SUPERVISED MACHINE LEARNING ALGORITHMS FOR ANALYSIS ON

SICKLE CELL ANEMIA

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Abstract

Sickle Cell Anemia(SCA) is one of the unresolved medical problems which is mostly identified as an inherited form of anemia. Apart from having different clinical tests to detect the disease, about 5% of the world's populations are healthy carriers of sickle cell anemia. High performance liquid chromatography (HPLC) Test is the high priority medical test used to screen/detect SCA exhibiting accurate disease diagnosis. The main objective of the proposed model is to compare and analyze the algorithms efficiency by implementing them on Sickle Cell Anemia dataset which is obtained through HPLC Test. Supervised Machine Learning Algorithms like Support Vector Machine(SVM), Naive Bayes(NB) and Random Forest Trees(RFT) have been applied in the proposed model. Initially, Feature Selection technique is implemented on the dataset and then data visualization is done using Histograms. Finally comparison of the accuracies between the models is done and the best is tuned to achieve the accuracy precisely. Even though the analysis is done with limited amount of data, SVM algorithm accomplishes highest accuracy of 56% when compared with the remaining two algorithms.

Keywords: Sickle Cell Disease(SCD), Sickle Cell Anemia(SCA), Hemoglobin(Hb), Sickle Cell Trait, Bioinformatics, High Performance Liquid Chromatography Test(HPLC), Machine Learning, Python, Jupyter Notebook, Support Vector Machine(SVM), Naive Bayes(NB) and Random Forest Trees(RFT).

1. Introduction:

Sickle cell anemia was previously identified in United States of America by James B Herrick and was later intended by Pauling in 19th Century[1]. It is a blood cell disorder that is developed gradually due to contamination of red blood cells. Generally, there are three types of blood cells present in the blood. They are classified as White Blood Cells, Platelets and Red Blood Cells. White Blood Cells help body to fight several infections. Platelets help body to clot all kinds of bruises that are obtained from accidents. Red Blood Cells are used to transport oxygen to all the tissues and organs due to presence of hemoglobin. In Sickle Cell Anemia, red bloods cells play a major role. Usually the Red Blood Cells are biconcave in shape time of 90-120 days. But once they are affected by Sickle cell Anemia the shape of RBC changes from biconcave to crescent moon shaped and also their life time is reduced to 10-20 days[2]. This condition causes Anemia. Within the Red Blood Cells, a protein called "hemoglobin" is used for transferring oxygen throughout the body. Sickle Cell Disease is caused due to transfusion of gene observed in the hemoglobin molecule. The major reason for sickle cell anemia is due to mutation in a specific gene named "Beta-Globin" chain present in hemoglobin. There are four elements present in hemoglobin. Two of them denote "Alpha-Globin" and the other two represent "Beta-Globin". All of these molecules are combined by a small iron molecule called "heme". The sixth position in the Beta-globin chain of chromosome no.11 comprises of Glutamic acid. After the gene is infected the glutamic acid is repossessed by Valine amino acid[3] which is shown in Fig 1, leads to generation of abnormal sickle molecules in hemoglobin. Abnormal type of hemoglobin HbS is observed in people affected with sickle cell anemia. The secondary cause for Sickle Cell Anemia is due to Inheritance. If either of the parents are having Hemoglobin (HbS), an abnormal gene then that gene would be continued to their child. This condition is known as Sickle Cell Trait [2]. Sickle Cell Trait means receiving a single copy of HBB gene from their parents would result in Sickle trait.
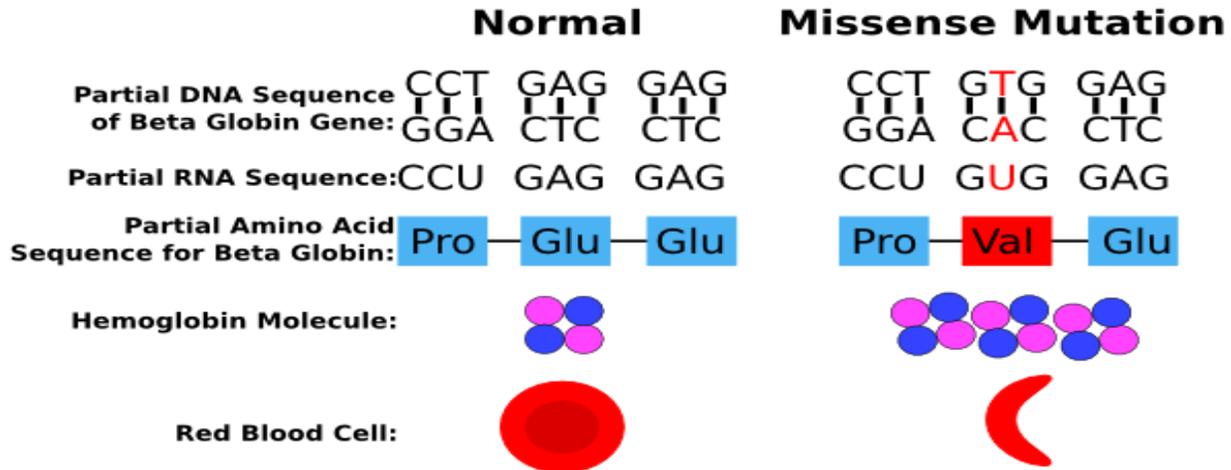
Fig 1:   **Gene Structure of Normal and Sickle Red Blood Cell.**

- Both parents have sickle cell trait→ if both parents have sickle cell trait, and then there is a 25 percent risk of the child having sickle cell anemia and a risk of 50 percent having sickle cell trait. Simultaneously there will a 25 percent chance of child not inheriting the mutated gene copy.

- One parent has sickle cell anemia and the other has sickle cell trait → if one parent has sickle cell anemia and the other has sickle cell trait, half of the percent may be at a risk with either sickle cell anemia or sickle cell trait.

- Both parents have sickle cell anemia→ if both parents have sickle cell anemia, then their children will also definitely have the disease.

The Third cause for sickle cell anemia depends on some phenomenal conditions like cold temperatures, dehydration, tobacco smoke, stress, excessive amount of activity and many more. It is mostly identified in some rural areas like Orissa, Araku and many more. Previously it is originated from other countries like United States and Africa. Now days, it has been identified and is developing day by day in and around Andhra Pradesh also. Research is going on to reduce the scope of this disease and some more measures have to be taken to increase the immunity power resulting in withholding of any such kind of infections.

2. Literature Review:

The field of informatics is a combination of computer programming accompanied by hardware equipment which can be used in health department for easy disease diagnosis or treatment. Informatics is enforced in the health care field especially for the management and use of patient health care information. This is defined as healthcare informatics. It is also termed as Bioinformatics, an evolving science with an increase in electronic health records associated with data analytic systems[5] which plays a major role acting as a collaborative field used in designing advanced devices or equipment which can be used in accessing biological data which reduces the work load for health experts. Efficient tools can be developed to interpret the results accurately and meaningfully. Bioinformatics will be helpful in disease diagnosis, severity detection, drug designing and treatment based on the data provided by centrally accessible global databases. In this paper the clinical data gathered is related to Sickle Cell Anemia and the computational techniques adapted are related to Machine Learning a sub module of Artificial Intelligence. These days every field is being tuned into machines based on Artificial Intelligence which perform wide range of tasks reducing the man power and simultaneously deriving the output as per human limitations. There are many sub fields of AI which are applied in various sectors. Some of them are Machine Learning, Deep Learning, Expert Systems, Natural Language Processing, Speech Processing and many more.

Machine learning is concerned with design and development of algorithms and techniques that allow computers to learn in the initial stages and later masters itself similar to humans. It is also termed as predictive analytics. Computational learning theory is a branch in which Computational analysis of machine learning algorithms and their performance are analyzed[6]. Machine learning can be applied in different approaches to teach computers for accomplishing the tasks where efficient algorithm is not used for obtaining desired results. Depending upon the nature of outcome desired, machine learning algorithms can be classified into three categories[14]. They are

- Supervised learning
- Unsupervised learning
- Reinforcement learning

Supervised learning

Supervised learning describes the effect of inputs on other set of expected outputs. It builds a mathematical model for any given set of data consisting of both inputs and outputs. Entire data is trained with a set of approaches which helps the machine in decision making and therefore improvising itself. This learning algorithm includes classification and regression. When outputs are controlled to limited set of values classification algorithms are used. Every training example can have one or more input and output can be termed as supervisory signal. All the training examples are represented either in the form of array/vector/feature vector and the respective output is fetched in the form of a matrix. Optimal function is used to determine the output for inputs that were not a part of the training data. There are many classification techniques in supervised learning which are indulged in performed essential tasks. Some of the techniques used in this model and SVM, RFT and NB. These algorithms give different prediction accuracies when they are compared to each other. They provide the efficiency of each algorithm in terms of specificity, precision, sensitivity and accuracy. Among all the three algorithms SVM has the highest efficiency. But the major disadvantage of this supervised learning model is that it cannot be implemented in learning models with deep hierarchies.

Unsupervised learning

In Unsupervised learning all the input observations are given but there is no availability of determined outputs and enables users to learn larger and more complex models. Principal Component and Cluster Analysis are two main methods available in unsupervised learning[7].

Reinforcement learning

In Reinforcement learning, the developed machine learning model is trained to make a sequence of decisions. This type of learning is based on interactions between an agent and its environment. The agent learns to achieve the goal in a complex environment. It is a popular technique for organizations which deal with large complex problems.

Bio informatics is a combination of biological science and computer programming[7]. Artificial intelligence is simulation of human intelligence in machines which are programmed to behave like humans. Implementing bioinformatics and artificial intelligence in the medical field gives the best outcome. The machine learning algorithms are applied to the medical data to obtain fast and accurate results when compared to the available clinical tests. In this paper accuracy of Sickle Cell Anemia is tested using some Machine Learning algorithms which represent a module of bioinformatics.

Sickle Cell Anemia is one of a group of disorders known as Sickle Cell Disease which is an inherited disease that affects Hemoglobin a protein present in RBC which is responsible for transferring oxygen to all cells present in the body. RBC is generated from bone marrow and when cell is converted from normal RBC to Sickle Cell, it gets terminated. Since, production of new RBC is a time consuming process and it leads to Sickle Cell Anemia. Some symptoms like Anemia, Vaso-occlusive Crisis, Hemolytic Crisis, and Acute Chest Syndrome with Stroke are developed in patients affected with Sickle Cell Anemia[8]. Anemia is one of the major symptoms which have the

highest priority. Person suffering from anemia is mostly intended to suffer from malaria. Lack of healthy RBC results in Anemia. Vaso-occlusive crisis is another symptom which refers to pain in abdomen. Pains are developed when sickle shaped RBC blocks the blood flow in the tiny blood vessels. Due to low blood flow, there is a decrease in oxygen levels consumed by the body which directs to a vascular necrosis of the hip, damage of organs like kidneys, liver and spleen and other major joints. Random change in hemoglobin levels leads to Hemolytic crisis. Quick destruction of RBC is observed in premature state whereas their reproduction takes more time. This is mostly observed in patients having G6PD which means genetic abnormality. Other causes for SCA are deficiency in proteins and hemoglobin molecules that are present in RBC, autoimmune diseases and some other infections. Chest pain, fever and difficulty in breathing are some of the symptoms observed in acute chest syndrome with stroke. The sickle cells block the blood vessels present in the lungs which lead to lung infection. The frequency and lifetime of these crises may differ substantially. Simultaneously if blood flow is blocked to brain it leads to Stroke. Some of the major symptoms for stroke are seizures, numbness of legs and arms. It remarks an emergency situation[8].

Sickle Cell Anemia can be diagnosed using different medical tests. The available tests are Complete Blood Count (CBC Test), Solubility Test, Hemoglobin Electrophoresis[9], High Performance Liquid Chromatography Test[10] etc are mentioned in Table 1.

- CBC Test is the primary test conducted for sickle cell anemia patients which provides the complete blood report that includes values of Hemoglobin, RBC, White blood cells, Hematocrit, number of cells in the blood, Platelet Count Etc. Hematological values are used for monitoring the status of SCA patients. RBC Count defines him or she is affected with anemia where further identification is done using other tests[9].
- Solubility test is the easy test to identify the sickle cell anemia. Sodium Dithionite is used in this test which is easily dissolvable and releases the Hemoglobin by breaking the RBC. When Hb S is present in blood it does not dissolve in Plasma it becomes cloudy with some crystals[9].

Table1: **Tests available to screen the presence of Hemoglobin S (HbS):**

Available methods for detecting Sickle Cell Anemia	Test principles	Sensitivity for HbS (for 100 percent)	Specificity for HbS (for 100 percent)
Solubility test with Sodium Hydro-Sulfite solvent	Tube test which reveals HbS in residue Format	99 %	99.9 %
Solubility test with Sodium Meta-Bi-Sulfite solvent	Blood slide test reveals Sickle RBC	97.3 %	99.6 %
Hemoglobin Electrophoresis test	Hemoglobin protein separated by electric charge	100 %	100 %
Iso Electric Focusing test (IEF)	Hemoglobin protein migrate to iso electric points	100 %	100 %
High Performance Liquid Chromatography test (HPLC)	Hemoglobin protein moves with different speed in column	100 %	100%

- Hemoglobin Electrophoresis is a more sophisticated test which gives information about the presence of HbS in sickle cell anemia patients. Blood particles are separated using electric charge because they move at random speed[9].
- High Performance Liquid Chromatography (HPLC) is recognized as high priority test which is mostly used to identify, quantify and separate each component in a mixture. User Software and Digital Microprocessor controls the HPLC instrument and provide the analysis of the data. Output is obtained in the form of graphs with peaks[10].

Any test used for sickle cell identification must check for Sensitivity and Specificity. Sensitivity is defined as how often a test generates positive results for the person who is being tested. Specificity is the proportion of healthy patients who are tested negative for a disease. The below table describes the tests that are used to identify Sickle Hemoglobin (HbS) with their respective working principles followed while performing the test displaying Sensitivity and Specificity of HbS in Sickle Cell Anemia patients[12].

Till now there is no proper reason to explain how the sickle cell anemia is an inherited disease as research is still being carried out and many questions are still unsolved. Sickle cell anemia is thoroughly diagnosed only through the available medical tests and there is no proper bio informatics application that can be implemented in identifying the sickle cell anemia. Further research can be done on this application.

3. Proposed Methodology:

High Performance Liquid Chromatography (HPLC) machine performs HPLC test on the blood samples using some solvents. This test has the highest priority to screen all types of hemoglobin. It gives accurate values of HbA, HbA2 and HbF along with HbS. It separates different constituents of a compound with high pressure, to push the solvents through the column. It is used to identify, quantify and separate compounds of a mixture. The charge will separate different hemoglobin's present in the blood sample[10].

Dataset:

Data used for the proposed model is collected from the HPLC machine after performing HPLC test. It is a process of gathering information which is given as an input to train and test the model. Values of different hemoglobin's are obtained and the null values are removed. Clinical data with 120 datasets consist of attributes like age, HbA0, HbA2, HbS, HbF[9] etc. HbA0 represent adult blood hemoglobin with two alpha and two beta chains, HbA2 is another type of adult blood with two alpha and two delta chains, HbS is the sickle hemoglobin mainly found in people affected with sickle cell anemia and HbF represents the fetal hemoglobin which will high in infants to toddlers and gradually decreases when the child becomes adult[9].

This is further continued by a process called feature selection in which the features are selected manually and the attributes are described for developing the model. Reduction in the number of input variables improves the performance of the model. Feature selection is often termed as variable selection, attribute selection etc.

After performing the feature selection, we move towards data visualization which is a visual representation of data using charts, graphs etc. Using this we can understand the data which is designed in patterns. Data is visualized using uni variate and multi variate visualization plots. Uni variate plots helps in understanding the position of observations in data variable. Whisker plots are used for Uni variate plotting of data. Whisker plot is also called as box plot is a convenient way of visually displaying the data distribution through their quartiles. Quartiles divide the dataset into quarters where one fourth of the dataset is stored in each quarter. Multi variate plotting is done using histograms. Histogram is an approximate representation for distribution of numerical data.
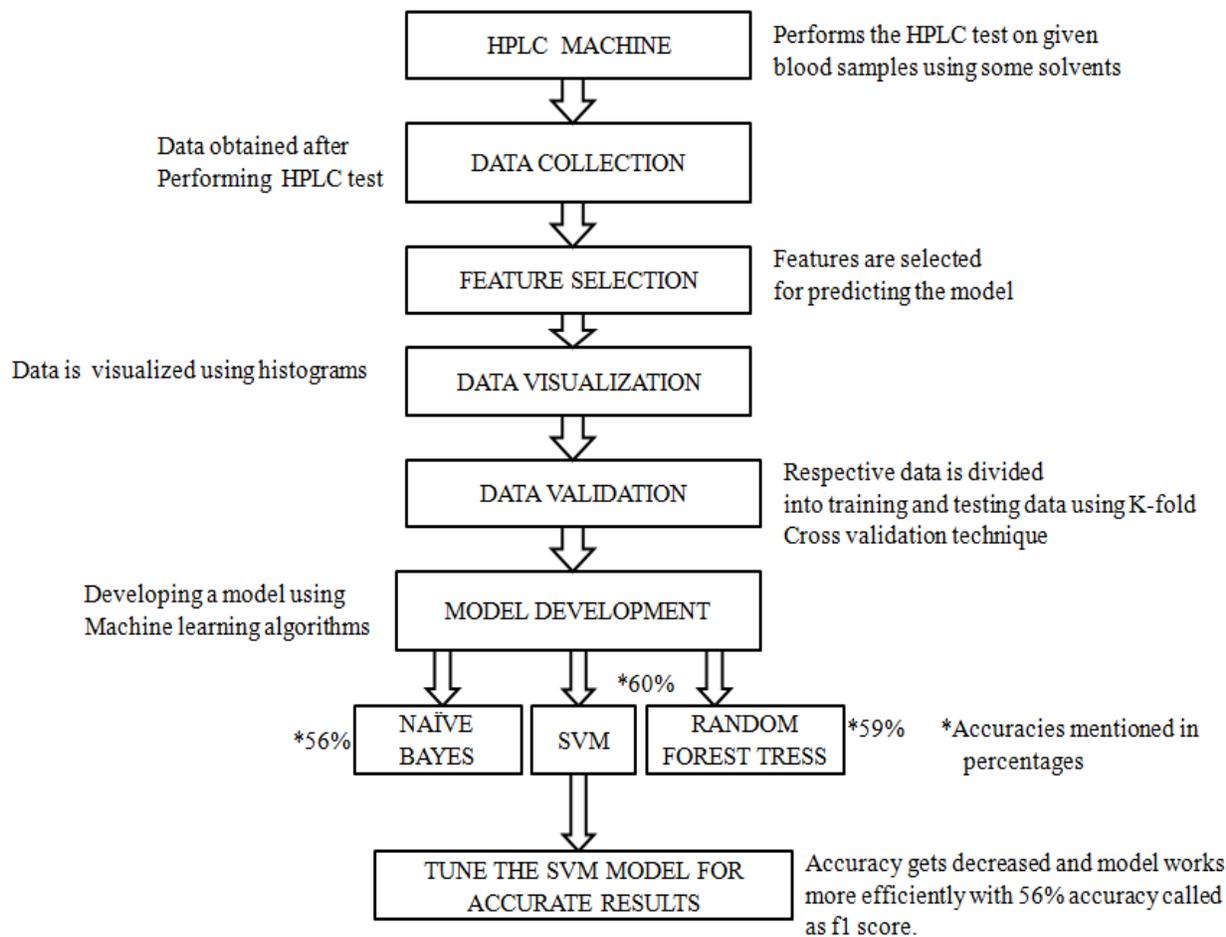
Fig 2: Structure of the Proposed Model

Validation of data is the important step because the data is partitioned into training and testing data using K-fold cross validation technique. Cross validation is a re-sampling technique used to evaluate machine learning models on limited dataset. Training data is used train the model. After training the model it is tested to obtain the accuracy. The complete methodology is described in Fig 2.

Developing a model is the main step used to predict the accuracies of the algorithms implemented on the HPLC Sickle Cell Dataset. Machine learning algorithms play an important role for developing and implementing the model. Classification refers to predictive modeling problem where class label is predicted for given input data.
Support vector machine, random forest trees and naïve bayes algorithms are some of the machine learning algorithms implemented on HPLC dataset respectively.
Support vector machine is a supervised machine learning algorithm which analyses the data for classification and regression analysis. This performs classification of data by constructing an N-dimensional hyper plane that optimally separates data points into two categories[13]. If an SVM constructs N-1 dimensional hyper plane in N dimensional space which separates data points with maximum separation margin between two datasets is said to be a Linear SVM Classifier. Using kernel function allows the SVM model to perform separations in complicated boundary scenarios.

Random forest trees are machine learning methods for classification, regression and other tasks that are performed by creating multiple decision trees. These are frequently used as black box models in business field as they generate

predictions across wide range of data. Decision trees are generated by this algorithm when implemented on the datasets and hence the best solution is predicted through method of voting.

Probabilistic classifiers have a sub module called Naïve Bayes classifiers. Therefore, bayes theorem can be applied along with their assumptions with their respective features. These are highly scalable and require more parameters and variables in a learning problem. Algorithm works efficiently for large datasets[14].

The last step in developing the model is tuning the best algorithm which is obtained with highest accuracy when all the algorithms are implemented on HPLC sickle cell data. After implementing the SVM algorithm, confusion matrix and f-1 score are generated. F-1 score is the measure of accuracy when the model is tested with the test data. To summarize the entire performance of the classification algorithm confusion matrix can be implemented.

The main purpose of this model development is to analyze medical data using available machine learning techniques. It has been a challenge working on this model because there have been no computational models involved in diagnosing the Sickle Cell Disease other than the Sickle Cell test Kit. Model is developed using python in jupyter notebook. This model obtains accuracy using computational techniques with a limited accuracy as it is a basic level analysis. During this study, by utilizing three main algorithms: SVM, RFT and NB algorithms on the datasets we tried to compare efficiency and effectiveness of those algorithms in terms of accuracy, precision, sensitivity and specificity to find the best classification accuracy.

4. Results:

HPLC dataset is loaded using Pandas displaying 10 records with showing 9 attributes is shown in Table 2. Binary Classification is implemented to sort the dataset into male and female groups. The attributes are age, Hb A0 is the adult blood, Hb A2 is another type of adult blood, HbF is fetal hemoglobin, HbS is Sickle Hemoglobin, Sex, Result1 and Result2.

Table 2: Displays Sample data records

Sl.No	Age	A0	A2	F	S	Result1	Result2	Gender
1	10.0	5.7	3.7	24.5	59.8	0	0	M
2	3.0	2.9	1.6	28.0	60.9	0	0	M
3	22.0	4.3	1.2	41.6	43.5	0	0	F
4	13.0	5.5	2.8	0.5	74.9	0	0	F
5	3.0	8.4	1.8	17.8	65.5	0	0	F
6	12.0	34.1	3.1	8.1	48.3	0	0	F
7	19.0	8.3	2.0	0.5	76.3	0	0	F
8	15.0	4.5	2.6	17.1	71.1	0	0	F
9	7.0	2.8	2.3	12.5	79.5	0	0	M
10	23.0	2.9	2.1	19.0	71.8	0	0	F

The accurate results are analyzed by the SVM algorithm.SVM is the popular supervised machine learning algorithm which predicts results efficiently when it is implemented on the HPLC dataset. It shows the highest accuracy of 60 percent as shown in Table 3. SVM algorithm comes under Linear Classifier and is also one amongst the Regression Techniques. Within this SVM algorithm, k-fold cross validation technique is used to achieve the accuracy of 60 percent. Similarly for RFT algorithm Gradient Boosting Algorithm is used giving moderate accuracy. Gradient boosting algorithm is also a machine learning algorithm applied to build a predictive model. This RTF algorithm is also used as a data visualization technique. Simultaneously, Naïve Bayes Algorithm comes under Probabilistic Classifiers and it is the least used algorithm for predicting the model as it gives least accuracy among taken algorithms. The complete result analysis is featured in Table3.

Table 3: Comparing Accuracy of Algorithms Implemented on the dataset.

Algorithms implemented	Accuracy obtained
Support Vector Machine(SVM)	60.8 %
Random Forest Trees (RFT)	58 .4%
Naïve Bayes (NB)	56 .3%

The Cost Function trains the SVM. Minimizing J(theta) value provides accurate SVM. In the above function $cost_1$ refers to cost of an example when y=1 and $cost_0$ refers to cost of an example when y=0. In SVM Kernel functions like linear, sigmoid, rbf and poly are used to determine the cost value.

$$(\theta) = C \sum_{i=1}^{m} \left[y^{(i)} cost_1(\theta^T x^{(i)}) + (1 - y^{(i)}) cost_0(\theta^T x^{(i)}) \right] + \frac{1}{2} \sum_{i=1}^{n} \theta_i^2$$

The accuracy comparison of all the three algorithms is shown in Fig.3 using Histograms. Therefore, the data is represented graphically in the form of bar displaying their respective statistics showing accuracies of 56.3 percent for NB, 60.8 percent for SVM and 57.4 percent for RFT.SVM algorithm is better when it is compared with other two algorithms. Partially, k-fold cross validation technique is used and later kernels are used to fine-tune the accuracy.
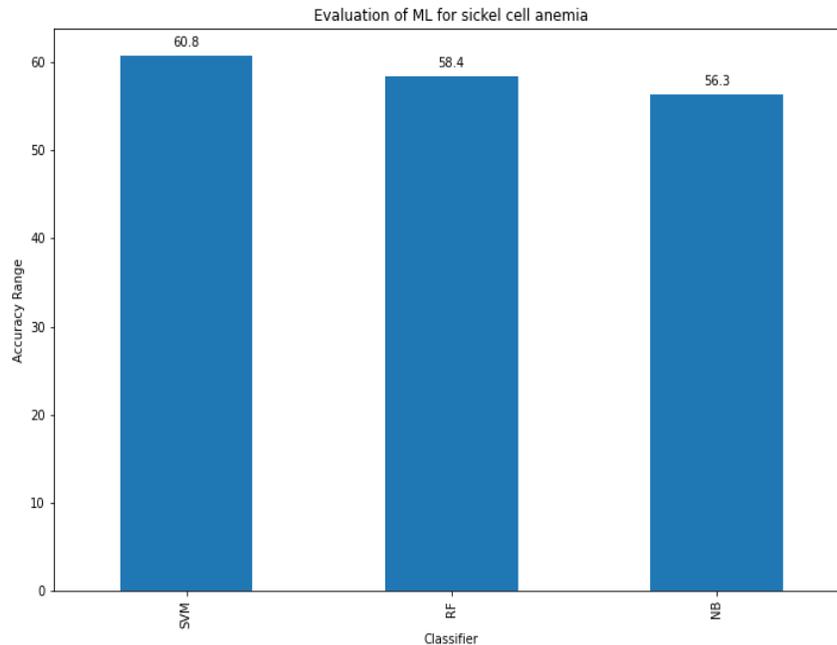
Fig 3: Bar Graph showing Performance of NB, SVM and RFT algorithms.

The SVM algorithm is further tuned to get efficient accuracy since it has attained the highest accuracy. SVM is tuned to obtain the best accuracy and generating the f-1 score, which is a measure of accuracy efficiency. Confusion matrix is also generated which is an N * N matrix used for evaluating the performance of the classification model displaying its true values. Finally, Support vector reaches the accuracy of 56% outperforming other algorithms. This model in future can be implemented with large datasets for greater accuracy.

Table 4: Classification report for SVM algorithm

Classification Report	Precision	Recall	F1-Score	Support
Female	0.45	1.00	0.62	9
Male	1.00	0.31	0.48	16
Accuracy	-------	-------	0.56	25
Macro Average	0.72	0.66	0.55	25
Weighted Average	0.80	0.56	0.53	25

The classification report for SVM algorithm is shown in Table 4. It shows the accuracy of SVM algorithm as 56%. Precision(P) is the ratio of number of true positives(T_p) over the combination of true positive numbers(T_p) and false positive numbers(F_p). It can be derived as follows:

$$P = T_p / (T_p + F_p)$$

The Precision value for female is 0.45 and 1.00 for males. Recall(R) is the ratio of number of true positives(T_p) over the combination of true positive numbers(T_p) and false negative numbers(F_n). It is derived as follows:

$$R = T_p / (T_p + F_n)$$

The recall value for female is 1.00 and 0.31 for males. The Weighted average of Precision(P) and Recall(R) is defines as f_1 score. It is derived as follows:

$$F_1 = 2 *((P * R) / (P + R))$$

F1 score for females is obtained as 0.62 and 0.48 for males. Micro average calculates the total number of true positives, false negatives and false positives. The micro average values for precision, recall and f_1 score are 0.72, 0.66 and 0.55 respectively. The weighted average values for precision, recall and f_1 score are 0.80, 0.56 and 0.53.

5. Conclusion:

Sickle cell anemia is a disease which is not detected by any computational methods. The aim of the proposed computational model is to find a solution for detecting sickle cell anemia using machine learning algorithms. In this paper, features are defined and a classification model is proposed in order to gain highest accuracy. In the proposed model feature extraction is performed to extract the features to build the model. To obtain the accuracy and to analyze the model supervised machine learning algorithms like SVM, NB and RFT are implemented on the dataset. After obtaining the accuracy efficiency of the algorithms and simultaneously comparison of algorithms is also performed. SVM algorithm is said to be having highest accuracy of 56% since limited dataset is used for the proposed model. In future, this model can be furtherly implemented on large datasets for attaining better accuracy.

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