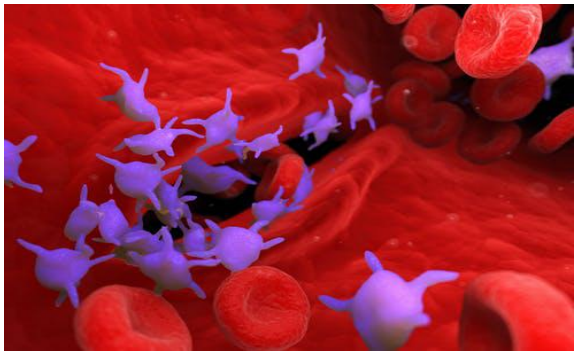

Figure 1.3: Platelets (Fathima et al., 2017)

The harvested white blood cells are placed on chilling slides and stained with Giemsa for an analysis of their chromosomes (Fathima et al., 2017).

Platelets, otherwise known as thrombocytes, are cell fragments without a nucleus. They are produced in the bone marrow by large megakaryocytes. They are implicated with the process of blood clotting through the formation of a platelet plug at the location of injury. This leads to the formation of a clot, which prevents further blood flow from the injury hence enhancing the healing process.

1.5 Applications of blood

Erythrocytes, leucocytes, and thrombocytes are manufactured in the bone marrow prior to their being introduced into peripheral blood. Plasma is greatly constituted of water, which is obtained through absorption from ingested food from the intestines. Circulating blood has a number of applications, which are vital for survival. These include:

- Blood supplies oxygen to body cells and tissues
- It provides required nutrients to cells like glucose, fatty acids and amino acids
- It removes waste from cells and tissues such as carbon dioxide, urea as well as lactic acid

- It protects the body from infectious agents via the action of leucocytes
- It transports hormones from a section of the body to another and as such, transmits signals as well as completes necessary processes
- It regulates acid levels
- It regulates body temperature
- It helps engorge body parts when required such as with penile erection as a natural response to sexual arousal
- Blood protects against infection. Leucocytes protect against infections, alien agents and diseased cells
- Thrombocytes help with blood clotting. In a situation of bleeding, thrombocytes clump together to produce a clot. This proceeds to become a scab which prevents further blood loss and as such prevents further infection of the wound.

1.6 Classification of White Blood Cells

The composition of the white blood cell population provides important information to aid in diagnosis for patients. The engagement in the automatic detection of white blood cells instead of the manual detection is a significant topic in cancer diagnosis. The microscopic differentiation of the white blood cell population is still conducted by hematologists. It is a vital procedure for the diagnosis of cancerous suspicions. Though a reference standard for blood samples with abnormal cells, the procedure is slow, subjective and results have poor reproducibility. As such, the automation of this procedure is necessary for improving the haematological process and enhance the diagnosis of many infections (Soltanian-Zadeh et al., 2009).

The texture, colour, dimensions and morphology of the nucleus and cytoplasm differentiate the different types of white blood cells.

In blood smears, the proportion of erythrocytes is always more than those of leucocytes. An image of about 100 erythrocytes would contain about 1 to 3 leucocytes. In laboratory setting, the main important or significant factors with respect to haematology exams include red blood

cell count, white blood cell count and the detection of blood disorders. The identification, location and counting of these cells is a demanding task. This makes an automated system for such procedures an utmost necessity. Leucocytes have more clinical significance than erythrocytes as they are implicated with a variety of infections. As such, the proper differentiation of these cells is employed for the determination of the presence of an infection in the human body.

The lymphocytes are more common in the lymphatic system. They are unique in their possession of a deep staining nucleus which may be centrally located relative to a very small cytoplasmic space.

Monocytes constitute about 6% leucocyte population and are implicated in human immune system. Their nucleus is kidney-shaped and are granulated. They bear an abundance of cytoplasmic space. Compared to other leucocytes, these live longer. They patrol peripheral blood scouting for bacteria, viruses as well as other waste substances which require removal. Faced with an alien particle, they phagocytize the foreign body. This is then followed by digestion of the foreign body into smaller bits and the presenting these fragments on their cell surfaces for passing T lymphocytes to familiarize themselves with the foreign body and so ease the killing of more of these by the T lymphocytes.

The function of neutrophils is in the defence against bacterial or fungal infections as well as a host of other minute inflammatory reactions, which are typical primary responses to pathogenic infections. Their action and death in extensive proportions form pus. They are typically known as polymorphonuclear (PMN) leucocytes. Their nuclei is multi-lobed which gives an appearance of multiple nuclei. Their cytoplasm may appear transparent as a result of fine grains which appear faintly pink. They are very active in the process of phagocytosis of bacteria and are available in extensive proportions in pus. They do not renew their lysosomes which was used in the digestion of microbes and eventually die after phagocytosis of a few microbes (Hiremath et al., 2010). Differentiation of these leucocytes is important as the accuracy of the subsequent isolation of characteristics and classifying relies on the proper segmentation of leucocytes. One of the challenges involved in the process results from the

complex nature of the cells as well as the uncertainty of the microscopic graphic. As a result, this step stands to be the most significant and crucial step and so improving the segmentation of cells has been a major area of research.

The microscopic investigation of blood slides generates vital information both qualitatively and quantitatively on the presence of hematic pathological infections. Two main analyses are involved in this procedure: the first of these is the qualitative investigation of the morphology of the cells. This provides knowledge of degenerative and tumor infections like leukemia. The second analysis is quantitative. It involves the differential numeration of white blood cell types. The use of automated cell counting systems like laser-dependent cytometers are commercially available but are not morphologically nor image-dependent. More so, blood cells are destroyed in the course of analyses. Furthermore, these cytometers do not permit direct classifying of white blood cells based on morphology such as the differentiation of tumor leucocytes from normal leucocytes (Piuri et al., 2004).

Leucocytes present the main defense against infections in the human body and their specific proportions can aid specialists discriminate the presence or absence of certain kinds of pathologies such as the presence of mononucleosis, hepatitis, diabetes, allergy, arthritis, anemia and so on. The drawback of this manual process in the accuracy of classifying cells and enumeration is subjective. The process of identification and differential enumeration of leucocytes is tedious and the reproducibility of results is poor.

The dissemination of extensive screening programs has placed a demand on the necessity for fully automated non-destructive systems for rapid and accurate analysis of blood samples. Such systems could also be considered a first step to the automated detection or monitoring of blood pathologies like different kinds of leukemia as well as an analysis of the different forms of leucocyte morphology.

1.7 Aim of Study

The purpose of this thesis involved the investigation of the automatic classification of leucocytes with the use of approaches involved with the augmentation of data and deep neural

networks as an alternative for manual laboratory procedures. These proposed novel techniques prove to be rapid, accurate as well as cost effective. Data enhancement approaches are operations which transform images as well as GAN-generated images. These techniques are used to classify leucocytes into neutrophils, eosinophils, basophils, lymphocytes and monocytes. A main advantage of this approach is the absence of specialized and complicated image preparation stage and characterizes engineering prior to classifying.

CHAPTER 2
LITERATURE REVIEW

2.1 Densely Connected Convolutional Networks

The prominent machine learning technique for visually recognizing images or objects is the convolutional neural network (CNN) techniques. Despite the fact that they have been in existence for over two decades (LeCun et al., 1989), it is only in recent years that there has been the enhancement of computer hardware as well as network systems have made possible the equipping of deep convolutional neural networks. The initial LeNet (LeCun et al., 1998). comprised of five layers, VGG comprised nineteen layers, and Highway Networks, as well as Residual networks known as ResNets, have over 100 layers.

With the increase depth of convolutional neural networks, there is a rise of a novel kind of challenge. The flow of information in the input or gradient through multiple layers could lead to the vanishing or washing out of information by the time it gets to the terminus or beginning of the network. A number of research publications have addressed or related to this challenge. ResNets and Highway Networks detour signals from layer to layer through identity links. The presence of stochastic depths (Huang et al., 2016), decrease ResNets. This is done by haphazardly dropping layers in the course of training or equipping to permit much improved information as well as the flow of gradient. FractalNets (Larson et al., 2016), unite multiple sequences of layers in repeat mode with various quantities of convolution blocks so as to achieve an extensive nominal depth while simultaneously ensuring multiple short paths in the network. Despite the fact these various techniques differ in network topology and the procedure of equipping, they all have a fundamental feature in that they generate shortened routes or detours from early layers to subsequent layers.

Exploring network structures has been a component of neural network investigations from the moment of their earliest discovery (Huang et al., 2017). This sector of research has been revived as a result of the increased rise in prominence of neural networks of late. The variations in architectures is amplified by the increasing proportion of layers in recent

networks. This further enhances the desire for exploring the various connection systems and the revisit of former research concepts.

An early such investigation dates back to the 1980s (Fahlman et al., 1989). This early work focused on completely connected multiple layer perceptions equipped in a sequence of layers. In recent times, fully linked cascade networks for equipping with batch gradient descent was suggested (Wilamowski et al., 2010). This approach proved efficient with minimal datasets as it scales to networks having just few hundred features. In investigations conducted by (Yang et al., 2015), it was found that the use of multiple layer characteristics in convolutional neural networks via skip-connections proved effective for different visual applications. Further investigations conducted by (Cortes et al., 2016), derived a conceptual structure for networks with cross layer connectivity.

Among the earliest structures which made it possible to efficiently equip end-to-end networks with over 100 layers was the Highway Networks (Srivastava et al., 2015). With the use of bypass routes coupled with gating units, these Highway networks with several hundred layers could be optimized with ease. The bypass routes are assumed to be vital elements which ease the equipping of the extremely deep neural networks. This fact is further advocated on by ResNets (He et al., 2016). With these, pure identity mappings are utilized as detouring routes. These ResNets have accomplished magnificent, accurate results on numerous hurdles concerned with the recognition of graphics, localization as well as detecting tasks like ImageNet and COCO detection objects.

In recent times, stochastic depths has been suggested as a means for a successful equipping of a 1202-layer ResNet (He et al., 2016). This stochastic depth enhances the equipping of deep residual networks by placing layers haphazardly in the course of equipping. From this, it is obvious that not every layer could be required. It also highlights the intense amount of redundancy in deep residual network architectures. Pre-activated ResNets equally ease the equipping of top quality network architectures with more than a thousand layers (Huang et al., 2016).

A possible approach of increasing the depth of networks such as with the aid of skip connections is by increasing the breadth of the network. GoogleNet utilizes an inception module. This module organizes feature maps generated by filters of various dimensions in a sequential pattern (Szegedy et al., 2015). A derivative of ResNets with broad generalized residual blocks was suggested. It was shown that merely increasing the proportion of filters in every layer of ResNets has the possibility of enhancing the operation so long as the depth is sufficient (Zagoruyko et al., 2016). Fractal Nets were also shown to accomplish satisfactory results on a number of datasets with the use of a broad network structure (Larson et al., 2016).

In place of obtaining representing power from very deep or extensive architectures, DenseNets investigate the possibility of the network via the reusability of features. This generates condensed patterns which are easy to equip and prove effective with respect to parameters. The sequential organization of characteristic-maps equipped by various layers improves differences in the input of other layers and enhances effectiveness. This makes a significant distinction between DenseNets and ResNets. In contrast to Inception network architectures that also organize in a sequential manner, characteristics from various levels, DenseNets have proven to be simpler and more effective. A host of other network architectures have also proven to generate satisfactory results. An example of this is the Network in Network architecture (Lin et al., 2014) which involves multiple micro layer perceptions into filters of convolutional layers to isolate more complicated characteristics. With Deeply Supervised Networks (DSN) (Lee et al., 2015), inside levels are directly monitored by auxiliary classifier this has the possibility of strengthening the gradients obtained from previous layers. Ladder networks are architectures which present lateral connectivity into auto-encoders thereby generating satisfactory and accurate results on semi-monitored training functions (Rasmus et al., 2015).

Deeply fused networks (DFN) were suggested to enhance the flow of information by joining intermediary levels of various base networks. The improvement of networks with routes which reduce reconstruction losses has proven to enhance the classification of image patterns (Zhang et al., 2016).

2.2 Image Segmentation and Classification of White Blood Cells

The enumeration of blood cells is a major sector in bioengineering. With the segmentation of human blood cells, a number of techniques have been investigated and employed for obtaining accurate outcomes (Ravikumar, 2016). In 2013, Tulsani suggested a technique for enumerating various blood cells in the course of a blood smear examination.

The most common form of adult blood cancer in Canada is chronic lymphatic leukemia (CLL). The investigation presented in 2013 by Mohammed and colleagues aimed at decreasing the over segmentation as well as under segmentation of faults of the watershed algorithm by a suppression of 1% of the local minima. Saba and colleagues in 2013 performed an investigation which was aimed at providing a contrasting investigation between artificially equipped and heuristics rule-dependent approaches employed for the recognition of prototypes in top notch technology with focus on the recognition of script pattern. Again in 2013, Mohasenzadeh and colleagues suggested a separable technique in characteristic and sample domains. With the adoption of a Bayesian approach as well as the utilization of Gaussian priors, the equipped model by RSFM is sparse in the sample and characteristics domains. This suggested technique is an extended form of the conventional RVM technique. The standard form only opts for sparseness in the sample sector. Dorini and colleagues in 2013 investigated novel techniques for segmenting the nucleus and cytoplasm of leucocytes. For the segmentation of the nucleus, the graphic pre-processing with SMMT proved to be significant for ensuring the effectiveness of two properly recognized image segmentation approaches known as watershed transform and layer set methods.

In recent times, the Extreme Learning Machine (ELM) for single hidden level feed-forward neural networks (SLFN) has grown in prominence and popularity as a result of its rapid learning speed and improved general operations than those of conventional gradient-dependent learning techniques. A derived learning technique suggested by (Han et al., 203), for overcoming the challenges of ELM utilizes an enhanced particle swarm optimization (PSO) technique for selecting the input weights, hidden discriminations as well as the Moore-Penrose (MP) general inverse for the analytical determination of the output weights. In 2013, Chyzhk

and colleagues conducted the segmenting of clinical pictures following an Active Learning technique which permits rapid interactive segmenting, decreasing the prerequisites for the interference with human faults. The automatic segmenting of white blood cells can aid pharmaceutical firms reach decisions on drugs as well as promote the development of an automatic white blood cell recognition system. In 2013, (Saraswat et al., 2013), suggested a new technique dependent on a differential evolution (DE) technique for the segmentation of white blood cells from pictures of mice skin sections exposed to H&E staining reagent which were gotten from 40× magnification.

The domain of medical imaging is a significant one with respect to techniques of image processing. Notably, the analyses of white blood cells has involved scientists from sectors of medical fields and computer visuals as well. Cueves and colleagues in 2013 suggested a technique for the automatic detection of white blood cells embedded into sophisticated and cluttered smear pictures which takes into consideration the full process as a circle detection challenge.

The aim of the investigation performed by (Mohapatra et al., 2014), was the improvement of the ALL diagnostic accuracy by the analyses of morphological as well as texture-based characteristics from the blood picture with the use of image processing. This study investigated the utilization of picture morphology as well as the recognition of pattern techniques for the sub classification of leukemia lymphoblasts based on the procedure outlined by French American-British classification.

Strzelecki et al. (2013) presented a software tool for the automated classification and segmentation of two-dimensional and three-dimensional clinical pictures. In 2014, Chinnathambi and colleagues suggested a rigid segmentation technique which can separate linked cells. Daniel and colleagues in 2013 identified that the clinical imaging is a significant sector of application of the techniques involved with the processing of images. To overcome these challenges encountered with the conventional methods of identifying white blood cells based on the colored or grey pictures obtained from light microscopy, a microscopy hyper-spectral imaging system was utilized for the analysis of the blood smears. This structure was

developed by (Li and colleagues, 2013). This coupled an acousto-optic tunable filter (AOTF) adaptor to a microscope and powered by an SPF model AOTF regulator that can capture hyper-spectral graphics from 550nm to 1000nm with a resolution of 2 to 5nm.

The process of classifying white blood cells can be performed by automated and manual techniques for the enumeration. As previously noted, the manual classification of white blood cells is prone to much challenges such as inaccuracies resulting from sampling, statistical probabilities, poor sensitivity, poor specificity as well as predictive values. More so, some automated techniques performed in the laboratories utilize tools like flow cytometry as well as automated counting machine for the detection and classification of white blood cells. These tools do not utilize image processing algorithms. They can enumerate and classify white blood cells only quantitatively but not qualitatively. As such, there is the necessity for designing an automated system which involves the processing of images, the processing of signals, the recognition of patterns or deep learning techniques for providing a qualitative as well as quantitative assessment, accurate outcomes and rapid results (Abbas et al., 2018).

Automated classifying of white blood cells comprises six steps as shown in the figure below:

1. The acquisition of the image
2. The pre-processing of the image
3. Segmentation
4. The isolation of characteristics and representations
5. The classification of the cells
6. The assessment

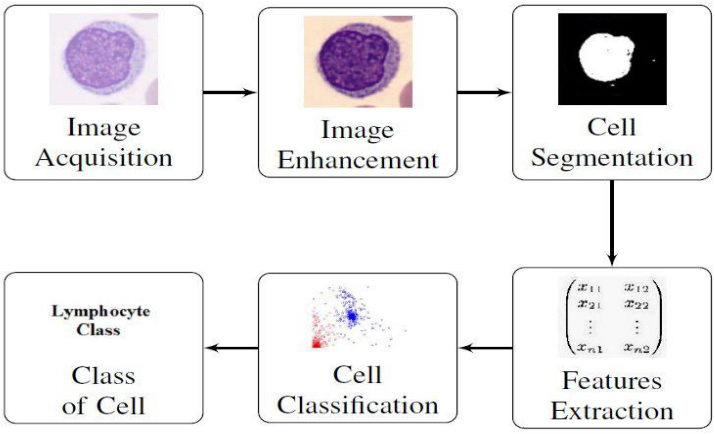

Figure 2.1: Steps of automated classification of white blood cells (Strzelecki et al., 2013)

2.3 Some MachineLearning Approaches

In recent times, deep learning has drawn much attention in computer visual applications as well as clinical imaging applications as a result of its automated and unsupervised and monitored properties in learning algorithms. It works by simulating the structure and performance of the human brain (Voulodimos et al., 2018). It is also widely used in the classification of white blood cells. Nonetheless, it requires an extensive amount of equipped data if to be trained from scratch. Transfer learning prototypes could decrease the equipping, but the approach still functions as a black box lacking proof-based output. More so, the use of deep learning techniques is quite costly as it may involve over a week of high-end graphical processing unit period for equipping.

With respect to the classification of white blood cells, knowledge from the afore-mentioned sector can accomplish highly precise performance with representational proof for the reasoning process. As such, other classifiers like support vector machines, relevance vector machines, classification trees and logistic regression are much suitable for making use of principles obtained from human expertise rather than deep learning. Thus, scientist tend to utilize the processing of signals and machine learning approaches in white blood cell classification with respect to segmentation and the isolation of characteristics for resolving

challenges involved with classification of white blood cells. For instance, studies conducted by (Al-Dulaimi et al., 2018), proposed a method for the classification of white blood cells into 10 classes based on bispectrality invariant features and support vector machines with classification tree. These bi-spectral invariant features are isolated based on the shape of the segmented white blood cell nucleus for dealing with intra-class differences of staining, shape cellular illumination as well as topology.

Studies conducted by (Al-Dulaimi et al., 2018), propose a novel technique for the classification of white blood cells which aims at increasing the robustness for taking into consideration the complexity, compactness and effectiveness. This suggested technique is utilized on L-moments (L-skweness, L-mean, L-scale and L-kurtosis) of the Radon projected input picture. This is coupled with the Linear Discriminant Analysis (LDA). The white blood cells are classified into ten classes with the use of support vector machines and classification tree.

Regardless of the extensive amount of research, the automated classification of white blood cells with respect to segmentation and the representations of characteristics still has several challenges and neither of the proposed techniques cover all challenges simultaneously. A full or complete blood cell (CBC) enumeration is a relevant exam frequently required by medical personnel for evaluating the health status of a patient. Since these blood cells are quite numerous in number, conventional methods of counting them with the traditional hemocytometer is extremely time consuming and tedious, liable to human errors and vastly depends on the professional skills of the operator. As such, an automatic procedure for enumerating these various blood cells from a blood smear image would ease the entire enumerating procedure (Alam et al., 2018).

The accuracy of the classification of images and the recognition of objects has increased in recent years since the advent and introduction of machine learning techniques. For this reason, machine learning techniques have a wide variety of applications across many different fields. Of notable significance of this is the application of machine learning techniques in many clinical tasks such as the detection of irregularities and the localization of characteristics in

chest X-ray examinations. Some others also include the automated segmentation of the left ventricle in heart magnetic resonance imaging, as well as the detecting of diabetic retinopathy in images of the retina fundus. As such, there is therefore the necessity of looking into the possible applications of deep learning techniques which can be possibly applied to the enumeration of blood cells in smear pictures.

Several deep learning techniques have been suggested based on the counting of blood cells. A method based on the detection of objects by deep learning for the detection of various blood cells was suggested by (Mohammad et al., 2018). In this study, taking into consideration prominent object detection techniques like regions with convolutional neural networks (RCNN), you only look once (YOLO), the YOLO algorithm was chosen due to the fact that it is about thrice faster than RCNN with VGG-16 algorithm. The YOLO algorithm utilizes a unique neural network for the prediction of bounding boxes and class probabilities directly from the complete image in a single evaluation. YOLO was retrained to autonomously recognize and enumerate red blood cells, white blood cells and platelets from blood smear pictures. For the improvement of the accuracy of the performance, an authentication method was developed for preventing repeat counts by the algorithm (Alam et al., 2018).

More so, the equipped algorithm was evaluated with pictures from a different dataset for the purpose of observing the generalization of the technique. The figure below demonstrates the suggested deep learning technique for the identification of the various blood cells as well as their counting.

On a general basis, two distinct approaches exist for the automatic enumeration of the blood cells. These are the image processing approach and the machine learning approach.

An image processing approach was suggested by (Acharya et al., 2018) for the counting of erythrocytes. In this method, the blood smear picture was processed to count erythrocytes as well as the recognition of normal and abnormal cells. They utilized the K-medoids technique for the isolation of white blood cells from the graphic and granulometric analysis for the separation of red blood cells from white blood cells. This was then followed by the counting of cells with the use of labelling algorithm as well as a circular Hough Transform (CHT).

A study conducted by (Sarrafzadeh and colleagues, 2015), suggested a circlet transform for the enumeration of erythrocytes on the greyscale picture. They utilized iterative soft-thresholding technique for identifying and enumerating the cells. A method presented by (Kaur et al., 2016), based on the automatic counting of platelets from the circular Hough Transform in a microscopic blood cell picture. They utilized the dimension and shape characteristics from the circular Hough Transform in the enumeration procedure.

Cruz and colleagues (2017), suggested a technique based on the processing of images for the enumeration of blood cells. They utilized hues, saturation, value thresholding technique as well as the constituent labelling for identifying and enumerating blood cells. A method proposed by (Acharjee and colleagues, 2016), based on semi-automatic process by the application of Hough Transform for counting erythrocytes by the detection of their oval and biconcave shape. (Lou and colleagues, 2016), suggested a technique for the automatic detection of and classification of white blood cells with the use of spectral angle imaging as well as support vector machine.

Zhao and colleagues (2017), suggested an automated identification and classification method for white blood cells with the use of convolutional neural network. Primarily, the white blood cells were detected from the microscopic images and then convolutional neural networks was utilized for the detection of various kinds of white blood cells.

Habibzadeh and colleagues (2013), proposed a system for the classification of five different kinds of white blood cells in which they utilized classifiers which involved two distinct kinds of support vector machines and one convolutional neural network classifier. They utilized previously trained convolutional neural networks, ResNets and Inception Net for the enumeration of white blood cells from segmented pictures. The pictures were segmented and employed color space analysis.

Xu and colleagues (2017), used a patch size normalization on previously processed pictures and then employed convolutional neural networks for the classification of red blood cell shapes from microscopy images of subjects of sickle cell disease.

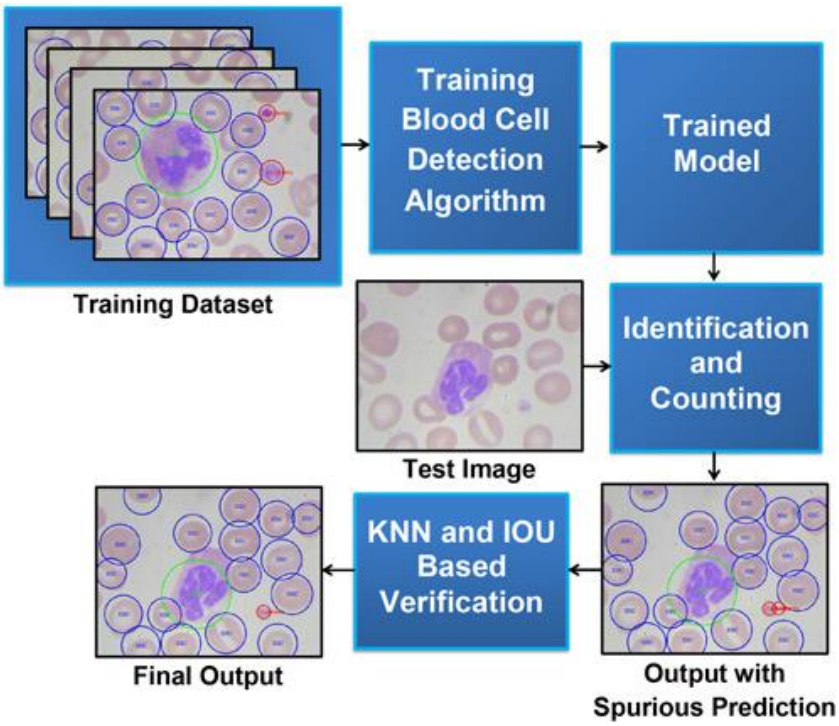

Figure 2.2: Block diagram for the automated detection and counting of blood cells (Voulodimos et al., 2018)

The suggested technique utilizes the YOLO for the detection of all three kinds of blood cells at the same time. This method does not require greyscale conversion or binary segmenting. This process was proven to be fully automated, rapid and accurate.

The conventional practice in medical practice involves the microscopy exam of peripheral blood which contributes significantly in diagnosis and monitoring of infections. This act makes it possible to discern relevant morphologic characteristics of hematopoietic cells as well as irregular white blood cells in lymphoma, leukemia, dysplasia and other infections. As with the majority of manual practices which rely on visual inspection with limitations in quality control and economic scalability, the preparation of blood smear techniques and interpretation are subject to observer discrimination, slide distribution faults, data sampling faults, clerical faults, laboriously intensive and the need for intensive skills.

Conventionally, much research has been conducted for automating the processes involved with geometric differential enumeration.

These automated processes often accomplish satisfactory results but rely on segmentation accuracies and the effectiveness of the traits. The ineffectiveness of one step in the process would affect the entire process.

Dan and colleagues (2019), characterized white blood cells with local features. In this investigation, three detectors were used; scale invariant feature transform (SIFT), oriented features from accelerated segment text (OFAST) and center surround extrema (CenSurE). These were employed for the acquisition of significant aspects such that these local features could represent the five white blood cell types. However, the accuracy of the procedure was unsatisfactory particularly for eosinophils and basophils.

Deep learning techniques for the classification of white blood cells have shown satisfactory results in different visual applications such as the classification of clinical pictures, the detection of objects and semantic segmentation. The principle of these deep learning techniques is that the process of isolation of characteristics is not designed by human engineers but is learned from information which utilizes a broad-purpose learning algorithm.

Convolutional neural networks provide satisfactory results with respect to the analysis of images and so are increasingly employed in applications involving the recognition of and classification of white blood cells. Investigations conducted by (Zhao et al., 2016), proposed a technique for the autonomous detection and classification of white blood cells from peripheral blood smear images. White blood cells were identified with respect to the location of the nucleus. The convolutional neural network system was designed with five convolution layers and two pooling layers for the isolation of characteristics in high level. This algorithm provided a possibility of dealing with the challenge of recognizing white blood cells by a combination of detection and classification of white blood cells. The white blood cells identified were of five different types and the precision for the identification of eosinophils and lymphocytes had to be improved on as they generated an accuracy of 70% and 74.8% respectively.

A study conducted by (Shahin et al., 2019), suggested a technique which utilizes convolutional neural network architecture for the recognition and classification of five mature white blood cells. This study accomplished a classification accuracy superior to that of the conventional or traditional approaches for the identification of white blood cells.

Choi et al. (2017) engaged an automatic differential counting process for white blood cells with the use of a dual phase convolutional neural network. This dual phase convolutional neural network system categorized pictures into ten kinds of myeloid and erythoid maturation stages. This investigation accomplished very satisfactory performance.

Based on deep residual learning concept and clinical domain knowledge, Qin and colleagues in 2018, suggested a fine granulated white blood cell classification technique for microscopy pictures. The suggested deep residual neural network was assessed on microscopy image data set with forty groups of white blood cells and obtained satisfactory results. This studies provided information on the research object which spanned from five types of peripheral blood to ten or forty kinds of bone marrow specimen. Also the quantity of training group ranged from 2174 to about 92480 pictures.

Despite the fact that deep convolutional neural networks and the conventional traditional machine learning techniques have demonstrated satisfactory outcomes in the classification of white blood cell pictures, they are limited with respect to exploiting the long term reliance between some vital characteristics of pictures and image annotations. In a bid to resolve this limitation, a convolutional neural network-recursive neural network (CNN-RNN) architecture was designed to improve the understanding of picture content and train the structured characteristics of the image.

Many of the afore-mentioned techniques were designed from the viewpoint of the classification of images. This involves the recognition of white blood cell as a classification function. This procedure necessitates that there be the availability of object samples in the input picture by segmentation. Also the number of objects do not exceed one by cropping the image manually or sophisticated segmentation step. These techniques are frequently aimed at

the recognition of five kinds of mature white blood cells that are frequent observed in circulating blood.

A major challenging task in computer visual systems is the generic detection of objects which is aimed at the localization of object instances from a wide array of predefined classes in images. Nonetheless, regardless of the possibilities presented by this automated architecture, the improvement of the techniques with regards to this challenge is still an ongoing challenge.

As a result, studies conducted by (Wang et al., 2019), deals with the recognition of white blood cells of multiple images from the standpoint of detecting objects instead of classifying images with the intent of appropriately differentiating the kind of white blood cells and its location in the image obtained directly from the microscope.

Two instituted series are available as representations of deep learning techniques:

- Two-phase detection architecture: it involves a pre-processing step for region proposal which makes the overall pipeline a two-stage system.
- One-phase detection architecture: it involves a region proposal free architecture which does not differentiate detection proposals thus makes the overall pipeline a one stage system with end to end.

The frequent structures for the two-phase pipeline include regions with convolutional neural network, spatial pyramid pooling in deep convolutional neural network, fast R-CNN, faster RCNN. Region-dependent fully convolutional neural network and mask RCNN.

Frequent architectures for one stage pipeline include DetectorNet, MultiBox, OverFeat, You Only Look Once (YOLO), YOLOv2, YOLOv3 and single shot multibox detector (SSD) of the afore-mentioned channels for the detection of objects, SSD is relatively fast and robust to overcome differences due to the fact that it employs multiple convolution layers and joins all prognostications from multiple characteristic maps with various resolutions for the detection of objects.

YOLO is a unified detector which casts the detection of objects as a regression challenge from graphic pixels to spatially separated bounding boxes as well as connected category possibilities. The improved versions of YOLO, namely YOLOv3 operates faster than the other detection techniques with contrasting performance. YOLOv3 stands out with respect to the accuracy of detection and computational speed.

Studies conducted by (Liang and colleagues, 2018), involved the treatment of urinary object recognition as the object detection and employed faster RCNN and SSD techniques together with their derivatives for the recognition of urinary objects. The satisfactory results gotten from this investigation inspired the study of (Wang et al., 2019), research for considering the recognition of white blood cells as the particle detection task and then exploiting two familiar convolutional neural network dependent detection techniques, SSD and YOLOv3 for the detection of white blood cells.

In adopting these techniques for the recognition of white blood cells, the mechanism of deep transfer learning was adopted which involved fine regulating of corresponding pre-equipped models and not necessarily developing them from scratch.

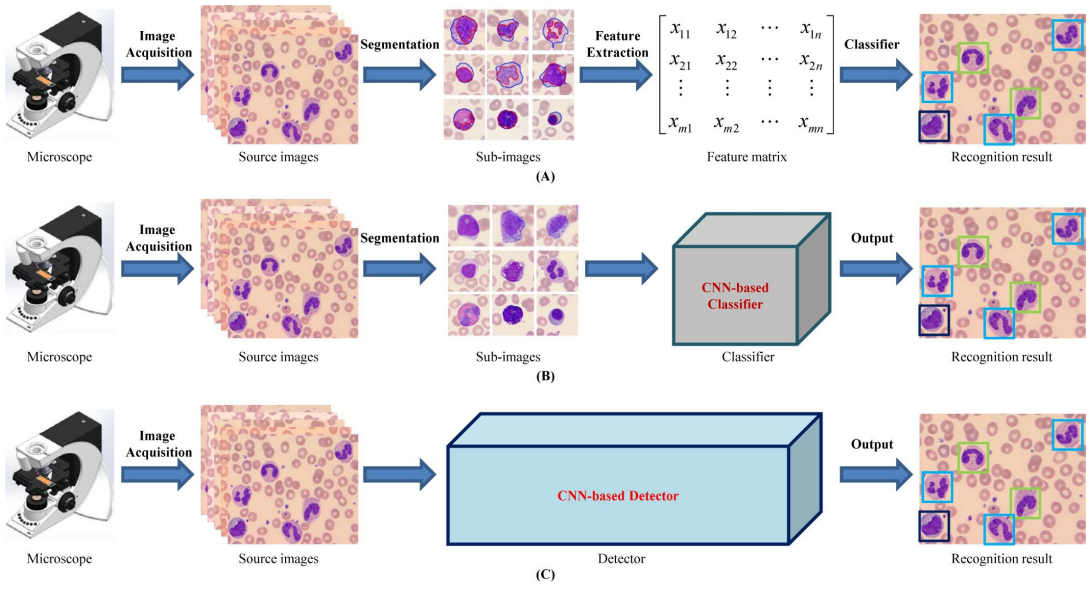

Figure 2.3: Channels of white blood cell recognition in peripheral blood circulation (A) treat leukocyte recognition as traditional feature engineering: segmentation, feature extraction & selection by manual and then classifier based on the feature matrix;

(B) treat leukocyte recognition as object classification: get patches containing leukocyte candidates from original image by manual or segmentation approaches, and then feed these patches into CNN-based deep learning classifier to output the leukocyte types; (C) treat leukocyte recognition as object detection: feed the original images into CNN based deep learning detector, and then output the leukocyte types and the corresponding locations (Liang et al., 2018)

2.4 Applications of Ensemble Artificial Neural Network for the Classification of White Blood Cells

The human immune system protects the body from a large number of pathogens like microbes, infections, parasites by recognizing and expelling them. White blood cells are manufactures from a multi-potent cell in the bone marrow that is responsible for acquired immunity, by generating antibodies and terminating diseased or malignant cells (Bain et al., 2016).

Abnormalities of blood cells are known as hematological disorders. There are many of these and some of them include: acute or chronic leukemia, inflammation, AIDS, thrombocytopenia, polycythemia. These disorders can influence the numbers as well as the effectiveness of these blood cells of the immune system. For the acquisition of optimum information from a blood cell, the operator conducts skilled analysis. The visual assessment or analysis of blood cells by humans is tedious and liable to errors. This is because it largely depends on the skills of the operator. As such, a computer assisted system for such identification and classification is necessary for the reduction of all such inconveniences. A few automated blood cell analyzers are commercially available. These assess the quantities of different cells in the blood smear. Laser based instruments such as the flow cytometry is used to assess the physical characteristics and the complicated characteristics of the blood cell.

These are expensive, requiring high maintenance as well as the need for actual real time blood specimens. As such, in an effort for reducing these concerns, much research have been going on for the invention of devices for the assessment of white blood cells which employ image processing techniques. A number of these techniques have been used for the segmentation of

white blood cells. But only few techniques have been developed for the segmentation of white blood cell images and this is as a result of their intrinsic structural morphology.

The use of image processing methods for the enumeration of blood cells in peripheral blood provides information on the cell morphology. These techniques require only a cell image and is cost effective compared to the laser-based methods (Putzu, 2016). A computer assisted classifying system is necessary for aiding operators diagnose infections or hematological disorders. The use of computer aided techniques results to the improvement of diagnostic potential by a reduction of human faults. The development of a computer assisted structure for the characterization of diverse classes of white blood cells is tedious as a result of the variety of obtained smear pictures with different noises and outliers. As such the benefit of visual smear evaluations integrate the recognition of irregularities in blood smears in an efficient and rapid manner (Rawat et al., 2017).

The human peripheral blood is replete with mature white blood cells which can either be granulocytes or agranulocytes. This classification is based on the nuclear morphology as well as the presence or absence of cytoplasmic granules. Based on the size and condition of nucleus, the cytoplasm staining color as well as by the ratio of nucleus to cytoplasm, white blood cells can be classed into neutrophils, eosinophils, monocytes, lymphocytes or basophils.

In studies conducted by (Rawat et., 2018), a novel automated classification and ensemble neural network-dependent classification system is suggested for the recognition of four types of white blood cells in microscopic blood images. The technique applies one or more neural processes to the input pictures directly and monitoring their outcomes. Every network is equipped to generate the closeness or lack of a nucleus. More so, the technique was suggested to be general with very little pre-processing for white blood cells. The outcomes are compared with the traditional and conventional results obtained by the hematology examiner. The suggested technique proved more efficient than the conventional approach. The set up for the white blood cell classification is shown by the figure below.

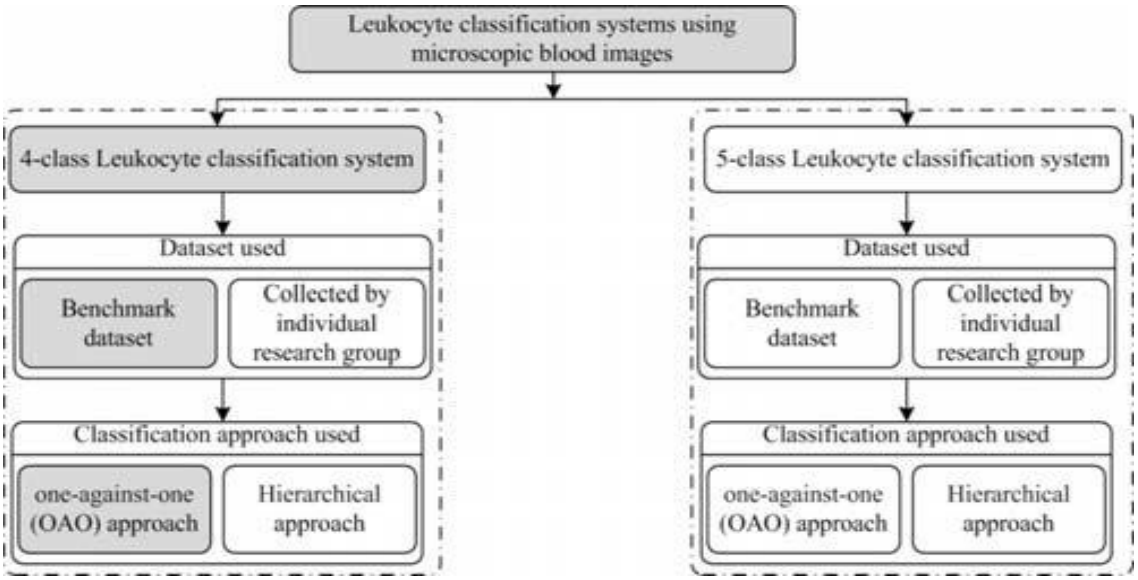

Figure 2.4: the classification structure for white blood cell (Rawat et., 2018)

Many studies have shown that the classification of white blood cells can be done on the premise of two classes:

- A 5-class classification problem
- A 4-class classification problem

Table 2.1: A detailed depiction of studies did on leukocyte classification

Considered class	**Authors and year**	**Isolated features**	**Classifier used**	**Images**	**Accuracy (%)**
5-class	Pang et al. (2015)	TFV	SVM	298	95.5
Neutrophils	Ravikumar and	SFV, TFV	RVM	85	91.0
Eosinophils	Shanmugam (2015)				
Basophils	Nazlibilek et al. (2014)	SFV, TFV	ANN	240	95.0
Monocytes	Habibzadeh et al.	SFV,TFV,CFV	SVM	140	84.0
Lymphocytes	(2013)				
	Rezatofighi et al.	SFV, CFV	ANN	400	96.8
	(2010)				

Table 2.1: A detailed depiction of studies did on leukocyte classification (Cntinued)

	Ramesh et al. (2012)	SFV, CFV	LDA	1983	93.9
	Rezatofighi and Soltanian-Zadeh (2011)	TFV	SVM	90	93.0
	Xie et al. (2010)	SFV	ANN	230	89.6
	Ghosh et al. (2010)	SFV	Naive Bayes	150	83.2
	Rodrigues et al. (2008)	SFV, TFV	SVM	241	85.4
	Bacusember and Gose (1972)	SFV,TFV,CFV	MGC	523	93.0
	Young (1972)	SFV, CFV	DT	74	92.4
4-class	Sabino et al. (2004)	TFV	SVM	50	97.0
Eosinophils	Sarrafzadeh et al. (2014)	SFV,TFV, CFV	SVM	149	97.7
Polymorphs					
Monocytes	Tabrizi et al. (2010)	SFV, TFV, CFV	SVM	302	97.0
Lymphocytes					
	Stadelmann and Spiridonov (2012)	SFV, TFV, CFV	AdaBoost	461	91.3
	Suapang and Chivaprecha (2015)	SFV, TFV, CFV	ANN	134	88.1
	Mircic and Jorgovanović (2006)	SFV	ANN	200	86.0
	Ferri et al. 1994	SFV	KNN	45	80.0

Notes: SFV: shape feature vector, TFV: texture feature vector, CFV: chromatic texture feature vector, MGC: multivariate Gaussian classifier, DT: decision tree.

From previous investigations, it is observed that the greatest characterization accuracy for the 5-class challenge is 97.7% and that for the 4-class challenge is 97.0%.

Studies conducted by (Rezatofighi and colleagues, 2010), for the 5-class white blood cells classification generated a 97.8% precision by neural network classifier and isolating chromatic and shape characteristics. For the 4-class leucocyte classification system conducted by (Sabino et al., 2004), a 97.0% accuracy was generated by the application of support vector machine classifier with statistical characteristics.

In investigations conducted by (Rawat et al., 2018), a 4-class white blood cell classification algorithm is directly compared to that of (Sabino et al., 2004). Textual characteristics are isolated and support vector machine is employed for the segregation of the four classes of white blood cells. This investigation presents a white blood cell classification system which has the possibility of segmenting the nucleus and file them into a leucocyte class subsequently. The k-means technique was used for the localization of the nucleus. This was then followed by textual characteristics (stastical texture characteristics, transfer domain dependent traits as well as signal processing dependent textual traits), characteristics based on shape as well as for color are isolated from the segmented nucleus for representing the difference between various white blood cells.

2.5 Segmentation and Classification of White Blood Cells

The development of automatic cell counters have transformed the arduous task of human subjects to automatic systems. But like every other system, it has its own drawbacks.

According to research conducted by (Bikhet et al., 2000), the aim was the recognition and classification of various kinds of normal leucocytes. With the analysis of blood specimens, examiners seek to identify three different types of cells: red blood cells, white blood cells and platelets. These three kinds are distinct from each other by dimensions and color. This study made use of grey level pictures because leucocytes appear darker than red blood cells and

platelets. With respect to dimensions, blood platelets are the tiniest whereas white blood cells are the largest.

A common challenge with respect to the acquisition of accurate identification and classification of cells is the differentiation of white blood cells from red blood cells, platelets and cell fragments. As a result, special techniques are developed for the separation of these white blood cells. The picture is primarily improved with the use of a medium filter. This is then thresholded to segregate the cells from the background. The classification of white blood cells depends on the recognition of cell nuclei with the use of syntactic analysis of the interior portion of the cell. The investigation further integrated the cell protoplasm characteristics into the classification process. This is accomplished by the identification and isolation of the various building blocks or components of the cell nucleus. Based on the number of blocks, the shape of each block, the dimension of the block, the association between the blocks and the dimension of then protoplasm, the cells can be differentiated into different classes which match the usual medical classification. The technique as well as the extracted traits were assessed and generated an adequate classification rate greater than 90%. Research is being undertaken for the development of a completely automatic system in which outcomes are formatted and presented on a high definition color screen.

Many scholars have suggested techniques for classifying and differentiating white blood cells. Ingram and colleagues (1970), suggested a technique for the identification of white blood cells dependent on the transformation of highly recursive picture, and this is known as Golay pattern transforms. These transforms generate information on such traits of the nucleus of the cell like area, dimensions as well as structure. Despite the fine accuracy of their technique, it is relatively slower in conducting the differential counting.

A technique was also suggested by (Young, 1972) which utilizes a cascade process dependent on the color of red blood cells to localize white blood cells in the visual field. The analyses of statistics on a group of 74 equipping groups generated a four-dimensional trait vector.

Monici and colleagues developed a technique while working with a group of white blood cells with known fluorescent properties, studied in suspension as well as on individual cells at

microscopic examinations. Lymphocytes, monocytes, neutrophils and eosinophils were differentiated based on the intensity and spectral shape of the automatic fluorescence radiation in the visible range from 440 to 580nm.

2.6 Automated White Blood Cell Classification Processes

The levels involved with the automated classification of white blood cells are:

2.6.1 Image acquisition

This is the initial phase of the classification process. This involves the input of images of white blood cells obtained from peripheral blood smear samples onto microscope slides. These pictures are acquired by placing the slides on the stage of a compound microscope or optical microscope subject to illumination levels with sufficient magnification as well as recording them with the use of a digital camera. The analyses with the microscope begins with the lower magnification powers to higher powers (10x to 1000x). A digital camera is utilized for the purpose of capturing images for demonstrating, enhancing and observing of blood cell. In some instances, digital cameras can be utilized separate of the microscope. These pictures are then stored on memory cards and downloaded into computers as 24-bitmap images or joint photographic experts group (jpeg) images or as videos (Abbas et al., 2018).

With some commercial cameras, there is need for supplemental optics to ensure connectivity to the microscope. The results are not always of good quality. Single lens reflex cameras can be linked to microscopes with the use of single lens reflex adapters which are available on many microscopes from which pictures can be introduced onto computers automatically.

Microscopy pictures of cells are acquired following staining which results in various coloration of the cell nucleus and protoplasm as well as the blood picture background. The technique of staining white blood cells is one which is utilized to improve contrast via changing the coloration of some components of the cell structure which permits a clearer visualization of cell components.

A number of these microscopy stains exist which can be utilized and the generic name of these stains is known as Romanowsky stains. The Romanowsky stain utilizes a solution of

methylene blue for the detection of malarial parasites in peripheral blood (Carleton, 1980). Examples of these kinds of stain include Jenner, Nocht, Leishman, Giemsa, Wright-Giemsa stain and Leishman stains. The stains in this category which are utilized for staining white blood cells include Giemsa stain, Wright stainm, Wright-Giemsa stain and the Leishmann stain. They are accurately formulated and perform optimally as well as predictably when utilized manually or in automated processes. The majority of these stains color the nucleus dark purple or pink. The stains may also reveal the granules in protoplasm of some white blood cells. The process of staining generates enough contrast for the process segmenting, enumeration as well as classification of individual cells. Pictures are then acquired with the use of various digital cameras with varied resolution powers.

2.6.2 The pre-processing phase

This is involved with the enhancement or improvement of the image data which overcomes unwanted distortions, removal of noise or the enhancement of some characteristics necessary for subsequent assessment in segmentation and classification phases. This phase also involves geometric variations of graphics like rotation, scaling and translation.

2.6.3 Segmentation

This phase is involved with the detection of white blood cells as well as their nuclei and cytoplasm. It differentiates them from red blood cells, background and plasma of peripheral blood smear pictures with the use of graphic processing as well as techniques of processing signals. The performance of these techniques are based on shape, color, edges and geometry for segmentation. A number of techniques have been suggested and combined with other strategies for the detection and segmentation of white blood cells. These strategies include thresholding techniques, operations on morphology, scale-space assessmemnts, the detection of edges and boundaries and phase set methods through geometric active contour (GACs). Some current techniques include color space like RGB, CMYK as well as HSV with Otsu threshold (Safuan et al., 2017).

2.6.4 Isolation of characteristics

This is a significant phase in the process of segmenting and classifying white blood cells. Characteristics which are isolated include geometric traits like area, radius, perimeter, convex area, major axis length, compactness and orientation. It also involves the isolation of textual traits like momentum, contrast, entropy and skew. Other isolated traits involve color features like the distribution of color and histogram.

2.6.5 Classification

This phase differentiates the different kinds of white blood cells. The process permits for the assessment and diagnosis of numerous infections. Various modern machine learning techniques are utilized for the classification of white blood cells. Some of these include random forest, support vector machines, deep learning techniques such as artificial neural networks, multiple layer perceptions as well as hyper-rectangular composite neural networks (Bishop, 2006). Nonetheless, support vector machine classifiers are the prominent methods for classifying white blood cells as a result of fast performance.

2.6.6 Evaluation

This is performed with the use of a numeric metric like accuracy; or a graphical representation of the performance like Receiver Operating Characteristic (ROC) graph. Accuracy is the most prominent assessment for performance and represents the degree of the total number of predictions phases that can be correctly classified and contrasts this to the actual class. Thepredictions are computed for the creation of a confusion matrix:

- True positives (TP): these are samples which have been properly categorized as positives
- True Negatives (TN): these are samples which have been correctly categorized as negatives
- False positives (FP): these are samples which have been wrongly categorized as positives

- False negatives (FN): these are sample which have been wrongly categorized as negatives

The above parameters can be gotten by the use of testing and equipping algorithms dependent on Hold-out method, K-fold cross validation and Leave-one-out cross validation techniques.

2.7 Application of WBC Classification

Two main elements which affect the accuracy of the classification procedure are the segmentation of white blood cells and the represented characteristics utilized. These characteristics ought to bear significant information but at the same time be robust to intra-class differences, cell morphology, and nucleus, stage of maturity, background, color, dimensions, location and non-uniform lighting.

Representations of isolated characteristics have been adopted with various machine learning methods for the classification of white blood cells into five different kinds as previously seen.

A suggested approach for the classification of white blood cells into neutrophils, eosinophils, lymphocytes and monocytes is based on the Beckman-Coulter Corporation provided by information on flow cytometry. The classifier utilized for this procedure was the support vector machine which grouped parametric information in a multi-dimensional section (Adjouadi et al., 2005). The outcome of this investigation proved that the accuracy of the classification process is dependent on the sample size of available data utilized for the process. As such, for a data set of 100 images, a classification accuracy of 86.6% was achieved. This method however has a number of disadvantages, some of which include:

- It requires intensive computational skills
- For the purpose of narrowing the misclassification ratio that is associated to different classes of information, there is the need for increased convergence rate
- Flow cytometry processes cannot generate pictures of white blood cells for subsequent evaluation of pictures as well as the authentication should there exist intra-class variations with respect to staining, morphology, lighting or overlapping of cells.

Another technique was proposed by (Ghosh et al., 2010), for the classification of white blood cells into five kinds. This investigation utilized T-test and kernel density applications for the acquisition of geometric characteristics from images of segmented white blood cells. A Naïve Bayes classifier was employed for assessing and training the system. Four statistical characteristics ensured the generation of satisfactory results during the process of classification. This investigation experienced a few drawbacks such as the faults which were generated in the course of isolating geometric characteristics as a result of the utilization of pictures with varied orientation of nuclei, shapes, dimension as well as phase of maturity. As such, the observed accuracy for the classification process was 83.2% with a sample size of 150 pictures.

In investigations conducted by (Rezatofighi et al., 2011), a local binary pattern (LBP) approach was utilized for obtaining the morphological and textual characteristics. These characteristics were employed for grouping the white blood cells into five different forms. Support vector machines and artificial neural networks were the employed classifiers used for equipping and testing the system. The outcomes of the experiment with the use of support vector machine as classifier and generated an accuracy of 86.10% outperformed that for the artificial neural network classifier. Experimental errors were encountered at the stage of isolation of features and were based typically on the variations in shapes of the cells rather than on nuclei. The errors also involved the variations of the phases of cell maturity and overlapping.

A method for the classification and numeration of white blood cells was again suggested by (Habibzadeh et al., 2013). This involved the classification and counting of white blood cells from microscopic pictures with the utilization of two groups of characteristics:

- An initial characteristic vector including shape, intensity as well as texture
- Invariant characteristics of the structure of white blood cells as well as shifting, rotation and magnification acquired with the use of a Dual-Tree Complex Wavelength Transform (DTCWT).

The classifier utilized for grouping these characteristics of white blood cells into five different groups. Nonetheless, the outcomes demonstrated that faults were as result of the poor quality

of samples and reduced resolution. The accuracy of the white blood cell classification which employed the linear support vector machine was 84%. In contrast, the accuracy was 76% for the support vector machine classifier which utilized the dimensional reduction kernel principal component analysis (KPCA).

Studies conducted by (Su et al., 2014), presented a suggestion for the classification of white blood cells into five different classes with the use of characteristics based on geometry, color as well as texture. A local directional pattern (LDP) approach was suggested for the extraction of texture characteristics. The local directional pattern technique has tolerance against changes in lighting as well as includes direction for every pixel in the picture. The system isolated twenty characteristics and engaged three various types of classifiers; multilayer perception (MLP), support vector machine (SVM) and hierarchical convolution neural network (HCNN). The operation between all three was contrasted and the results proved that multilayer perception classifiers have greater performance than those of support vector machines and hierarchical convolution neural networks. As a result of incorrect segmentation, some cells were however wrongly classified.

In investigations conducted by (Schneider et al., 2015), a flow cytometer dataset was utilized for differentiating between three kinds of white blood cells; granulocytes, lymphocytes and monocytes. The information comprises three significant functions of white blood cells as well as asserting a microfluidic flow in a narrow canal, microscope imaging and sorting. An optical neural network was utilized for the classification of these white blood cells and the approach generated an accuracy of 89%. Nonetheless, faults were due to cells like monocytes which were insufficiently represented in the sample.

An approach proposed by (Ravikumar et al., 2016), utilized the conventional extreme learning machine (ELM) techniques and fast relevance vector machine (Fast RVM) for the classification of white blood cells into five different categories. The extreme learning machine approach was employed for the segmentation of the cell and then the creation of biased characteristics based on a threshold technique. Extreme learning machine and fast relevance vector machine classifiers were employed for the equipping and assessment of the system. The

outcomes prove that the fast relevance vector machine classifier yielded better results than the extreme learning machines classifier and generated an accuracy of 80%.

A technique which involved the detecting and classifying of white blood cells from peripheral blood pictures was proposed by (Zhao et al., 2017). White blood cells were identified from microscopy pictures with the use of the association of red and blue colors, as well as by morphological characteristics. A characteristic based on granularity was utilized with the support vector machine classifier for the classification of basophils and eosinophils from other white blood cells. Subsequently, a convolution neural network was employed for the isolation of traits in high level from the white blood cells. For the purpose of classification, a random forest was employed for the recognition of other forms of white blood cells namely the lymphocytes, monocytes and neutrophils. The accuracy of this technique was 92.6%. The drawback of this technique resulted from the fact that some cells were incorrectly classified.

Studies conducted by (Habibzadeh et al., 2017), involved the use of a monitored technique for classifying white blood cells based on hierarchical topological isolation of characteristics with the use of inception and ResNet structures as well as subsequent deep learning framework for the process of classification.

A number of techniques involved with the classification of white blood cells have encountered a number of challenges involving aspects such as time complexity, poor or insufficient recognition of cells, poor quality of the sample pictures, as well as limited size of the data base. More so, some techniques utilized flow cytometry data which are limited in the fact that they cannot generate pictures of white blood cells for subsequent assessment of images and authentication should there be intra-class differences with respect to staining, shape lighting and overlapping of cells.

2.8 Use of Convolutional Neural Network Optimized Through Genetic Algorithm

The recognition of pictures is one of the significant patterns for the significance of artificial intelligence. Deep learning techniques permit for computational models which comprise

multiple processing levels for equipping data characteristics with numerous levels of abstraction. These deep learning techniques have enhanced top quality speech identification, the visual recognition of objects and more (LeCun et al., 2015). A type of these deep learning techniques is the convolution neural networks which have introduced much in the processing of pictures, videos, speech as well as audio.

The identification of images is employed for numerous tasks. They are employed for safety purposes like facial recognition. They are fundamental in self-driven vehicles. They are abundantly applied in medical tasks such as the diagnosis of infections, the identification of infectious agents as they ease the reduction of costs and time for the analysis of laboratory samples. The techniques of convolutional neural networks are prominent in the majority of recognition and detection applications and functions and even in human performance of some functions (Bani-Hani et al., 2018).

With the possibility of scanning and loading clinical pictures into computers, scientists have developed architectures for the automated analyses of samples. From the 1970s till the mid-1990s, the assessment of clinical images was performed through a cascade of applications of low-level processing of pixels which involved edge and line detector filters and region growing as well as computational modeling which involved fitting lines, circles and eclipses for the construction of compound rule-dependent systems for particular applications (Litjens et al., 2017).

Towards the end of the 1990s, applications of machine learning have increasingly gained prominence in medical applications with respect to the classification of pictures. This has brought about a complete shift from human designed systems to computer assisted systems which utilize trained data for learning in which characteristic vectors are isolated. Another aspect involved is the employment of computers to learn the traits which optimally represent the available information wherein the concept is the fundamental focus of deep learning, specifically neural networks which comprise multiple layers. These multiple layers transform information to outputs or results while simultaneously learning increasingly greater levels of characteristics.

Novel techniques are presented frequently for the institution of automated image representation that could result to advanced diagnosis as well as enhanced comprehension of the progress of infection. Requirements for efficient classification of medical images are an adequate classification structure and an appropriate number of training samples. A number of tailored medical diagnostic systems have been developed for assisted medical practitioners diagnose infections of white blood cells and red blood cells which provide significant information for practitioners on the infection.

Conventional systems comprise of information pre-processing whereby a combination of different pictures is processed which involves the removal of noise, the correction of color as well as the improvement of the image. The vital phase is the segmentation step. This is because the precision of the subsequent isolation of characteristics and classification steps rely of the proper segmenting of the lone white blood cells and red blood cells.

Previous studies have depicted the segmentation of blood cells to be more prone to faults in the segmentation of red blood cells from the protoplasmic region from white blood cells as a result of a close color resemblance among them in the intrinsic nature of the blood cells surrounding (Poon et al., 1992). White blood cells each has its unique or distinct morphology and color. This makes it a challenging feat to generate a general segmentation and the multistage classification equally enhances the overall sophistication which results to greater processing times.

The conventional or traditional techniques for the identification of white blood cells involved the enumeration of the frequencies of white blood cells in a definite sample size. This was usually performed by microscopy, by a human expertise which involved the analysis of the percentage of the frequency of each white blood cell type, a process popularly known as differential counting. This procedure may also involve the indication of any undefined objects which may be significant for diagnosis. This manual process, as previously seen was limited in a number of ways as a result of the slow, tiring and repetitive nature of the process. The accuracy of the technique was uniquely dependent on the operator skills (Hiremath et al., 2010).

Owing to the slow and tedious nature of the manual process in the analysis of white blood cells, there has been the emergence in recent years of automatic, accurate and efficient systems for enumerating and classifying white blood cells. The employment of such systems have resulted to the performing of diagnostic procedures in a rapid manner, at cost effective rates as well as the achievement of better accurate results. On the basis of previous investigations that have been conducted on the process of enumerating white blood cells and classification, the suggested techniques basically fall into one of three fundamental models; the segmentation of cells with the use of thresholding, the recognition of patterns and deformable model.

In 1992, Cseke employed the thresholding approach in his study involving cell segmentation which was previously introduced by (Otsu, 1979). In this method, thresholds utilize multiple step color characteristics. The differentiation and identification of white blood cells of the blood smear picture was done by increasing the variation between dark, grey and bright colors. Color contradiction was observed as the white blood cell nucleus collided with the background. As such, thresholding works by isolating the white blood cell nucleus and this is defined by subtracting the nucleus from the white blood cell images. The segmentation was achieved by using a digital single processor. The investigation generated an accuracy of 92%.

A similar method was utilized by (Putzu et al., 2013). As white blood cells appear darker than the background, it involved the application of image or color thresholds. This made their identification easy which resulted to segmentation on the basis of the different kinds of white blood cells. The segmentation of the white blood cells was based on morphology and defined by their frequency, prominence and their contradiction against specific color thresholds. The observed accuracy for this investigation was 92%. A study conducted in 2015 by Suryani and colleagues employed an application of fuzzy rile-dependent structure based on the morphology of white blood cells for the identification of Acute Lymphocytic Leukemia (ALL) as well as Acute Myeloid Leukemia type M3 (AMLM3). The morphological characteristics employed in this investigation include the area of white blood cells, ration of the nucleus and the granular ration. The algorithms utilized for processing include thresholding, the detection of canny

edge and the recognition of color filters. This method used a fuzzy rule dependent system coupled with the Sugeno method and demonstrated an accuracy of 83.65%.

In 2011, a study conducted by Rezatofighi and colleagues suggested a system for the analysis of images for the classification of five types of white blood cells. The suggested technique is based on Gram-Schmidt orthogonalization together with a snake technique for the segmentation of the nucleus and the protoplasm of cells. The results obtained from their use of artificial neural network were contrasted to that obtained with support vector machine and it was found that the result obtained with support vector machine was better. With respect to the classification of basophils, the support vector machine obtained an accuracy of 89.69%, whereas for the other four white blood cell types namely eosinophils, lymphocytes, monocytes and neutrophils, the observed accuracy was 96%.

Hiremath and colleagues (2010) suggested a technique for segmentation based on color and the isolated morphological characteristics for each segment for the identification of white blood cells, specifically lymphocytes, monocytes and neutrophil. Four feature groups (F) were isolated for which the accuracy for F1 ranged between 92% and 98%, whereas the accuracy for F4 ranged between 98% and 99%.

A novel technique for segmentation of white blood cells was suggested by (Su et al., 2014). It involved localizing a biased region of white blood cells on the hue, saturation and intensity (HSI) color space. Neural networks were utilized and three kinds of characteristics namely geometric characteristics, color characteristics and LDP dependent textual characteristics which were isolated as input data. The accuracy for this investigation was 99.11%. Prinyakupt and colleagues in 2015 suggested a technique for the segmentation of white blood cells which involved a joined thresholding, geometric operation and ellipse curve fitting for classifying white blood cells. With these isolated characteristics, linear and Bayes Naïve classifiers were employed and an accuracy of 98.7% and 97.3% were respectively achieved.

In 2007, Theera-Umpon and colleagues investigated the likelihood of the sufficiency of nuclear data alone for the classification of white blood cell. They investigated a group of white

blood cell nucleus dependent characteristics with the use of computational morphology. The accuracies achieved for equipping and assessment sets were respectively 81% and 77%.

As earlier seen, the microscopy examination of blood provides diagnostic information as regards the patient's health condition. The differential white blood cell enumeration depict an extensive range of relevant hematological infections. For instance, they can provide information on leukemia and certain forms of cancers from the results of classification and white blood cell count.

Many different techniques have been suggested for the purpose of implementing a white blood cell identification architecture which is based on the processing of images. The quality of operation of the automated detection and classification of white blood cells relies on proper segmentation algorithm for segmenting white blood cells from the background.

Studies conducted by (Sona et al., 2019) involved the extraction of three kinds of features from the segmented region. The traits that were isolated were further introduced into three different neural networks for classification of the white blood cells into their five different types.

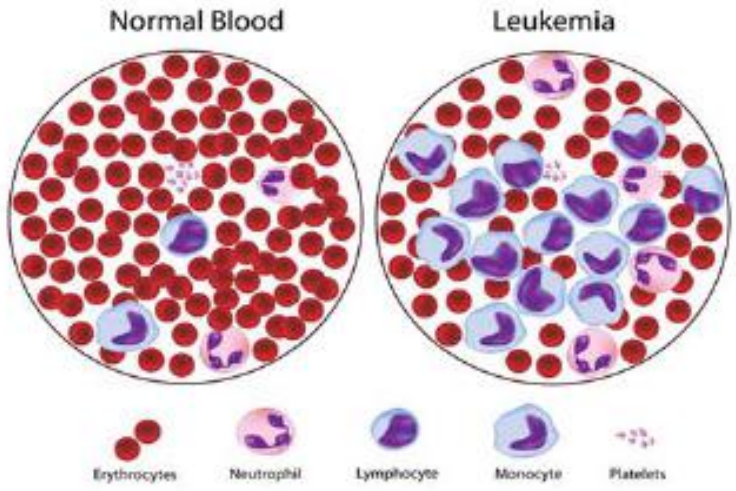

Figure 2.5: A comparison of leukemia blood and normal blood (Suryani et al., 2015)

A contrast of segmentation techniques reviewed by (Adollah et al., 2008), assert that the traditional color-dependent techniques and thresholding approaches are simple to sacrifice accuracy. On the contrary, approaches such as region-expansion can provide increased accuracy with high costs of computation. Some techniques operate directly on the RGB (red, green, blue) color space whereas others operate directly on HIS or CMYK (cyan, magenta, yellow and key black) color space. On a general basis, techniques based on S-component are superior to techniques based on RGB.

By leveraging the cyan-magenta-yellow-key black color models, (Putzu et al., 2013), endeavor to develop the characteristic vector. It was found that all other constituents except white blood cells have traces of yellow color in them whereas white blood cells depict a good contrast in the CMYK color models Y constituent.

Young and colleagues (1972) employed four features and a minimal distance classifier for the classification of five sell types. (Sheik et al., 1999), utilized wavelength transform coefficients as well as artificial neural networks for the recognition of white blood cells, red blood cells and platelets.

Bikhet et al. (2000) chose ten characteristics and employed a minimum distance classifier for developing an automated classification structure which attained a classification accuracy of 91% for a seventy-one-leucocyte data base. (Piuri and colleagues, 2004), suggested an automated recognition and classification system dependent on twenty-three geometric features and a neural classification architecture. A structure of classification was suggested in (Yampri et al., 2006), which depends on own-cell and parametric traits.

Nulifer et al., suggested a classification technique which is based on combined histogram-dependent traits and a vector support machine (Nulifer et al., 2008) (Osowski et al., 2009) suggested a genetic approach and a support vector machine for the identification of white blood cell in the bone marrow.

A technique presented by (Rezatofighi et al., 2010) involved the extraction of geometric and texture dependent characteristics from local binary pattern (LBP) followed by the training of two types of neural networks for classification.

Studies conducted by (Tabrizi et al., 2010) involved the adoption of major component analysis for the isolation of characteristics and then utilized a neural network of learning vector quantization for the classification of five kinds of leucocytes. Gosh and colleagues employed the Naïve Bayes classifier with four statistically relevant characteristics for the classification of five kinds of white blood cells and achieved an overall accuracy of 88.2 % (Ghosh et al., 2010).

2.9 Convolutional Neural Networks for Recognition of Lymphoblast Cell Images

One of the acute cancerous infections of white blood cells is acute lymphoblastic leukemia (ALL). This infection is characterized by the over manufacturing of immature lymphocytes called lymphoblasts in the bone marrow. The infection rate is fast and prevents the production of normal white blood cells and ultimately leads to death among children and youngsters. It is a heterogeneous infection. By this, it requires distinct therapeutic procedures for different groups of sufferers based on the subtype of leukemia. As such, individual sub types of the infection respond differently to chemotherapy. For this reason, the recognition of the sub type of the leukemia is significant for diagnosis and effective therapy.

According to the WHO classification, acute lymphoblastic leukemia can be grouped as:

- T-lymphoblastic leukemia (pre-T)
- B-lymphoblastic leukemia (pre-B)
- Mature B-lymphoblastic (mature B)

The recognition of the various sub categories necessitates a multi-parametric approach as well as morphology, immune-phenotyping, cytogenetics as well as molecular features.

Regardless of the advanced techniques available, a required initial stage of the process is a morphological assessment of the blood smear specimen. This can be performed by computer aided systems. Much interest has been geared to the development of instruments and techniques for the analysis of images and the recognition of patterns for enumerating and identifying white blood cells (Piuri et al., 2004). With these automated techniques, much efficiency is accomplished in the analysis with respect to time management, accuracy, reduction of human labor hence human errors and the understanding of various patterns or cells from microscopy pictures. Due to the fact that this techniques require only images and not blood specimen, it makes available low-cost methods and makes available data for subsequent utilization in diagnosis.

The geometry of lymphocytes and acute lymphoblastic leukemia subcategories demonstrate extensive differences among cells in same class. Simultaneously, they also depict numerous features which resemble cells belonging to various categories.

With respect to morphology, lymphocytes have a compact nucleus with smooth edges, blue-purple nuclear color and low nucleus/cytoplasm ratio. On the contrary, lymphoblasts demonstrate irregularities with rough edges, sparse red-purple nucleus coloration, and high nucleus/cytoplasm ratio (Labati et al., 2011). Taking into considerations the acute lymphoblast leukemia subcategories according to the classification set forth by WHO, pre-T and pre-B lymphoblasts have these features:

- **Pre-T cells**

  They vary significantly from tiny blasts with a condensed nuclear chromatin and indistinct nucleoli, to bigger blasts with well dispersed chromatin and prominent nucleoli (Borowitz et al., 2008). It is also characterized by a limited amount of cytoplasmic space. Cytoplasmic granules are also a common phenomenon with appearance as specks of dust and in some instances may show visible large grains. Nuclear morphology range from round to irregular to lobed. The nucleus may also be cleaved, may exhibit cytoplasmic protrusion or hand mirror form.

- **Pre-B cells**

  These demonstrate many features like small-sized cell with sparse cytoplasmic space, condensed nuclear chromatin, indistinct nucleoli. The cells may also be medium sized with moderate quantities of light blue protoplasm, infrequent well disseminated nuclear chromatin and a distinct nucleoli. The majority of these cells have a high nucleus/cytoplasm ratio. Other features include an elongated form, hand mirror form, circular or irregular nuclear convolutions. All these subtypes are sorted out by the automated cell recognition process.

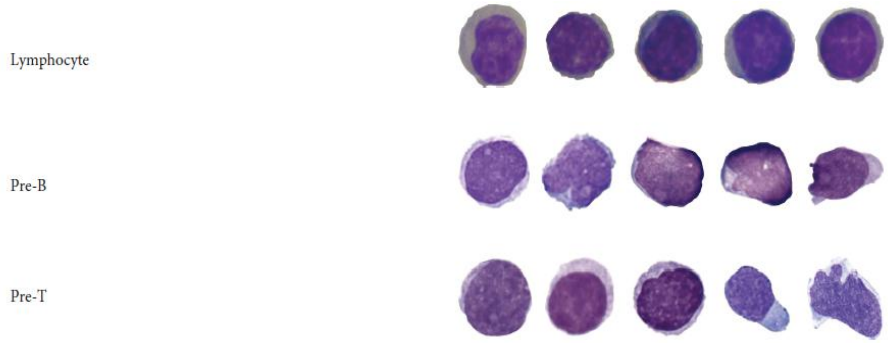

Figure 2.6: Sample images of the considered white blood cells: lymphocyte, pre-T, and pre-B lymphoblasts

A prominent technique is hand-crafted characteristic engineering with classification algorithms like support vector machines (SVM), k-nearest neighbor (KNN) and multi-layer perceptron (MLP). This approach involves the isolation of characteristics with image processing techniques and domain knowledge. This is then followed by the combination of selected significant characteristics as data for the classification process. This hand crafted algorithm however has a number of disadvantages:

- The technique requires expertise on domain knowledge for the determination of useful characteristics.
- The technique is dependent on the techniques involving the processing of images for the isolation of useful traits without the introduction of additional discrimination and faults.

- The operations involving the isolation of characteristics are challenging to automate and are time consuming.

Studies conducted by (Pansombut et al., 2019) utilized a deep learning technique which involved the implementation of a convolution neural network. This network directly receives pixel values from graphics and then gradually develops significant characteristics via the employment of multiple layer architecture. The characteristics are then utilized for the recognition of pattern significant to the challenge encountered with classification. In this study, a significant factor which was considered was the size of dataset. Techniques for the augmentation of data were utilized to increase the proportion of input images for equipping. The objective of the investigation was the application of deep learning technique for the development of a recognition pattern for lymphocytes and acute lymphoblastic leukemia sub categories as well as pre-T and pre-B cells derived from blood microscopy pictures. The recognition of B-cells was left out due to the fact that they are less frequent compared to the other two sub groups. The assessment of the performance of this deep learning approach was performed by comparing the accuracy and sensitivity of the utilized convolutional neural network classifier with support vector machine which employed hand-crafted feature engineering. For ensuring fair comparison, the support vector machine classifier is promoted with the selection of traits as well as the optimization of GA-dependent factors.

The assessment of hematologic pictures is broadly differentiated into four major steps as previous seen; the pre-processing of images, segmentation, the isolation of features and selection, and finally the classification process. (Mohapatra and colleagues, 2012), suggested a technique for segmentation which employs color-dependent aggregation for obtaining nuclear region and the cytoplasmic region from stained blood smears. Support vector machines are utilized with significant characteristics and they showed satisfactory outcomes.

Investigations conducted by (Osowski et al., 2006), proposed a fully automated technique for the recognition of seventeen categories of myelogenous leukemia from pictures of bone marrow aspirates. The segmentation of cells was done with watershed algorithm coupled with techniques involving region-growing and the detection of edges. 117 characteristic features

were generated and chosen with the use of linear support vector machine. This technique was further improved by (Osowski et al., 2006), which proposed the selection of characteristics with the use of genetic techniques for the extraction of features with the use of genetic algorithms for the selection of traits coupled with support vector machines learning algorithms. This algorithm was found to have an improved accuracy by over 25%.

Reta and colleagues (2010), suggested a technique for the categorization of two kinds of leukemia; acute lymphoblastic leukemia (ALL) and acute myeloid leukemia (AML). The process of segmenting blood cells is conducted with the use of contextual color and textual information for the identification of nucleus and the cytoplasm region and the separation of overlapping blood cells. Following the segmentation step is the isolation of the morphological, statistical, textual, dimensional, relative and eigen characteristic features for use by various machine learning classifiers in Weka.

Convolutional neural networks have found applications in microscopy analysis.

Studies conducted by (Song and colleagues, 2014), made use of a deep learning technique dependent on a super-pixel and convolution neural network for the detection of the cytoplasm in the segmentation procedure. This convolution neural network technique is contrasted to various algorithms that are reverse propagation neural network, probabilistic neural network, support vector machine as well as learning vector quantization algorithms. Convolution neural networks was proven to outperform other algorithms and generates an accuracy of 94.50% for the detection of nuclear region. For the segmentation of cytoplasmic and nucleus, convolution neural network was found to be superior to all three standard techniques as assessed by F-measure, accuracy and recall.

Investigations conducted by (Zhao et al., 2016), suggested a technique for the automatic detection of white blood cells from peripheral blood smears as well as the classification of five types of white blood cells. Eosinophil and basophil are initially categorized from the other forms of white blood cells by using a support vector machine classifier with a granularity feature. The remaining three types of white blood cell are identified with the use of convolution neural network for the extraction of characteristics and random forest utilizes

these features for the classification of these white blood cells. Studies conducted by (Litjens and colleagues, 2016), presented a deep learning technique for improving the objectivity and effectiveness of histo-pathologic slide assessment. Two experiments are performed by the training of convolutional neural networks which are the identification of prostate cancer in biopsy samples as well as the detection of breast cancer dissemination in sentinel lymph nodes.

2.10 Classification with Improved Swarm Optimization of Deep Learning Features

Many people around the world suffer from leukemia which is a malignant tumor of the white blood cells. This disease starts in the lymphatic system where blood cells are produced.

Firstly, it starts in the bone marrow and then is spread in blood cells of the human body. The growth of white blood cells is based on the demands of the body. However, in the case of leukemia, they blood is filled with immature white blood cells which are inefficient for carrying out their usual functions. Despite the fact that they can be readily identified from their dark-purple apparition, the assessment and subsequent processing could be complicated as a result of differences with respect to shape and texture. Despite the fact that white blood cells can be differentiated from each other, there is however the necessity of separating them from other blood components like red blood cells and platelets.

As depicted in the figure below, lymphocytes from normal healthy people are regular in shape with smooth nuclei of regular edges. On the contrary, lymphocytes from patients suffering from acute lymphocytic leukemia (ALL) otherwise known as lymphoblasts are irregular and bear tiny cavities in their cytoplasm known as vacuoles, along with round particles in their nuclei called nucleoli. The increased morphological variations mentioned above depict the increased severity of the infection.

Deep learning techniques with the use of convolutional neural networks is at present the method of choice for the recognition and classification of white blood cells in applications involving medical imaging. As the convolutional neural networks accomplish satisfactory outcomes on extensive datasets, they need much data as well as computational resources for

training. In a number of instances, the data set is restricted and may be insufficient for training a convolutional neural network from scratch. Faced with such a situation, in a bid for leveraging the potency of convolutional neural networks while simultaneously decreasing the cost for computation, transfer learning can be employed (Sharif et al., 2014).

With transfer learning, the convolutional neural network is primarily pre-equipped on an extensive and diversified generic image data set and then applied to as specific function. A number of these internationally recognized pre-trained neural networks include VGGNet, ResNet, NasNet, MobileNet, Inception and Xception.

In studies conducted by (Shin et al., 2016), an assessment of various convolutional neural network structures was conducted and transfer learning accomplished satisfactory results on the classification of thoraco-abdominal lymph node and interstitial lung infection. Mean pooling classification was employed in studies conducted by (Khan et al., 2019), for the differentiation of malignant from non-malignant cells following the isolation of characteristics from breast cancer pictures with the use of previously trained convolutional neural network structures that were introduced into a fully connected classification layer. The outcome of the investigation demonstrated that the detection accuracy of their technique performed better than other convolutional neural network techniques in the recognition of cytological picture-dependent and classification of breast tumors.

The work of a variety of other researchers was based on a combination of multiple deep learning techniques for the improvement of the usefulness of transfer learning for cell-dependent classification of graphics. Transfer learning has been employed for overcoming limitations of past published techniques.

The fundamental factor among these techniques is the utilization of a number characteristics from previously trained convolutional neural network models. Due to the fact that many of these characteristics are redundant or may be faulty, this technique could be inefficient with respect to time management and computational resources. In addition, the accuracy of the classifier can benefit from restricting the size of the characteristics. In studies conducted by 20, the detection of white blood cells was conducted by isolating various characteristics as

well as color, texture, shape and hybrid characteristics with the use of classical image processing. Next was the application of a social spider-inspired optimization to select the most significant characteristics. The algorithm was examined on ALL-IDB2. The results for the segmentation were 99.2% for accuracy, 100% for sensitivity and 97.1% for specificity.

In studies conducted by (Abdeldaim et al., 2018), a new technique is presented for the differentiation of benign from malignant white blood cells as shown in the figure below.

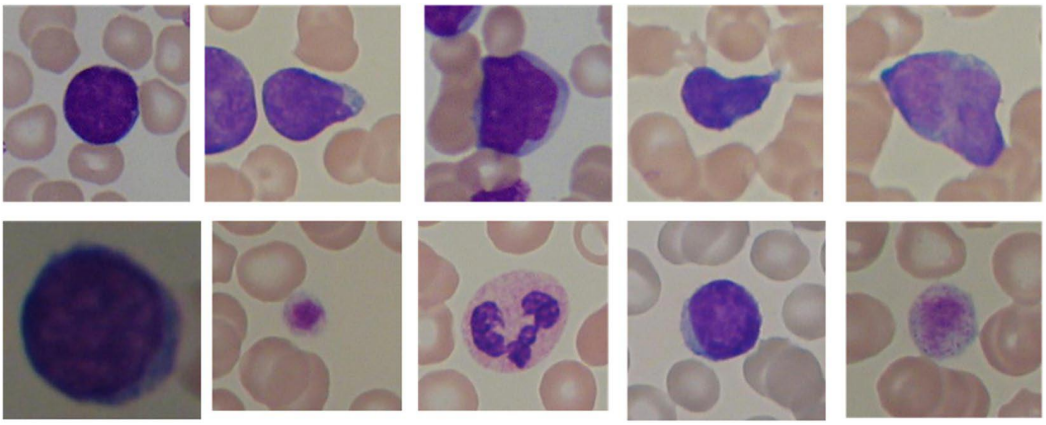

Figure 2.7: Samples from the ALL-IDB2 dataset2 showing benign (top) and malignant (bottom) lymphocytes (Khan et al., 2019)

The suggested technique uses a combination of convolutional neural networks and an improved salp swarm algorithm (SSA) dependent on statistical operators. A derivative of convolutional neural network known as VGGNet that had been previously equipped on millions of pictures is employed for the process of extraction of characteristics. The final layer of the VGGNet can be dismounted such that an image can be introduced through the remaining network for acquiring its characteristic vector. As such, the convolutional neural network can be utilized for the isolation of a massive matrix for every image which can then be introduced to an external classifier for the classification of the image. The dataset utilized in the investigation has only two classes; benign and malignant. As such, the algorithm was accordingly modified.

The characteristic matrix generated by the convolutional neural network is adjusted so as to suit the classification of the image. As such, a statistically enhanced salp swarm algorithm (SESSA) was developed for the enhancement of the operation of the classification by excluding correlated and noisy characteristics and choosing only significant characteristics.

The purpose of this investigation was the proposal of a technique for the selection of image characteristics dependent on enhanced swarm optimization and to demonstrate the fact that it outperforms numerous current techniques for classifying white blood cells for the detection of leukemia. A major challenge of many techniques involved with the classification of white blood cells is the limited availability of data set. This suggested technique however overcomes this challenge. The challenge in the detection of leukemic cells from such pictures is in the morphological resemblance as well as variability of the subject. This makes defining suitable image characteristics challenging. Deep convolutional neural networks operate properly at this function though not quite efficient as a result of their extensive and redundant space of equipped characteristics.

The classification of white blood cells for the detection of leukemia provides the optimum assessment scenario for swarm-dependent optimization of the isolation of characteristics. Though this investigation does not provide a readily usable clinical instrument for the diagnosis of leukemia, it however offers a novel and effective technique for the optimization of deep learning dependent approaches for the classification of clinical images.

CHAPTER 3
DEEP LEARNING AND METHODOLOGY

3.1 Proposed classification of white blood cells

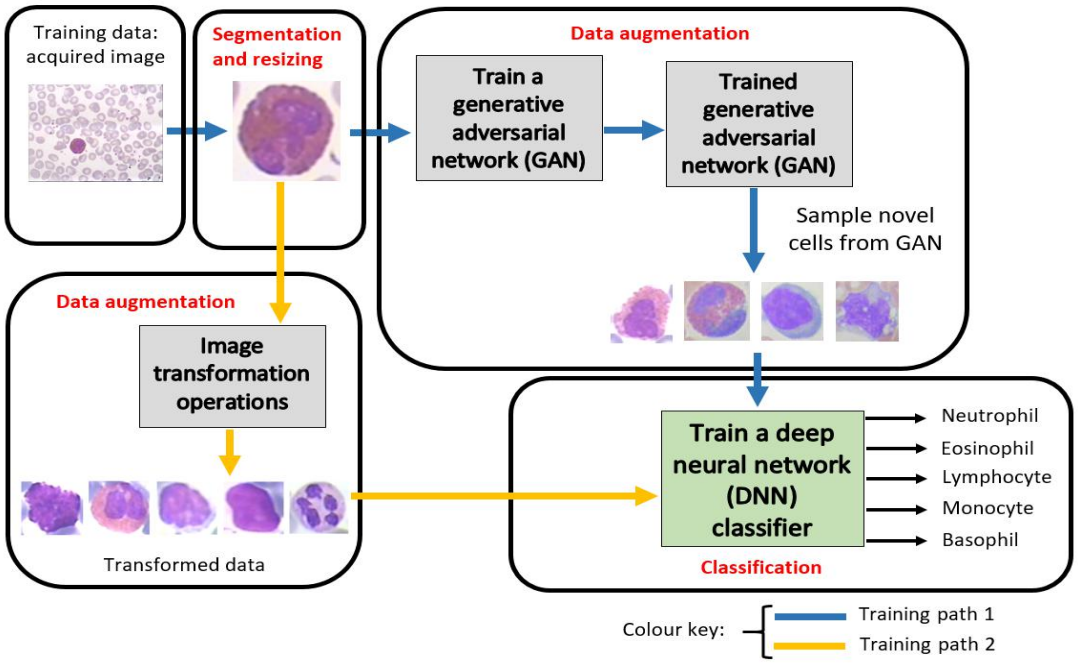

Figure 3.1: Suggested structure for the enhanced classification of leucocyte types. Equipping route 1: GAN-dependent data enhancement for equipping DNN classifier. Equipping route 2: transformation performance-dependent data enhancement for equipping DNN classifier

In this part of the thesis, the suggested frame of study is presented for classifying leucocytes into their five various categories. The suggested structure is depicted in Figure 3.1. The major constituents of the suggested structure include (i) the segmentation and resizing of leucocytes (ii) systems involved with the enhancement of data through operations of transformation or GAN-based data scenarios as well as the equipping of Deep Neural Networks. The afore-mentioned constituents are elaborated on in the following pages.

3.2 VGG-16

This was developed by Simonyan and Zisserman. It accomplishes an accuracy of 70.5% and is computationally costly neural network of the ILSVRC competition as a result of the extensive proportion of aspects and convolutional levels it contains. The task of the competition was the classification of 1,000RGB pictures from ImageNet dataset. VGG-16 architecture comprises sixteen layers in which thirteen convolutional levels with 3x3 filters and 2x2 max pooling layers are stacked. The ReLu activation function is sandwiched in between the layers. The other three layers are fully linked and contain the majority of the parameters of the network. A softmax function is utilized for generating the probabilities for every class. A challenge with the VGG-16 is the demanding memory utilization due to its enormous quantity of parameters (140M) and this leads to decrease in performance and waste of power consumption (Goodfellow et al., 2014).

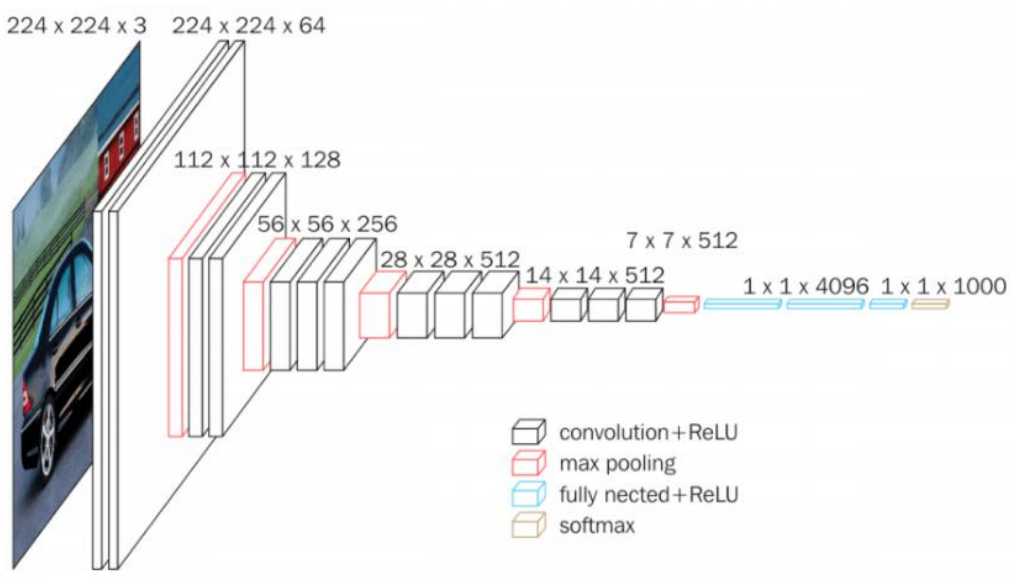

Figure 3.2: architecture of VGG-16

The input data into layer 1 is of definite size 224 x 224 RGB image. The picture is subjected through a sequence of convolutional layers wherein the filters are utilized with a very tiny receptive field 3*3. This is the least size for capturing the notion of left/right, up/down, center.

In a configuration, it also uses 1*1 convolution filters which are observed as a linear variation of the input flow paths (followed by non-linearity). The stride of convolution is definite to 1 pixel. The padding between layers is such that the resolution is preserved after convolution. That is to say, 1 pixel for 3*3 convolutional layers. Spatial pooling is conducted by five max pooling levels. Max pooling is conducted over a 2*2-pixel window with stride two.

Three completely connected levels follow a sequence of convolutional levels with different depth in different models. The first two are each of 4096 channels, the third conducts 1000 way ILSVRC classifying and so bears 1000 channels per class. The last level is the soft max. This configuration is so for all completely connected levels in all architectures. The latent levels are trained with rectification (ReLu) nonlinearity (Paganini et al., 2018).

Two major challenges exist with the VGG-16. One of these is the fact that it is very slow to train. Another is that the network model weights are very large in terms of disk/bandwidth. As a result of its depth and proportion of fully linked nodes, VGG-16 is more than 533MB. As such, deploying it is tedious.

3.3 VGG-19

This is a derivative of the VGG architecture which comprises 19 layers; 16 convolutional layers, three completely connected layers, five max-pooling layers and a soft max layer. VGG-19 has 19.6 billion FLOPs.

The VGG-19 architecture has the following parameters:

A definite size of 224*224 RGB image is utilized as input for this network implying the shape of the matrix is 224*224

Preprocessing was performed by subtracting the mean RGB value from every single pixel calculated over the entire equipping set.

Kernels of 3*3 sizes with a stride dimension of 1 pixel were used for enabling them to cover the entire nation of the image

Spatial padding was utilized for preserving the spatial resolution of the picture. Max pooling was conducted across a 2*2 pixel window with stride 2

Next was the introduction of non-linearity using Rectified Linear unit (ReLu) for improving the classification properties of the architecture as well as improve the time of calculation as previous models utilized tanh or sigmoid functions.

The architecture also implemented three completely linked levels from which the first two are of dimensions 4096 each. Following this is a layer with 1000 channels for 1000-way ILSVRC classifying and finally is the last layer which is a function of soft max.

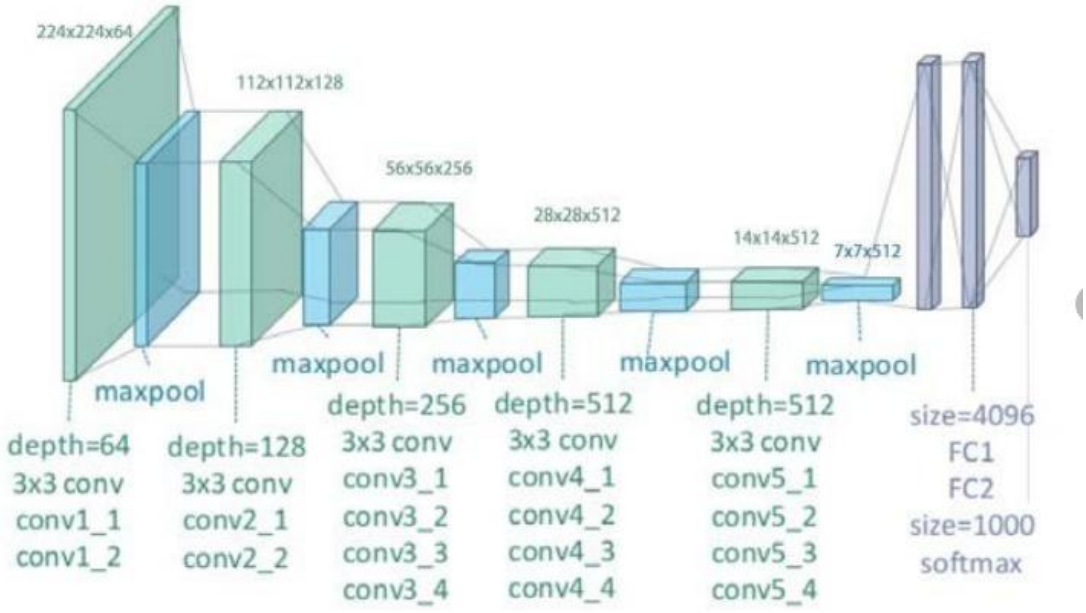

Figure 3.3: VGG-19 architecture

3.4 Densely Connected Convolutional Networks

Work in recent times has proven that convolutional neural networks can be deeper, accurate and more effective at training should they bear shorter connections between levels proximal to the input as well as close to the output. These dense convolutional neural networks (Densenets) connect a layer to every other layer in a feed-forward system.

- Densenets have several benefits.
- They solve the problem of vanishing gradient
- They strengthen the propagation of traits
- They encourage the reuse of characteristics
- They decrease to a significant extent, the number of parameters

Densenets require fewer parameters compared to the equivalent conventional CNN since there is the absence for learning repetitive feature maps (Bengio et al., 2013). More so, some derivatives of Resnets have shown that multiple layers are barely contributing and can be left out. The proportion of parameters of Resnets are large since each layer has its weights to learn. On the contrary, the layers of densenets are narrow and they only add a tiny set of novel feature-maps.

Densenets present a pattern of connection which solves the problem of vanishing gradient in the course of training deeper architecture while maintaining maximum data as well as gradient flow across the network. Each level is connected to the other layer in a feed forward pattern and as such, input from each level is the concatenated characteristic map of all previous layers and output from it is utilized for all later layers. The benefit of this is in decreasing the proportion of parameters used as it decreases the amount of repetitive feature maps learned by the encouraging of feature reuse (Ciresan et al., 2012). Densenets are made of sequential dense blocks as well as transition blocks. Inside a dense block, the sizes of the characteristic maps stay the same so as to permit their concatenation although the volume changes. On the contrary, transition blocks conduct down sampling between dense blocks via 1*1 convolution as well as 2*2 pooling levels. This network model has a hyperparameter increase rate that influences the proportion of feature maps that is added by every layer and so regulates the

quantity of data added by every layer to the entire state. Densenets have accomplished top quality output on the identification of images.

Densenets 121 and 169 each denote the depth of the ImageNet models with 121 layers and 169 layers respectively.

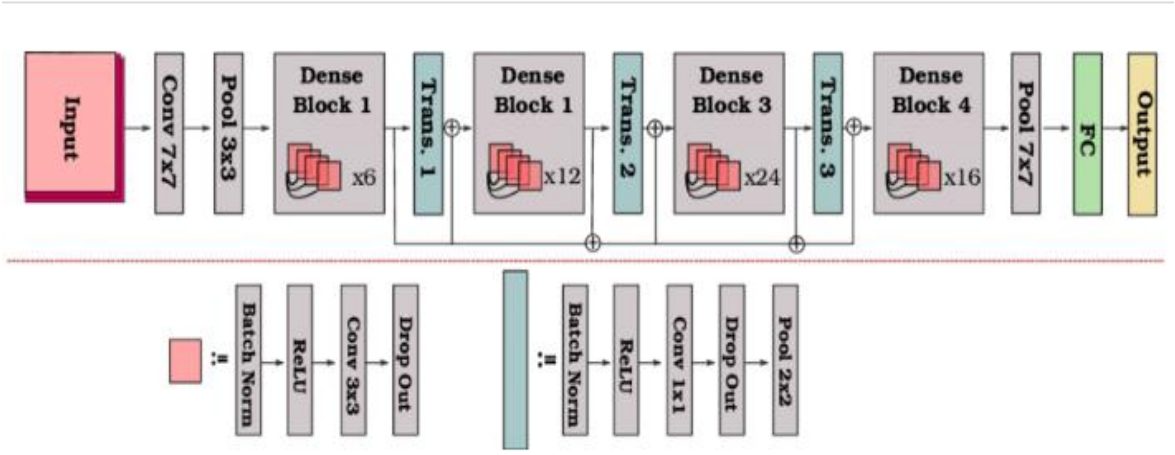

Figure 3.4: Densenet 121 architecture

3.5 Generative Adversarial Network (GAN)

GAN is a category of machine learning architecture developed by Goodfellow Ian and colleagues in 2014. Provided a training set, the technique learns to produce novel data with same statistics like that of the training data. For instance, a generative adversarial network equipped on images can produce novel images that superficially resembles an authentic one to human observation with many real features. Initially suggested as a type of generative architecture for unmonitored learning, generative adversarial networks have demonstrated to be of significance for semi-monitored learning, completely monitored learning as well as reinforcement learning (LeCun, 2016).

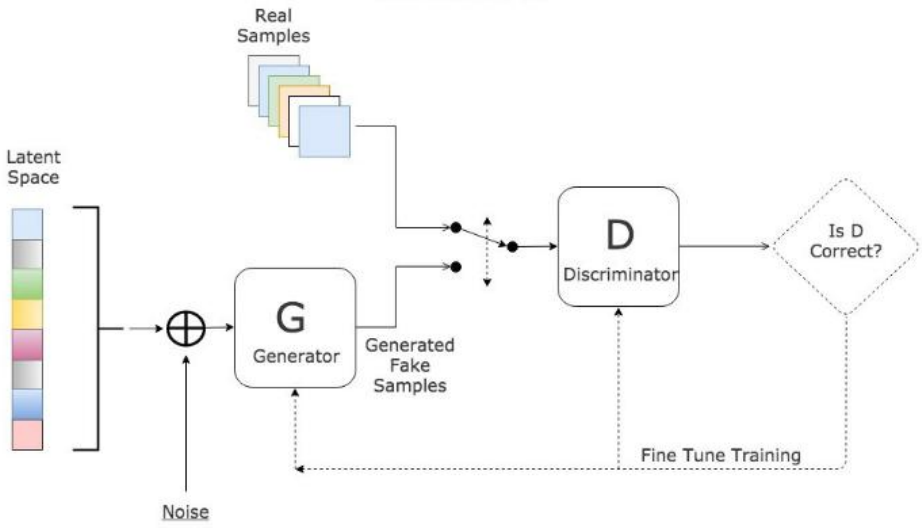

Figure 3.5: Generative adversarial network

The GAN produces subjects while the discriminative network assesses them. This contest functions with respect to the distribution of data. GAN learns to map from a hidden space to a data dissemination of concern whereas the discrimination network differentiates subjects generated by the generator from the authentic data distribution. The aim of the training of the generative network is for the expanding of the error frequency of the discrimination network; to deceive the discriminator network by generating new subjects which the discriminator considers not synthesized, not a constituent of the authentic data distribution.

An identified dataset is used as the original training data for the discriminator. Equipping this entails to present it with samples from the equipping dataset to the point of it achieving satisfactory accuracy. The training of the generator is dependent on if it succeeds in deceiving the discriminator. In essence, the generator is randomly seeded with data from a previously defined hidden space such as multi-variant normal distribution. Subsequently, samples are produced by the generator and assessed by the discriminator. Back-propagation is subjected to both networks so that the generator generates improved images while the discriminator becomes more accurate in flagging produced images. The generator is essentially a de-convolutional neural network while the discriminator is a convolutional neural network (Erdmann et al., 2019).

One of the challenges working with GAN is the fact that they sometimes from mode collapse in which they fail to adequately generalize, miss out on whole modes from the input information. For instance, a GAN trained on the MNIST data set possessing numerous samples of every single digit could however miss out a sub set of the digits from its output. This problem could be due to a feeble discriminative network, which fails to identify the pattern of omission. Another possible cause of this problem may be a wrong choice of objective application.

With GANs, two networks are setup against each other. The generator fools the discriminator by generating urging fake inputs. The discriminator differentiates if the input is authentic or artificial.

The three main steps in the process include:

- Using the generator to generate fake inputs on the basis of noise
- Equipping the discriminator with the real and artificial inputs
- Equip the entire model. This architecture is developed with the discriminator chained to the generator. In this third phase, the weights of the discriminator are frozen.

The aim of chaining the networks is to disallow for any possible feedback on the output from generator.

GAN has a number of applications as follows:

- They are employed for the creation of image models of imaginary style without necessarily hiring a model, photographer, makeup artist and so on.
- They have been used to enhance images of astronomy as well as simulate gravitational lensing for investigations in dark matter. In 2019, they were engaged in successfully distributing dark matter in a uni-directionally in space as well as to foretell the occurrence of gravitational lensing (Erdmann et al., 2019).
- They have been suggested as a rapid and precise means of modeling high energy jet production as well as to model showers via calorimeters of high energy scientific investigations.

- GANS have been equipped for the accurate estimation of bottlenecks in simulations whose computation is costly like in scientific studies involving particle physics (Paganini et al., 2018).
- GAN techniques have been demonstrated to accelerate the simulation and enhancement simulation fidelity in functions involving CERN experiments.
- GANs are employed in video game modeling as a means of scaling up low resolution two dimensional textures in video games by having to recreate them in 4k or higher resolutions through the training of pictures and then sampling them down to fit the native resolution of the game with outputs which resemble the super sampling technique of anti- aliasing. With adequate training, GANs make provision for a much clearer and sharper two dimensional texture picture with magnitudes greater in quality compared to the original, whereas fully retaining the level of details of the original. Some examples of the employment of GANs in video games include Final Fantasy VIII, Final Fantasy IX, Resident Evil and Max Payne (Musella et al., 2018).

3.6 ResNets

Residual neural networks (ResNet) is an artificial neural network that is developed on constructs known from pyramid cells found in the cerebral cortex. This is conducted by using skip connections or shortcuts for skipping some levels. Actual ResNet architectures are employed with double or triple jumps which contain non-linearities (ReLu) as well as batch normalization between. Extra weight matrix could be utilized to learn the jump weights. Such architectures are referred to as HighwayNets. Architectures with numerous parallel jumps are known as DenseNets. With respect to ResNets, a non-residual network is referred to as plain network.

An advantage of jumping over levels is the avoidance of the challenge involved with vanishing gradients through the reuse of activations from a prior level to the point where the nearby level becomes familiar to its weights. In the course of training, the weights adjust to mute the upstream level as well as amplify the layer which was previously jumped. In the

simplest instance, just the weights of the nearby layer's link are adjusted in the absence of explicit weights for the upstream layer. This performs adequately when a single non-linear level is skipped or when the intermediary layers are all linear. Otherwise, an explicit weight matrix ought to be learned for the jumped connection.

- **ResNet 18** is a convolutional neural network with 18 layers in depth. A previously trained derivative of the network equipped on more than a million pictures from the ImageNet database. The previously equipped network has the ability to classify pictures into 1000 object classes like keyboard, mouse, pencil and more. As such, the network has learned the representations of rich characteristics for an extensive range of pictures. The network has an image input dimension of 224*224.

- **ResNet 50** is a convolutional neural network with 50 layers in depth. A previously equipped derivative of the network equipped on over a million images from the ImageNet database. The previously equipped network has the ability to classify pictures into 1000 object classes like keyboard, mouse, pencil and more. As such, the network has learned the representations of rich characteristics for an extensive range of pictures. The network has an image input dimension of 224*224.

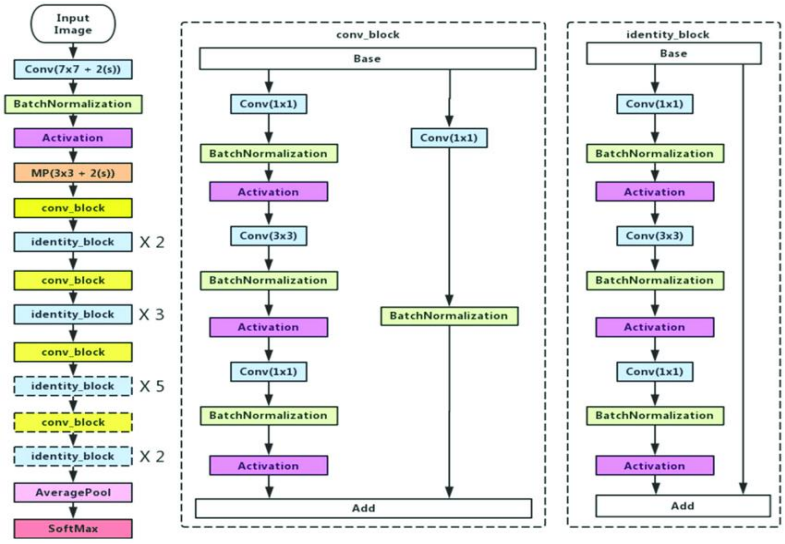

Figure 3.6: ResNet 50 architecture

3.7 Transfer learning

State-of-the-art deep neural networks (DNNs) typically have millions of parameters (i.e. weights) so that they can easily overfit datasets with small number of training samples. One method that has been shown effective for alleviating this problem is transfer learning or weights pre-training, where the parameters of the DNN are first trained on another large dataset (Tan et al., 2018). The DNN at this stage is referred to as a 'pre-trained DNN'. In this fashion, the early layers in the pre-trained DNN is expected to have learned primitive features such as strokes, edges, corners, etc. from the large dataset. Interestingly, the primitive features learned are general to many vision tasks so that learning (i.e. features) can be transferred from pre-trained DNNs to other DNNs (Tan et al., 2018; Weiss et al, 2016). As such, the new task, where we have a small dataset can benefit from transfer learning. After pre-training, the second stage for transfer learning is referred to as 'fine-tuning'. The goal of the fine-tuning stage is to align the weights of the pre-trained DNN for the new task using the dataset of interest. That is, we retrain the pre-trained DNN using the new dataset.

Generally, for transfer learning, some of the early layers in the pre-trained DNN are frozen (i.e. the weights are excluded during the backpropagation training updates), while the other layers are updated during backpropagation training. In this manner, one can consider that the starting (i.e. initial) weights for the new task with small dataset are the weights learned on the previous task using a large dataset. Furthermore, the output layer of pre-trained DNN is replaced with a new layer, where the number of output units corresponds to the number of classes in the new task. In addition, since we expect that most of the features learned during pre-training are general and useful for the new task, a small learning rate is used for the fine-tuning stage.

3.8 The Segmentation of White Blood Cells

In this write-up, the dataset employed is the LISC dataset (LISC dataset 2019). The initial graphics contain the leucocytes coupled with other background factors which are insignificant for the classification of the various leucocytes. These insignificant background factors are responsible for an extensive portion of the graphics. Figure 3.7 thus the outcomes in a

decreased signal to noise proportion for equipping; this can be of detrimental effect on the operation of equipped DNN classifiers.

As a result, the section of graphics with leucocytes was segmented with the use of masks according to the dataset; the bounding points which capture the non-zero pixels in the masks is utilized for cropping out the leucocytes to fitness as the input of the developed DNN prototypes. Figure 3.7 presents samples of leucocytes with their corresponding masks.

3.9 Data augmentation for Improving DNN Classification Operation

The main obstacle involved in the development of a classification architecture for leucocytes is the limited availability of training data; numerous data for covering the variability of these cells are frequently not readily available. The limited availability of information from a class generates imbalance which discriminates learning; prototypes trained from imbalanced data frequently underperform in the course of testing (Johnson et al., 2019). The subsequent subsections elaborate the various techniques which are explored for the generation of additional information that can be utilized for the improvement of the accuracy of classification of the DNN classifiers.

3.9.1 Additional data via data transformation operations

In this section, the performance on image transformation are applied for the production of surplus data instances from the initial data. Precisely, the graphic transformation performance that are employed involve haphazard rotations within an angle of 0 to 360 degrees, haphazard shearing within an angle range of 0 to 20 degrees, anti-clockwise, haphazard horizontal tosses as well as random height and breath shifts of up to 0.2 of the graphic height and breath.

The above performances of transformation are employed to produce the required proportion of data instances.

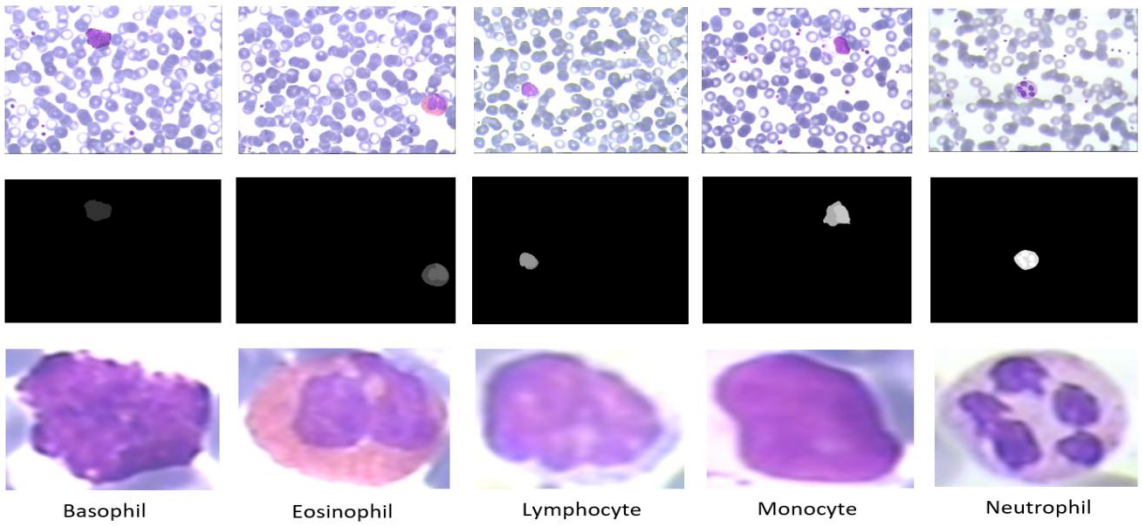

Figure 3.7: Leucocyte segmentation. Top: original graphics of various leucocytes. Middle: masks for segmentation of leucocytes. Bottom: segmented leucocytes from the initial images

3.9.2 Additional data with the use of generative adversarial network (GAN)

Generative adversarial network is an architecture which can be utilized to produce new data points from a distribution with similar traits to that of the learning data. GAN is fundamentally dependent on the min-max game concept (Goodfellow et al., 2014) in which the differentiator and generator operate in opposites so as to outperform each other. The function of the generator is the produce fake new data cases with the semblance of the reality whereas the differentiator operates by identification of false cases. The objective is for the generator to learn to produce data instances which have similarity to the actual data scenarios.

As a result, the generation of novel data points by equipping GAN on the initial data is suggested in this investigation. The data points produced from the equipped GAN vary from the initial data cases and as such are of significance to the training characteristics which generalize to unrecognized cases in the course of testing. Of particular interest is the consideration of traditional GAN (Goodfellow et al., 2014) for the generation of new data points as surplus data.

3.9.3 Additional data employing both data transformation operations and a trained GAN

In this technique concerned with the generation of surplus data for equipping, data scenarios achieved from the performances of transformation are coupled with new scenarios produced from equipped GAN. This novel data is then utilized for equipping the various DNN prototypes. In this case, close attention is paid on the likelihood of such data combination on improving the operation of the equipped DNN prototypes.

3.10 Deep Neural Networks for Leucocyte Classification

With respect to the classifier, various top quality DNNs such as VGG-16, ResNet and DenseNet are equipped on the established. In addition, three main training scenarios are considered which can affect the operation of the DNNs, particularly with the unavailability of training data. These scenarios are considered below:

3.10.1 Random initialization of the DNN

The weights of the DNN are haphazardly initialized and equipped from scratch with the use of prominent initialization strategies such as (Glorot et al., 2010; He et al., 2015). For the haphazard initialization, the objective is the symmetrical disintegration of weights at the onset of training. This is to provide for ease of exploration of different components of the solution space by the DNN. In other words, haphazard initialization prevents the optimization of DNN from being hooked in a certain basin of attraction which could be sub-standard in the solution space.

3.10.2 The initialization of DNN weights from weights trained on a large dataset

The initialization of DNN weights are equipped on the CIFAR-100 classification dataset. This contains 60,000 natural equipping graphics which can be identified to 100 various classes (CIFAR dataset 2019). The initialization of DNN weights from trained weights on extensive sets of data have demonstrated an improvement on the generalization of prototypes particularly with the limitation with accessible equipping data (Cote-Allard et al., 2019; Yang et al., 2019). The paramount idea responsible for this success is the fact that DNNs frequently possess numerous proportions of characteristics and so have the likelihood for over-fitting

even in the lack of an extensive equipping data. Strikingly, the weights in the initial layers of the DNNs equipped on extensive sets of data have the semblance to generic traits and so can be used for the isolation of characteristics in other functions (Yan et al., 2019). On a general basis, following the initialization of the DNN with weights equipped on CIFAR-100 sets of data, the precise layer weights requiring training with the use of current sets of data are heuristically decided on through investigation, a process known as fine regulation (Kornblith et al., 2019).

Frequent techniques for fine regulation of DNNs include: (i) upgrading all layer weights (ii) upgrading the weights of some specific layers and fixing those of other layers. On a general basis, the soft max (output) layer is haphazardly initialized and equipped from scratch. By investigating with the various techniques mentioned above concerning the initialization of weights of DNNs, the outperformance of one technique can be seen over the others.

3.10.3 Deep convolutional neural network depth

The number of layers of DNNs is a significant aspect for their performance (Oyedetun et al., 2018). The trend is predictable as deeper DNNs often produce improved results compared to shallower ones (Oyedotun et al., 2018; He et al., 2016; Srivastava et al., 2015). Therefore, from the DNNs previously mentioned, the effect of the number of layers or depth on their operation for classifying white blood cells are readily seen. With respect to the VGG prototypes, 16 and 19 architectures are taken into consideration. For the ResNet, the 18 and 50 architectures are taken into consideration. With respect to DenseNets, architectures 121 and 169 are taken into consideration.

CHAPTER 4
RESULTS AND DISCUSSION

4.1 Experiments

This portion of the thesis presents the details of the data set as well as the experiments that were performed, coupled with the precise settings, outcomes of experiments and the discussions. Every experiment was conducted with the use of a work station with 32GB RAM, an intel core-i7 processor, NVidia GTX1080Ti GPU as well as a functional Windows 10 operating system.

4.2 Original Dataset

For the purpose of showing the improvement in leucocyte classification of this suggested technique, the LISC dataset is employed (LISC dataset 2019). This dataset encompasses all five classes of leucocytes. In total, the dataset possesses 242 data cases. The proportion of data cases per in every class in the initial dataset is shown in Table 4.1.

4.3 Training Settings for Models

This portion introduces the details of the various learning settings as well as data enhancement techniques.

4.3.1 GAN training setting

The information provided in Table 1 are utilized with two convolutional levels and a single fully linked level for the generative and biased networks. Based on the studies conducted by (Goodfellow et al., 2014) the generative adversarial network is learned for sixty epochs with the use of a training frequency of 0.01 and a momentum frequency of 0.5.

4.3.2 DNN classifier training and evaluation settings

The various deep neural networks are learned with the use of mini-batch gradient descent technique. A batch sample of 128 is utilized for every prototype. All the DNN prototypes with haphazardly initialized weights are equipped with an original training frequency of 0.1 and for

300 epochs. All DNN prototypes initialized with weights equipped on CIFAR-100 dataset (CIFAR dataset 2019) are equipped with an original training frequency of 0.005 and for 150 epochs. A momentum frequency of 0.9 is utilized for all prototypes and the original training frequency is decreased by a factor of 0.1 for every moment the training loss is not decreased by 0.001 for five sequential epochs. A weight decay factor of 0.0001 is employed for the regularization of all DNN prototypes. The segmented leucocyte graphics are cropped to 32×32 pixels for input to every DNN prototypes.

For the evaluation of the performance of the equipped DNNs, a 10-fold cross-validation scheme is utilized. In essence, the data is partitioned into ten segments, the DNN prototype is equipped on nine distinct data folds and validated on the left over data fold. This process is redone ten times with the use of distinct nine data folds for equipping and one distinct data fold for assessment. The mean authentication accuracy over the ten distinct data folds is recorded.

4.4 Data Augmentation Methods

4.4.1 Transformation operations for data augmentation

In this section, the previously mentioned data transforming functions are applied. These functions are provided in Section 3.10.1 to the data cases in the various classes for the augmentation of the initial dataset. Three novel datasets known as Trans_aug1, Trans_aug2 and Trans_aug3 which presently respectively have 100 data classes, 150 data instances and 200 data instances. Every one of the previously mentioned data sets are utilized for training and authenticating the distinct DNN prototypes.

4.4.2 GAN method for data augmentation

Three various data sets are developed from the equipped GAN which are referred to as GAN_aug1, GAN_aug2 and GAN_aug3 with 100, 150 and 200 data classes respectively. Some of the data classes developed from the equipped GAN are depicted in Fig. 6.

4.5 Results and Discussion

The outcomes of the DNN prototypes equipped and evaluated on the segmented leucocytes are shown in Table 4.2 to 4.9. Table 4.2 demonstrates the outcomes of the deep neural networks equipped on the initial data (void of the data being augmented) with the use of haphazardly initialized weights. Table 4.3 depicts similar outcomes to Table 4.2 safe the fact that the deep neural network weights were initialized with the weights previously equipped on the CIFAR-100 data set. Table 4.4 depicts the outcomes of the deep neural network prototypes which were initialized haphazardly and equipped with Trans_aug1, Trans_aug2 and Trans_aug3.

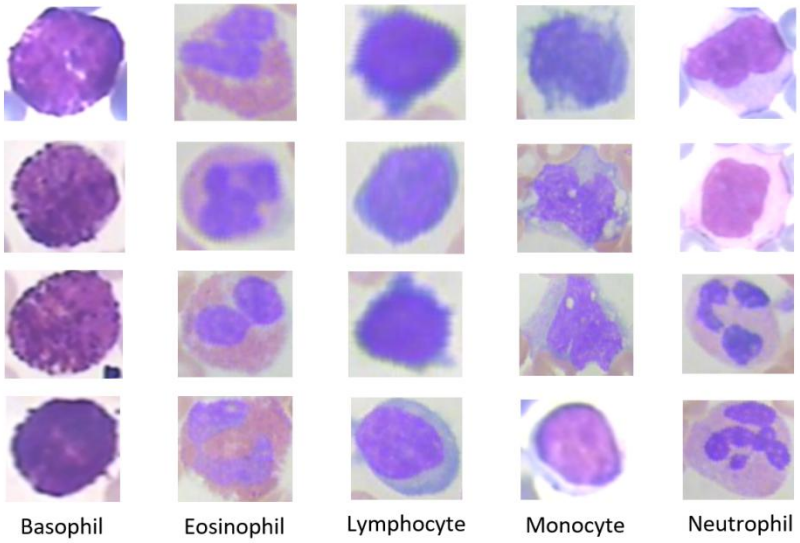

Figure 4.1: Samples of data instances generated from the trained GAN for data augmentation

Table 4.1: Original LISC data set specifics

White blood cell type	Number of instances
Neutrophils	50
Eosinophils	39
Lymphocytes	52
Monocytes	48
Basophils	53

Table 4.2: 10-fold cross authentication of DNN prototypes initialized with random weights

Model	Original data (without augmentation) %
VGG-16	90.6%
VGG-19	91.8%
ResNet-18	91.1%
ResNet-50	92.7%
DenseNet-121	93.9%
DenseNet-169	94.4%

Table 4.3: 10-fold accuracy cross validation of DNN models initialized with pre-equipped weights

Model	Original data (without augmentation) %
VGG-16	90.9%
VGG-19	92.4%
ResNet-18	91.5%
ResNet-50	93.3%
DenseNet-121	94.5%
DenseNet-169	95.2%

Table 4.4: 10-fold cross validation accuracy of the DNN prototypes initialized with haphazard weights

Model	Trans_aug1 (100 inst./class)	Trans_aug2 (150 inst./class)	Trans_aug3 (200 inst./class)
VGG-16	91.5%	92.1%	92.9%
VGG-19	92.3%	92.8%	93.4%
ResNet-18	91.4%	92.6%	93.2%
ResNet-50	93.5%	94.0%	94.7%
DenseNet-121	94.4%	94.8%	95.4%
DenseNet-169	94.9%	95.4%	95.8%

Table 4.5: 10-fold cross validation accuracy of the DNN models initialized with pre-equipped weights

Model	Trans_aug1 (100 inst./class)	Trans_aug2 (150 inst./class)	Trans_aug3 (200 inst./class)
VGG-16	91.4%	91.8%	92.5%
VGG-19	92.9%	93.6%	94.4%
ResNet-18	91.2%	92.2%	92.8%
ResNet-50	94.1%	94.8%	95.5%
DenseNet-121	95.2%	95.7%	96.4%
DenseNet-169	95.8%	96.4%	96.9%

Table 4.6: 10 fold cross validation accuracy of the DNN models initialized with random weights

Model	GAN_aug1 (100 inst./class)	GAN_aug2 (150 inst./class)	GAN_aug3 (200 inst./class)
VGG-16	91.9%	92.6%	93.4%
VGG-19	92.6%	93.1%	93.5%
ResNet-18	92.7%	94.0%	94.6%
ResNet-50	93.8%	94.5%	94.9%
DenseNet-121	95.0%	95.6%	95.7%
DenseNet-169	95.3%	95.4%	95.8%

Table 4.5 shows the outcomes of DNN prototypes which were initialized with the previously equipped weights with Trans_aug1, Trans_aug2 and Trans_aug3 datasets. In Table 4.6, the outcomes of the DNN prototypes initialized with haphazard weights and equipped with GAN_aug1, GAN_aug2 and GAN_aug3 datasets are shown. The results of the DNN prototypes equipped with previously trained weights on GAN_aug1, GAN_aug2 and GAN_aug3 datasets are given in Table 4.7.

Further investigations are conducted by joining the data cases gotten from translation operations and the equipped GAN. Hence, three distinct datasets known as Trans_aug1+GAN_aug1, Trans_aug2+GAN_aug2 and Trans_aug3+GAN_aug3 with 200 data cases, 400 data cases and 600 data cases respectively. In Table 4.8, the outcomes of the DNN prototypes initialized with haphazard weights on Trans_aug1+GAN_aug1, Trans_aug2+GAN_aug2 and Trans_aug3+GAN_aug3 datasets are shown. The outcomes of the DNN prototypes initialized with previously equipped weights and trained on Trans_aug1+GAN_aug1, Trans_aug2+GAN_aug2 and Trans_aug3+GAN_aug3 are shown in Table 9. The final observation deduced from the experimental outcomes are thus:

The DNN prototypes which utilized previously equipped weights perform on a consistent basis, same DNN prototypes trained on a similar dataset though with haphazardly initialized weights.

Table 4.7: 10-fold cross validation accuracy of the DNN prototypes initialized with pre-trained weights

Model	**GAN_aug1 (100 inst./class)**	**GAN_aug2 (150 inst./class)**	**GAN_aug3 (200 inst./class)**
VGG-16	92.3%	93.0%	94.1%
VGG-19	93.3%	93.7%	95.0%
ResNet-18	92.9%	93.7%	94.2%
ResNet-50	94.7%	95.5%	95.8%
DenseNet-121	95.4%	96.2%	97.2%
DenseNet-169	96.1%	96.9%	97.2%

Table 4.8: 10-fold cross validation accuracy of the DNN prototypes initialized with random weights

Model	**Tran_aug1 + GAN_aug1 (200 inst./class)**	**Tran_aug2 + GAN_aug2 (300 inst./class)**	**Tran_aug3 + GAN_aug3 (400 inst./class)**
VGG-16	92.5%	93.2%	93.9%
VGG-19	93.3%	93.7%	94.4%
ResNet-18	93.2%	94.5%	95.1%
ResNet-50	94.2%	95.2%	95.6%
DenseNet-121	95.5%	96.1%	97.3%
DenseNet-169	95.9%	96.3%	97.3%

Table 4.9: 10 fold validation accuracy of the DNN prototypes initialized with pre-trained weights

Model	**Tran_aug1 + GAN_aug1 (200 inst./class)**	**Tran_aug2 + GAN_aug2 (300 inst./class)**	**Tran_aug3 + GAN_aug3 (400 inst./class)**
VGG-16	94.3%	94.9%	95.7%
VGG-19	94.8%	95.4%	95.9%
ResNet-18	94.1%	95.2%	95.4%
ResNet-50	95.8%	96.7%	97.4%
DenseNet-121	96.3%	97.4%	98.3%
DenseNet-169	96.9%	98.1%	98.8%

It is readily observed from Tables 4.2 to 4.9 that the ResNet and DenseNet models with numerous parameterized levels and skip links perform better than the VGG models. In addition, it is seen that augmenting the data enhances the operation of every other model as depicted by contrasting Table 4.2 with Table 4.3 to Table 4.9. Utilizing similar quantity of data classes, the enhanced data sets gotten from the equipped GAN result to improved DNN performances compared to utilizing augmented datasets obtained from graphic transformation

functions. The combination of data classes gotten from the equipped GAN with data classes obtained from operations of graphic transformation result to much improved outcomes compared to utilizing either the enhanced data obtained from trained GAN or operations of image translation.

From the viewpoint of computations, Figure 4.2 reports the period needed by the various DNN models to conduct inference with the authentication data from the 10 fold cross validation training scheme. It is observed that the most appropriate models ResNet-50, DenseNet-121 and DenseNet-169 took up the greatest inference time. This is not unusual owing to the fact that they possess numerous parameterized levels and so need more time for the computation of their final outcomes.

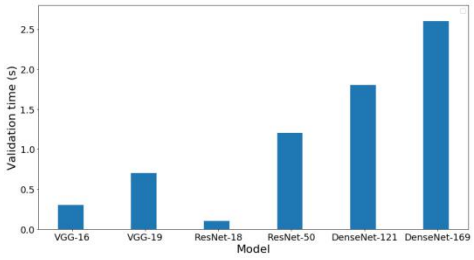

Figure 4.2: Time for the DNN models to perform inference on the validation data. The original data without data augmentation given in Table 4.1 is used for this experiment

Table 4.10: Results comparison with other works

Model	Accuracy (%)
ResNet-50 (Tran_aug3 + GAN_aug3)	97.4
DenseNet-121 (Tran_aug3 + GAN_aug3)	98.3
DenseNet-169 (Tran_aug3 + GAN_aug3)	98.8
Neural network (Hegde et al., 2018)	96.5
Linear discriminant analysis (LDA) (Ramesh et al., 2018)	93.9
W-Net 45 (Jung et al., 2019)	97.0
W-Net 45 **(**Jung et al., 2019)	96.0
Neural network + PCA 44 (Nazlibilek et al., 2014)	95.0
Neural network (Zheng et al., 2018)	95.2

Table 4.10 presents a contrast of leucocyte classification accuracy from prior studies. The contrast with prior studies is conducted which perform classification of leucocytes into five classes. The DNN models suggested in paper (highlighted in bold) perform better than the models from previous works.

CHAPTER 5
CONCLUSIONS AND RECOMMENDATION

5.1 CONCLUSION

Blood is one of the major compositions of the human body. It is composed of plasma, erythrocytes, leucocytes, and platelets also known as thrombocytes. However, the use of deep learning has over the years proven to be very effective in different diagnosis with blood included.

Deep learning techniques with the use of convolutional neural networks is at present the method of choice for the recognition and classification of white blood cells in applications involving medical imaging. As the convolutional neural networks accomplish satisfactory outcomes on extensive datasets, they need much data as well as computational resources for training. In several instances, the data set is restricted and may be insufficient for training a convolutional neural network from scratch. Faced with such a situation, in a bid for leveraging the potency of convolutional neural networks while simultaneously decreasing the cost for computation, transfer learning can be employed.

In this thesis, the classification of white blood cells have been addressed using deep convolutional neural networks. The proposed approach tackles the problem of insufficient data for training white blood cells classification systems to reach decent performances. Specifically, data augmentation techniques such as image transformation operations and trained generative adversarial networks (GANs) are employed for increasing the size of training data. For the the classification networks, we rely on modern models such as VGG, ResNet and DenseNet, which are either trained from scratch or already trained. The obtained results show a marked improvement in the performance of the different classifier networks in correspondence with the additional data obtained via the aforementioned data augmentation techniques. Against several earlier approaches, the proposed classification systems yield results that are more

interesting. On top of this, the proposed classification system require no advanced image pre-processing stages that are common in many earlier works. This feature dramatically improves the development time and effort, along with the simplicity of the proposed classification systems.

5.2 RECOMMENDATION

The use of deep learning has been very effective in several diagnosis studies. However, it is recommended in future studies that a combination of different techniques as well as the use of other networks such as VGG-19 is explored to experiment the level of diagnosis in terms of accuracy and precision level. Moreover, the use of Support Vector Machine (SVM) have been reported in several studies to be very effective as a combination technique with other networks. However, the use of ResNet50-SVM, DenseNet121-SVM, and DenseNet169-SVM might be very effective in getting a high level of accuracy.

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APPENDICES

APPENDIX 1
ETHICAL APPROVAL LETTER

NEAR EAST UNIVERSITY  YAKIN DOĞU ÜNİVERSİTESİ

ETHICS APPROVAL LETTER

TO GRADUATE SCHOOL OF APPLİED SCİENCES

Re: Khaled Abdalla Almezhghwi (20166682)

I would like to inform you that the above candidate is one of our Ph.D. students in the Electrical and Electronic Engineering department. He is taking the thesis under my supervision, and the thesis entailed: IMPROVED CLASSIFICATION OF WHITE BLOOD CELLS WITH GENERATIVE ADVERSARIAL
NETWORK AND DEEP CONVOLUTIONAL NEURAL NETWORK. The data used in his thesis does not require any ethical report.

Please do not hesitate to contact me if you have any further queries or questions.

Best Regards,

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APPENDIX 2

SIMILARITY REPORT

AUTHOR	TITLE	SIMILARITY	GRADE	RESPONSE	FILE	PAPER ID	DATE
Khaled Abdalla Almez...	Abstract	0%	--	--		1349395644	25-Jun-2020
Khaled Abdalla Almez...	Chapter 4	0%	--	--		1349396557	25-Jun-2020
Khaled Abdalla Almez...	Chapter 5	0%	--	--		1349396682	25-Jun-2020
Khaled Abdalla Almez...	Chapter 3	8%	--	--		1349396413	25-Jun-2020
Khaled Abdalla Almez...	Chapter 1	9%	--	--		1349395847	25-Jun-2020
Khaled Abdalla Almez...	Chapter 2	12%	--	--		1349396186	25-Jun-2020
Khaled Abdalla Almez...	PhD Thesis	13%	--	--		1349397104	25-Jun-2020

IMPROVED CLASSIFICATION OF WHITE BLOOD CELLS WITH GENERATIVE ADVERSARIAL NETWORK AND DEEP CONVOLUTIONAL NEURAL NETWORK

Turnitin result

Assist. Prof. Dr. Sertan Serte