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ADVANCEMENT IN MACHINE LEARNING TECHNOLOGIES TO SCREEN SICKLE CELL ANEMIA.

Shadman Moiz[1], Ajay Nath Jha [2], Vishal Upmanu[3] Ravinder Singh Mann[4], Mohammad Saquib Ashraf [5]*

1. Department of Biotechnology, Lalit Narayan Mithila University, Darbhanga, Bihar, India.
2. Department of Zoology, Lalit Narayan Mithila University, Darbhanga, Bihar.
3. Department of Electronics and Communication Engineering, R D Engineering College Ghaziabad, UP.
4. Department: Computer Science & Engineering, Guru Nanak Institute of Engineering & Management Naushehra, Hoshiarpur.
5. Department of Medical Laboratory Sciences, College of Applied Medical Sciences, Riyadh ELM University (REU), Riyadh, Kingdome of Saudi Arabia.

**corresponding author and email address:*

Dr. Mohammad Saquib Ashraf

Riyadh ELM University, Riyadh, Saudi Arabia.

Abstract

Sickle Cell Anemia is a hereditary disorder caused due to abnormal red blood cells which affect more than 300k newborn babies globally every year. The present-day treatments for this health problem require adept medical professional, gives fallible results, and are costly and time-consuming. These are major impediments to the timely diagnosis of this blood disorder. Modern techniques like artificial intelligence and machine learning are used to elucidate medical data and support medical decisions. Here we have reviewed the advancement in machine learning models like Plain Convolution Neural Networks (PCNN), data augmentation of Plain Convolution Networks (DAPN-48), Very Deep Convolutional Networks (VGG19), and Multi-Layer Perceptron (MLP) models that can aid in the estimation of clinical complications and development of effective therapies for sickle cell anemia.

Keywords: Sickle Cell Anemia, Machine Learning, Multi-Layer Perceptron, Data Mining Techniques, Neural Networks, Diagnosis, Convolution Neural Networks (PCNN), data augmentation of Plain Convolution Networks (DAPN-48), Very Deep Convolutional Networks (VGG19), Residual Networks (RESNET-50)

1. Introduction

1.1 Sickle Cell Anemia

Sickle Cell Anemia (SCA) is a genetic blood disorder that is caused by a mutation in the oxygen-carrying protein hemoglobin (Hb) present in red blood cells [1,2]. Normal RBC with wild-type hemoglobin is smooth and disk-shaped which can advance through the blood vessel undisrupted. The wild-type Hb contains heme which binds to oxygen and functions to transport oxygen from the respiratory tract to the tissues.

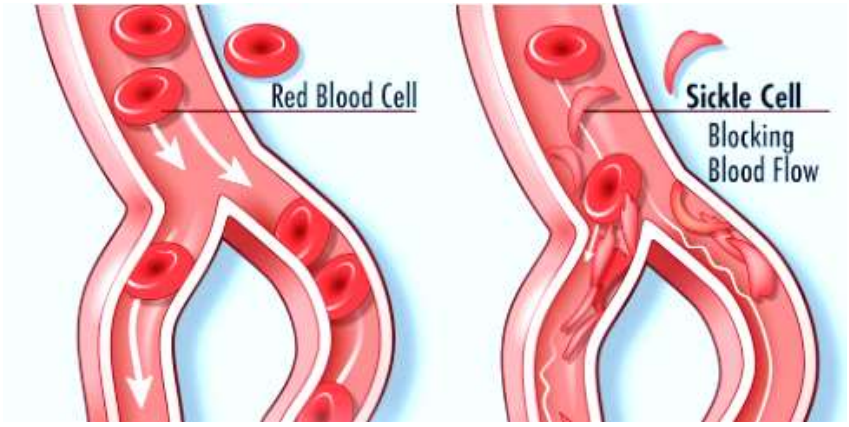

Figure 1: Comparison of Normal Red Blood Cells and Infected Cell with Sickle Cell Anemia. The morphological differences and how it affects blood flow can be seen. (The image is taken under a Creative commons license from https://www.flickr.com/photos/nihgov/27669979993)

As evident from Figure 1 that there are morphological differences in the shape of wild type and mutated Hb that causes the SCA disorder. The abnormal Hb is horse-shoe (crescent) shaped due to which the flow of RBC is obstructed in the blood vessel (Fig. 1) [4]. They are rigid and tend to stick together. This causes an insufficient supply of oxygen to the tissues. The life span of an infected RBC (20 days) is about six times lesser than the normal RBC (120 days).

Anemia is a medical condition in which healthy red blood cell is deficient in the body [5]. The obstructed flow of healthy RBC in the case of SCA is accompanied by the filtration of infected RBC with SCA by the spleen. The less flow of healthy RBC in the body leads to anemia.

The SCA is caused by a mutation in a single gene that codes for valine, a hydrophobic amino acid, in the mutated state instead of glutamic acid, a hydrophilic amino acid, in the normal state in the beta chain of the hemoglobin. This monogenetic change results in a change in the protein structure and shape of the red blood cell. The two dominant gene forms of Hb (Hb^A) are present in the normal individual whereas one gene of the mutated form (Hb^S) is present in the carrier and two genes of defective Hb^S are present in the sickle cell anemic patient. The carrier individual lives a healthy life. The disorder increases morbidity and mortality [6], especially in individuals in lower-income countries with inadequate facilities.

1.2 Medical Symptoms

Sickle cell anemia disorder symptoms can be different from individual to individual [7]. The symptoms of the disorder start occurring as early as the age of five months. It includes bones, ulcers, and joint aches in adults. This is a result of insufficient blood supply to the body. Another symptom that is commonly seen in the case of SCA is swelling of arms and feet. Patients infected with SCA have diminished immunity due to which they are prone to get frequent infections. Medical experts often prescribe medications to patients to prevent other infections like pneumonia. Another symptom observed in these patients is aberrant development due to lack of oxygen which is important in cellular respiration and metabolism. A lack of oxygen (Hypoxia) results in improper growth and development of embryos and

organs. Lack of supply of oxygen also results in vision issues including retinal damage or even loss of vision.

The complications that are associated with SCA include an increased possibility of heart stroke [8] which leads to numbness in arms, consistent speech problems, unconsciousness, and fatigue in limbs. This is the result of a lack of blood supply to the brain. They also suffer from leg ulcers. Another medical complication seen in the patients is acute chest syndrome which can be life-threatening and requires proper medications. Pulmonary hypertension in kids and adults are observed in these patients.

1.3 Sickle Cell Anemia Types:

The disorder has been classified into the following different types based on a mutation in Hemoglobin and the severity of the disease thereof [9]. Hemoglobin constitute of two alpha chains and two beta chains. The mutation in the protein is responsible for the disorder.

1) Hemoglobin SS Type: This is the most severe type. Here the patient receives the mutated gene from both of the parents. This is the most common type where the patient gets the maximum severity and highest symptoms from the disease. This is commonly seen in Indian and African traits.

2) Hemoglobin SC Type: In this type of disorder, the patient receives the HbC gene from one parent and the HbS gene from the other parent. The HbC is the result of another type of mutation in the Hb Beta chain. This is less severe than the Hemoglobin SS type due to a better flow of healthy blood cells in the body. This is mostly seen in West African, Mediterranean, and Middle Eastern traits.

3) Hemoglobin S beta-plus thalassemia Type: In this type, there is beta-globin gene mutation for both the Hemoglobin beta chains. The red blood cell size is reduced. If it is accompanied by HbS gene mutation inheritance, this leads to hemoglobin S beta-thalassemia. This is mostly seen in Mediterranean and Caribbean traits.

4) Hemoglobin SD Type: Another type of hemoglobin (hemoglobin D) interacts with the sickle cell Hb gene. It has a moderate infection and is found in Asian and Latin American traits.

5) Hemoglobin SO Type: Another type of hemoglobin (hemoglobin O) interacts with the sickle cell Hb gene. It has a moderate infection and is found in Arabian, North African, and Eastern Mediterranean traits.

1.4 Sickle Cell Anemia and Malaria

Notably, individuals suffering from sickle cell anemia are more resistant to malarial infection than those with wild-type hemoglobin [10]. There is almost 60 percent less occurrence of malarial parasites in the infected individuals compared to normal individuals. They have less malarial severity, blood transfusion, mortality, and blood infection.

It is interesting to understand how one infection can mitigate the effect of another infection. It has been observed with other infections as well. But how does it happen? Malarial infection initiates when the parasite occupies wild-type red blood cells and restructures their content. The parasites reproduce and caused red blood cells to stick. In the case of mutated hemoglobin, the parasite is unable to complete its reproduction cycle and the immune system compliments it by clearing the parasite-infected red blood cell. The carrier is protected against malarial infection but the infected individuals with the HbSS gene. This is due to the wrecked immune

system in the affected homozygote. The malarial parasite can proliferate better without elimination. Such a trait is called polymorphism where one trait is good for one and bad for others. It is also believed that SCA can be a result of natural selection for those areas where malaria is prevalent.

1.5 Diagnosis and Current Treatment

The diagnosis of the disorder can be done by a blood test. In several countries like the USA, a blood test is routinely conducted on new borne babies for screening diseases [11]. The blood is taken which is then sent to the laboratory for screening of the disease. A genetic test can also be performed to screen for the disorder. A genetic test can also affirm if the patient is a carrier or normal or carries two copies of the mutated hemoglobin. The diagnosis can be conducted in newborn babies where a sample of fluid is taken for testing from amniotic fluid. Complications associated with the disorder can also be diagnosed with different techniques. Assessment of stroke risk can be done by using an ultrasound machine.

The major symptom of the disorder involves pain crises so the treatment and management of it involve relieving the pain and accessing the complications and appropriate treatment for those complications with medications and blood transfusion or even stem cell transplant. Hydroxyurea (Droxia, Hydrea, Siklos) [12,13]relieves the pain crisis, and Crizanlizumab (Adakveo) and L-glutamine oral powder (Endari) reduces pain crisis frequency. Voxelotor (Oxbryta) is another medication that can help in ameliorating blood flow throughout the body and treat SCA. SCA disorder complications can be prevented by taking penicillin or childhood vaccinations. The medications can have side effects so appropriate precautions have to be taken. Surgical treatments include blood transfusions and stem cell transplants. Modern medical studies are also focusing on clustered regularly interspaced short palindromic repeats (CRISPR) and gene therapies. It is important to timely diagnose the disease and the complications associated with it. New machine learning methods are being currently studied for better diagnosis of the disease in timely a and cost-effective manner.

2. Machine Learning Models in Sickle Cell Anemia

Modern-day medical diagnosis involves the use of advanced technologies like machine learning in developing therapeutics for diseases [14-16]. In the case of sickle cell anemia, machine learning techniques are used to automate the process of screening the sickle cells from microscopic images (Fig. 2). Here we will focus mainly on Plain Convolution Neural Networks (PCNN), data augmentation of Plain Convolution Network (DAPN-48), Very Deep Convolutional Networks (VGG19), and Multi-Layer Perceptron (MLP) models.

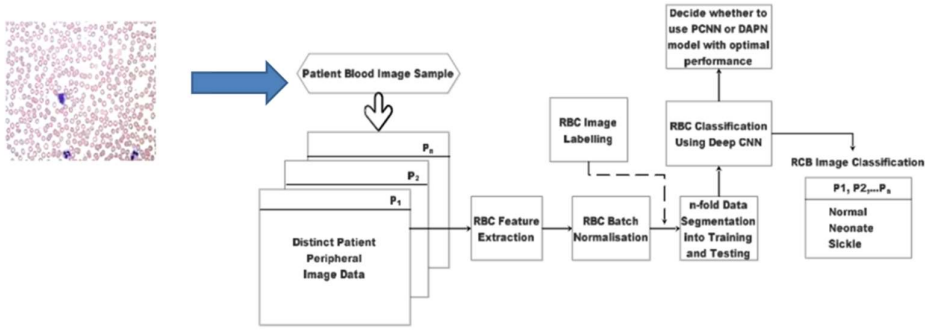

Figure 2: General Architecture of Machine Learning Algorithm [1].

2.1 Plain Convolution Neural Networks (PCNN):

Plain Convolution Neural Networks (PCNN): The images that have to be diagnosed can have normal, sickle cell, or neonate RBCs. The major components of this deep neural network consist of the image input layer, batch normalization layers (eleven in this case), batch normalization layers, rectified linear units, and one softmax layer (Fig 3 A). The function of the batch normalization layer is to optimize the gradients across the networks. Rectified linear units enhance network training and mitigate network affectability. Here the deep neural network is composed of consecutively linked layers. The image input is of 30 heights, 30 weights, and 3 channels. Several filter sizes are present in three convolutional layers. The number of layers can be increased to achieve better results (PCNN-48). This method for automating the diagnosis of sickle cell anemia is under study and has future applicability for researchers in the field of Life Science and Machine Learning.

2.2 Data Augmentation of Plain Convolution Network (DAPN-48)

It is one of the most effective methods that have given an accuracy of up to 99.2 percent. As depicted in Fig. 3 (B), the general organization is very similar to a plain convolution neural network but the number of layers is increased and followed by a data augmentation technique where training sets are artificially increased by generating altered copies of a dataset from existing data.

2.3 Very Deep Convolutional Networks (VGG19)

This method of classification contains VGGNet with 4096 channels for two completely connected layers which are accompanied by another layer having 1000 channels. Ultimately for the categorization, the Softmax layer is utilized. This has also been under study for automatic diagnosis of SCA disorder.

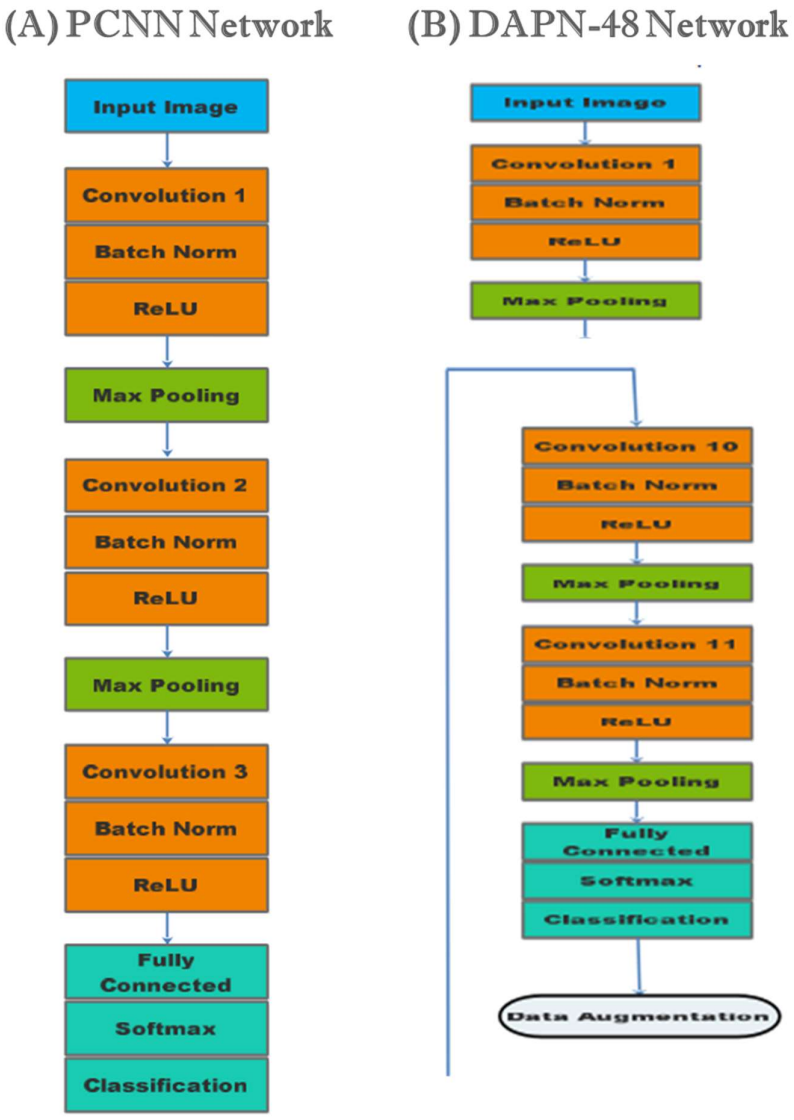

Figure 3: Flowchart for PCNN and DAPN-48 Network models [1].

2.4 Multi-Layer Perceptron (MLP) models

Multi-layer perception represents a neural network (Artificial Neural Network). They involve 'secret layers' which can be used to generate output from input as shown in Fig. 4. The algorithm is utilized in speech recognition and image recognition. It constitutes four layers of non-linearly triggering nodes. This is one of the illustrations of controlled learning and generalization of the mean square technique.

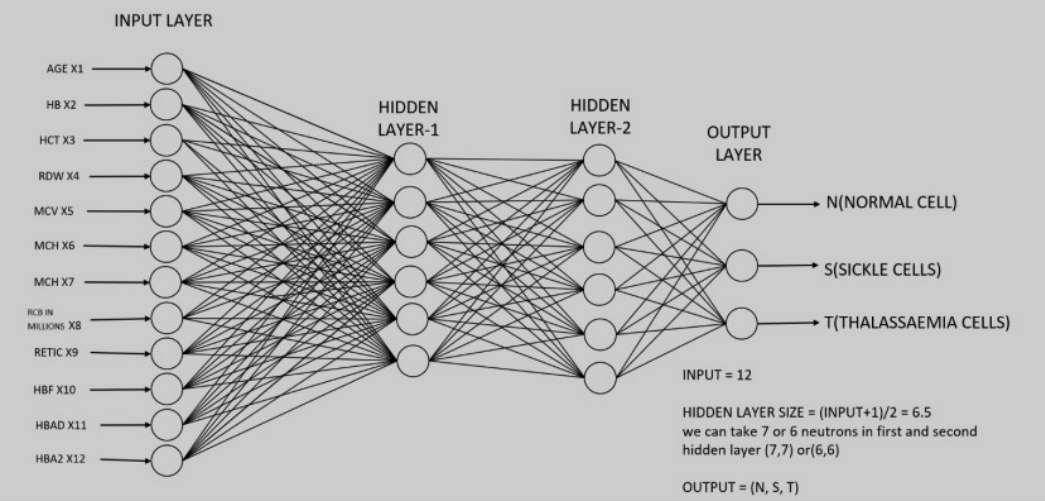

Figure 4: Flowchart for MLP model [2].

3. Conclusion

Sickle Cell Anemia (SCA) is an inherited disorder with an increasing number of carriers and infected individuals every year globally. It is accompanied by many complications. A timely diagnosis and treatment are important for tackling the health issue. Several ongoing studies are in progress that uses machine learning techniques and health issues including Plain Convolution Neural Networks (PCNN), data augmentation of Plain Convolution Network (DAPN-48), Very Deep Convolutional Networks (VGG19), and Multi-Layer Perceptron (MLP) models. The DAPN-48 model is one of the very successful models with more than 99 percent accuracy. It is an open avenue for Life Sciences and Data Sciences enthusiasts for developing better diagnosis in healthcare against Sickle cell anemia disorder.

4. Declarations:

All the authors agreed and provided their consent for the publication of this review article.

5. Ethics approval and consent to participate

Not applicable. The study does not involve any human subjects, tissue samples, or cell lines.

6. Consent for Publication

All authors consent to the publication of the manuscript

7. Competing interests

The authors declare no conflict of interest.

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