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Human Papillomavirus Targeted Immunotherapy Outcome Prediction Using Machine Learning

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Abstract: Warts caused by the Human Papillomavirus (HPV) is a highly contagious disease, and affects several million people across the globe every year, in the form of small lesions on the skin, commonly known as warts. Warts can be treated effectively with several methods, the most effective being Immunotherapy and Cryotherapy. Our research is focused on the performance comparison of modern Machine Learning classification techniques to predict the outcome (positive or negative) of Immunotherapy treatment given to a patient, by using patient data as input features to our classifiers. The precision, recall, f-measure and accuracy were used to compare the performance of the various classifiers considered in this study. We considered Logistic Regression, ZeroR, AdaBoost, K-Nearest Neighbours (KNN), Support Vector Machines (SVM), Gradient Boosting, Repeated Incremental Pruning to Produce Error Reduction (RIPPER), Decision Trees and Random Forests. The ZeroR classifier was used as a baseline to provide us with insights into the skewed nature of the data, so as to enable us to better understand the comparison in performance of the various classifiers.
Keywords: Machine Learning, Classification, Immunotherapy, Human Papillomavirus, Warts, Performance Comparison, ZeroR

I. INTRODUCTION

Warts are known to be common dermatological conditions that are caused by the Human Papillomavirus (HPV). Although it is a benign condition, not only does it cause disfigurement, but it also has the tendency to koebnerize. In addition to this, it is highly contagious. Being contagious, it renders apposite and timely treatment of the utmost importance. Several conventional treatments are available; however, topical and systemic immunotherapy [44-45] has proven to be the most significant mode of treatment of warts because of it being non-destructive in nature, easy to administer and has proved its effectiveness in extensive studies [48]. In our research, we use Machine Learning techniques to predict the outcome of Immunotherapy treatment for Warts, in order to find insights between patient features and the probability of success of the treatment. We used a dataset comprising 90 samples, which consisted of various biological measures; various Machine Learning classifiers were used to form correlations between the said measures and the output, i.e., the outcome of the treatment, to obtain the predicted outcome of Immunotherapy.

Warts are small, non-cancerous rigid protrusions that appear on the skin, which are typically caused by one of the many viruses that belong to the Human Papillomavirus (HPV) family [7]. Extra cell growth is triggered by the virus, causing the epidermis skin layer to thicken and become hard around that particular site [8]. Warts can grow anywhere, but are more commonly found on the hands, feet, around the fingernails, and near the knees. Warts are more common in children than adults. A fleshy, painless and slightly rough growth on the skin is the most common symptom of this ailment. Since the immune system of each person responds differently to the virus, not everyone who comes in contact with HPV will get a wart. Having injured or damaged skin can result in higher chances of being infected by the HPV virus. This is why people with chronic skin conditions such as eczema and rosacea, or those who bite their fingernails, have a higher probability of getting warts. As children and adolescents do not have completely developed immune systems, they stand higher chances of getting infected with warts, as compared to adults. Warts are highly contagious, and spread by direct skin contact. There are two main types of warts; common and plantar [9]. Common warts are flesh coloured, and are mostly found on the back of the hands, fingers, feet and around the skin near the fingernails. They are small and their size can vary from a pinhead to a pea. Plantar warts appear on the heel or places of the feet that are known as weight-bearing areas. The pressure on the wart may cause it to grow inwards, under the thick and hard layer of the skin, known as the callus.

Great progress has been made over the past decade to further our understanding of the Papillomavirus (PV) biology. Advancement in technology has given researchers a better understanding of the relationship between PV and its host. Immunotherapy is a method of treatment that boosts the body's natural defence mechanism. It uses substances, either made by the human body, or in a laboratory, to improve the immune system's response to find and destroy undesirable entities in the human body [44-45]. There are many variants of Immunotherapy; monoclonal antibodies and tumour-agnostic treatments, such as checkpoint inhibitors, oncolytic virus therapy, T-cell therapy, and vaccines.

The intensity of the treatment and schedule depends on many factors, which include the type of growth, size and location, and the type of spread of the warts. In oncolytic virus therapy, viruses that have been genetically modified in a laboratory are used to destroy the Human Papillomavirus infecting the patient. T-cells are essentially immunity booster cells, that fight infection. In T-cell therapy, the body is loaded with extra T-cells in order to give it an edge over the HPV infection. Vaccines are also a part of Immunotherapy where micro quantities of HPV are injected into the body, which triggers the immune system to produce antibodies for HPV, in turn rendering it capable of fighting the disease.

II. AN OVERVIEW OF MACHINE LEARNING

Machine Learning is a modern technique of solving problems in the scope of prediction, classification, clustering and modelling [49-50]. It is a subset of Artificial Intelligence (AI), and has gained immense popularity in the recent decades. The fundamental concept of Machine Learning revolves around the computer, or machine, “learning” from data given to it, i.e., finding patterns and correlations in the given dataset, to predict or model the output accurately. As more data is given to the machine, more insights are found by it, thus increasing the accuracy of the output. Unlike previous optimization techniques, most Machine Learning models do not have explicitly programmed rules. Machine Learning typically uses implicit learning, and formulates its own rules of modelling by minimizing the error between the predicted output, and the true output (ground truth), until saturation [51].

Machine Learning has been in use for several decades for the analysis of large datasets, and to discover and extract patterns from within the data. It has been widely employed as a tool for the analysis of medical data, including medical signals of various dimensions. Machine Learning has also played a crucial role in applications such as crime detection, stock market trading, speech recognition, autonomous vehicles in both civilian and military settings, logistical optimization, and several others. Several industries such healthcare, banking, marketing, automobile, logistic and education have benefited tremendously from the use of machine learning to reduce costs, improve product quality, and increase customer satisfaction. Machine Learning can be used to improve the quality of life in numerous ways, a chief direction being its application to healthcare. The recent resurgence of the use of Artificial Intelligence can be attributed to the extensive research into Machine Learning Techniques in the recent past. There are two major factors that have contributed to the increased utility of Machine Learning. The first factor is that there has a been an exponential growth in the amount of data being generated and stored, due to the rapid advancement of electronic and telecommunication technologies. Data has now become more accessible than ever before, with millions of terabytes of data being freely available for use and analysis on the internet. The internet boom is only growing larger every day, causing the data availability to continue to expand. Several valuable insights can be found by deploying Machine Learning techniques to this vast amount of data. The second factor has been the phenomenal increase of computational power available even on a simple Personal Computer (PC). In 1985, an average Personal Computer had about 256 kilobytes of Random-Access Memory (RAM); in 2020, the average PC has 4 gigabytes of RAM. There has been a growth of more than 1,500,000% in the last 35 years. This enables Machine Learning algorithms to perform more efficiently and accurately than ever, with the performance metrics showing promise to increase over time. The three major problem statements solved by machine learning algorithms are clustering, prediction and classification. In this research, we use classification algorithms such as Logistic Regression, ZeroR, AdaBoost, K-Nearest Neighbours (KNN), Support Vector Machines (SVM), Gradient Boosting, Repeated Incremental Pruning to Produce Error Reduction (RIPPER), Decision Trees and Random Forests. As the availability of medical data has increased, researchers in the field of medicine and engineering now have access to more efficient computational resources, and many applications of Artificial Intelligence and Machine Learning have emerged, due to this very reason. These applications have aided healthcare professionals tremendously in making better diagnoses, and generally improving the quality of patient care and patient outcomes.

III. PAST APPLICATIONS OF MACHINE LEARNING IN MEDICINE

In [1], Wolterink et al proposed a method for noise reduction in low dose Computed Tomography scans (CT scans), by using adversarial Convolutional Neural Networks (CNNs) to predict routine dose CT scan values from low-dose CT images, thereby reducing noise, generally found in low-dose CT scans. This was achieved by using a mimization technique known as voxel wise loss minimization. To differentiate between the output of the trained generator and true routine-dose CT scans, an additional adversarial discriminator CNN was trained, to ensure increased accuracy. As can be seen in [2], Kubendran et al addressed the trade-off between computational power, accuracy and algorithm complexity in biomedical devices. It was found that using single tone sinusoidal waves as inputs to the device provide the best accuracy. The trade-offs of using such waves are the power consumption, and that they are difficult to generate on a hardware chip. It is easier to generate square waves than single tone sinusoidal waves, but they result in higher errors, due to higher harmonic terms when the square wave is converted into a Direct Current (DC) signal.

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In [3], a high-resolution multi-scale encoder-decoder network (HMEDN) was proposed by Zhou et al. Extensive experimenting on medical datasets, including a pelvic CT scan dataset, a multimodal brain tumour dataset, and a cell segmentation dataset, demonstrated the efficacy of the algorithm for two-dimensional and three-dimensional semantic segmentation and two-dimensional instance segmentation. Furthermore, in [4], Gupta et al presented an approach for automatic classification of Parkinson's Disease (PD) based on the severity estimation. The mentioned study put across a model which estimated the disease severity with Gradient Boosted tree regression. Novel features from the gait signal were generated which better estimated the severity of PD patients. In [5], Prasad et al. Used speech to automatically classify the seven different types of eating disorders. It was proposed that a hierarchical classification approach for automatic classification be used by exploiting the confusion between the different food types from a direct seven-way classification scheme. Finally, in [6], Sayantan G et al. proposed a new novel method for the classification of ECG beats. The proposed method was based on the Gaussian-Bernoulli deep belief network, with a linear SVM classifier and active learning.

IV. INFORMATION ABOUT THE DATA

A. Origin of the Dataset

The aim of the research is to predict the outcome of Immunotherapy treatment on a patient with warts, given patient data, which is to be used as dependent variables for the machine learning models studied. This data was obtained from the Machine Learning Repository by University of California, Irvine. (https://archive.ics.uci.edu/ml/datasets/Immunotherapy+Dataset) The data was part of an original work in which a study was conducted by the dermatology clinic of Ghaem Hospital, Mashhad, Iran
[44-45]. This study aimed to identify the appropriate treatment for two common types of warts (plantar and common). The study was conducted on 180 patients, of which 90 received Immunotherapy treatment and the remaining patients received Cryotherapy. It was found that patients responded better to Immunotherapy, with a success rate of 83.33%, whereas the success rate of Cryotherapy was only 80.7%. We used the data of the patients who were given Immunotherapy treatment, and the patient data was collected as follows:

1) Sex
2) Age
3) Time elapsed before treatment from the first observation of the disease
4) Number of warts present on the patient's body
5) Type of warts (common, plantar, or both)
6) Area of the largest wart (in mm^2)
7) Induration diameter of the initial test (in mm)

Feature name	Values	Mean +/- SD
Response to treatment	Yes or no	
Gender	41 Male 49 Female	
Age (years)	15-56	31.04 +/- 12.23
Time elapsed before treatment (months)	0-12	7.23 +/- 3.10
The number of warts	1-19	6.14 +/- 4.2
Types of wart (Count)	1-Common (47), 2-Plantar (22), 3- Both (21)	
Surface area of the warts[1] (mm^2)	6-900	
Induration diameter of initial test (mm)	5-70	

[1] Area of the largest Wart

Table 1: Features from patients receiving Immunotherapy treatment for HPV, obtained from the study at Ghaem Hospital Mashhad, Iran [44-45]

B. Observations from the Data

1) The outcome of the Immunotherapy treatment is slightly more positive for females (79.59%) than for males (78.05%).
2) Immunotherapy treatment has a higher chance of success with younger patients than older ones.
3) The sooner the treatment is sought by patients since their observation of the warts, the more likely a positive outcome of the Immunotherapy treatment.
4) The smaller number of warts on a patient's body, the higher the chance of success of the Immunotherapy treatment.
5) From the test sample, 47 patients had only common warts (the rate of success was 78.7%), 22 had only plantar warts (77.3%), and 21 had both common and plantar warts (85.7%).
6) A strong correlation between the size (area in mm2) of the largest wart on the patient's body and the success of the Immunotherapy treatment wasn't found. The success rate was similar in all ranges of size.
7) From the data, we observed that the larger the induration diameter of the largest wart on the patient's body, the lower the chance of success of the Immunotherapy treatment.

V. MACHINE LEARNING CLASSIFIERS: BACKGROUND AND RELATED WORK

Classification (both binary and multi-variate) is a standard problem statement, that often uses Machine Learning techniques. Machine Learning Classifiers "learn" from examples given in the dataset that they are trained upon, and predict the label of the classes (predefined in the dataset) of new inputs given to the algorithm. The most popular modern Machine Learning techniques, relevant to our problem statement, have been chosen for analysis, and are summarized in the following subsections.

A. ZeroR

ZeroR is one of the simplest algorithms used for classification. True to its name, the ZeroR classifier follows zero rules based on which classification occurs; it simply assigns any new data the probability outcome of the majority of the data. If the majority of the data is labelled with a positive outcome, it will assign all new data a positive outcome, and vice versa. It cannot be considered a learning algorithm, as the rules do not change based on the error of classification; the machine does not "learn". In our research, we use the ZeroR classifier as the baseline classifier; all the other algorithms explored are compared to this algorithm to gauge their performance. In [10], Mohammed et al used ZeroR as the baseline classifier in a study involving anaemia prediction. In [11], Elekar et al used this algorithm to assess the performance of their data mining algorithm for intrusion detection. Joshi and Jetawat used this algorithm to evaluate their classification algorithms used in Medical Decision Support Systems in [12]. ZeroR is a very common baseline classifier, as it also provides researchers with insights of how skewed the data is, i.e., how much disparity exists between the number of positive and negative outcomes in a classification problem.

B. RIPPER

The Repeated Incremental Pruning to Produce Error Reduction (RIPPER) algorithm is a traditional machine learning algorithm, invented by William W. Cohen. It is based on a rule-learning approach. The rules of classification are learnt by this using a compendium of pruning functionalities to repeatedly simplify the set of generated classification rules. At every iteration, the pruning functionality is chosen to minimize the error in classification produced by the set of rules at that point. In [13], the RIPPER algorithm was used to classify preictal and interictal brain states from long term EEG Data, which is a very important application of ML to healthcare. In [14], Toledo et. Al used this classification technique to predict the outcome of patients with subarachnoid haemorrhages, and in [15], Tsiouris et al used the RIPPER algorithm to enhance the baseline evaluation of the progression of Parkinson's disease in patients; these references highlight the extend of the possible implementation of Machine Learning to improve patient outcomes. Another application of RIPPER can be seen in [16], where the research was based on creating distributed multi-class rule-based classification system, using this algorithm.

C. Naïve Bayes (NB)

Naïve Bayes is a statistical based classification approach that has gain popularity in the recent years. It can foresee the conditional probability between two events occurring and form a correlation between the parameters and the output. As the concept behind this algorithm is conditional probability, it also deals well with missing data by omitting the respective probabilities for those data points. In Naïve Bayes classifier, each of the inputs has an independent probabilistic relationship with the output; this is known as class conditional independence.

In [17], Bohra et al discussed and reviewed the applicability of the Bayes algorithm where, when the symptoms of a patient are given as input prediction of disease would be obtained as the output. In [18], K.M. Al-Aidaroos et al. focused mainly on Naïve

Bayes where it was mentioned by the said authors that's it's the most effective and efficient classification algorithms. It was also noted that it proved successful with medical data. Finally, in [19], Langarizadeh et Al. carried out a systematic review and concluded stating that of all the available machine learning models and algorithms NBN performed the best when involved medical data. In addition to this, it was also mentioned that NBN can help health practitioners make decisions more confidently during diagnosis.

D. Logistic Regression (LR)

Logistic Regression (LR) is one of the most popular algorithms used for classification in modern machine learning. It is a probabilistic model, that uses the sigmoid function to predict the probability of an event occurring in a classification problem statement. The sigmoid function constrains the hypothesis of the model to lie between 0 and 1, thus making the interpretability of the algorithm similar to a probability. Like multiple linear regression, logistic regression analysis can be used to determine which independent variables and interactions are required to satisfactorily get the probabilistic classification of the dependent variable. The hypothesis is that the probability of an event occurring will be a linear, weighted combination of all feature-engineered parameters, passed into the sigmoid function. The independent variables include attributes and contextual features, based on which the dependent variable will be classified. In the context of our work, various patient details are the independent variables, using which we classify them into patients upon Immunotherapy treatment will be successful, and those upon which it will not.

In [20], Pyke and Sheridian used a Logistic Regression classifier to ascertain the probability of graduate student retention at a large Canadian university. This is an apt example of Machine Learning techniques being used in the education industry, for the benefit of students and the institute. In [21], Thabtah et. al used LR to find critical insights related to Autism screening and in [22], Anderson et. al used LR to interpret clinical reports; this demonstrates how Machine Learning can be used for improving healthcare.

E. Support Vector Machine (SVM)

Support Vector Machines (SVM), [43] is one of the other popular machines learning based classification techniques used extensively for a variety of predictive analytics. A SVM is another supervised machine learning model which is based on the use of classification algorithms for two-group classification problem. After training a SVM model with labelled data they would be able to categorize new data. In comparison to newer found algorithms like neural networks SVM are superior due its higher speed and better performance with a limited number of samples. Hence, we can state that these characteristics makes the SVM based algorithms very suitable for text classification problems. In most cases SVM is used as a binary classifier where information is sorted by its class, either class 0 or class 1. For this to be achieved, a hyperplane is chosen in the vector machine. A hyperplane can be defined as a function that can take part into the variable space. With the use of a hyperplane, the vector machine learning calculation finds the coefficients bringing about the best detachment of the classes. When the hyperplane takes on a linear form, the algorithm is referred to as SVM. However, based on the best fir for the separation margin between two classes, the hyperplane may take on the form of any function; polynomial, gaussian, radial basis function (RBF), Laplace RBF, or a sigmoid function. When the hyperplane takes on a non-linear function, it is referred to as Kernel SVM.

Cited prior research work, Yu et al. [23], used support vector machine for the prediction of medication adherence in Heart Failure Patients where it was concluded that SVM was indeed a suitable classification approach for predicting medication adherence in HF patients. In [24], Janardhanan et.al had used SVMs to evaluate the effectiveness of medical data mining and finally in [25], Gopi Battineni et al. used SVMs to evaluate the performance calculation of dementia prediction where it was concluded the model achieved an accuracy and precision of 68.75% and 64.18% respectively. In [28], a comparison is made between SVM and KNN classifiers, applied to medical textual data. In [40], a comparative study was conducted between Kernel SVM and ANN for brain neoplasm classification.

F. K-nearest neighbours (KNN)

Another classification algorithm, K-nearest neighbours (KNN). It is a simple and easy-to-implement supervised machine learning algorithm that can aid the process of solving not only classification but also regression problems. In a supervised machine learning algorithm, the available labelled data is used as an input to train the and this would result in an output when unlabelled data is given as an input. KNN is a type of instance-based learning, or rather lazy learning [43].

In the KNN classification technique, the local approximation is taken into account and the computation is kept on hold until classification. The distance function known as Euclidean distance, Manhattan distance or Minkowshi distance, and is used as a similarity measure during the process of classification.

Following this, the neighbours, the K most comparable occasions, are used to classify. Past research work in the same area have used KNN classifier in the area of medical data classification. For instance, Mai Shouman et al. used KNN to diagnose heart disease patients which achieved an accuracy of 97.4% which was higher than any other findings published on the said benchmark dataset. [26] In [27], Iqhal H et al. a k-nearest neighbour learning based model to predict and analysis diabetes mellitus for eHealth services and in [28], J. S. Raikwal et al compared the used of Support Vector Machine and KNN and concluded that KNN is a good classifier but over textual data it performs poorly as the size of the dataset increases in size.

G. Decision Trees (DT)

A very popular, well-known and highly discussed classification technique is decision trees. It is known as the most powerful tool for prediction and classification. It is a flowchart which has a similar structure to that of a tree. Each internal node denotes a test on an attribute, each leaf or terminal node holds a class label and each branch represents an outcome of the test.

Decision trees classify the instances by sorting them down the tree from the root to some leaf node, which provided the classification of the instance. It is classified by starting from the root node of the tree by testing the attribute specified by the particular node, following which, moving down the tree branch corresponding to the value of the attribute. This process is then repeated for the subtree which is rooted at the new node.

In the area of classification and prediction using medical data, Heping Zhang et al. [29] has used decision trees to get prediction of the effectiveness of clinical trial and in its application to the study of ovulation in women with polycystic ovary syndrome. (PCOS) In [30], Hu et al. had proposed decision tree-based learning to predict patient-controlled analgesia readjustment and consumption.

H. Random Forest (RF)

Random forests are a standard machine learning technique used for classification problems. It was invented by Tim Kan Ho et al in 1995. It is known as an ensemble machine learning method that takes multiple machine learning classifiers into account, and accordingly produces a predictive classifier. Bootstrap aggregation (also known as bagging) and random feature selection are used in conjunction to construct a set of decision trees, which demonstrate controlled variation. Overall, the random forest algorithm generates multiple decision trees, and the output is based on learning the mistakes of each tree, to produce higher performance and accuracy.

In [31], Alam et al used a random forest-based predictor for the classification of medical data, using a feature ranking approach, in which all parameters, or features, are ranked in order of their relevance to the output class. In [32], Popescu et al used this classifier to predict disease risks of patients from highly imbalanced data. Demographic medical data available is often imbalanced due to unconscious biases; thus, using such data provides more insights into the performance of the algorithm on real-time data. In [33], Random Forests were used for clinical risk prediction by Wongvibulsin et al. As can be seen, the Random Forest classifier is a staple classifier used in the prediction and analysis of biomedical data.

I. AdaBoost

Adaptive boosting is often described as a machine learning “meta-algorithm”, which was formulated by Yoav Freund and Robert Schapire in 2003, for which they won the prestigious Gödel Prize. This technique can be used to solve both classification and prediction problem statements. The output of several learning algorithms, known as “weak learners” are combined to produce an effective classifier that learns from the mistakes made by the “weak learners”. It is known as an adaptive classifier, as it improves the performance of the weak learners by a very large margin, to produce one of the most accurate classifiers. It is considered one of the most powerful modern Machine Learning techniques.

In [34], Lu et al. Used Adaboost techniques in conjunction with a genetic algorithm, to create a hybrid function applied to the classification of gene expression data. In [35], Bhattacharya et al used this classification algorithm for classification of EEG Motor Imagery. These two references showcase the implementation of the AdaBoost algorithm to classify biomedical data. In [36], Fleyeh et al used AdaBoost classification, along with SVM for traffic sign detection.

J. XGBoost

XGBoost is a popular machine learning algorithm, used for both classification and prediction problems. It is a modified version of gradient boosting, which is a supervised learning algorithm which accurately classifies data by combining the results of “weak learning” models. The “weak learners” consist of classification decision trees. XGBoost minimizes a regularized objective function that is a combination of a convex loss function, and an additional penalty term, in order to train the classifier.

Like many algorithms, the learning process in the XGBoost is iterative, and at every iteration, it adds new classification decision trees, that are then combined with the previous trees, so as to learn from the errors of previous trees. After a set number of iterations, the final classification rules are developed. Stochastic gradient descent is deployed in this model to minimize losses when adding new trees. In [37], Raipal et al used an XGBoost-based classification algorithm for the analysis and classification of 12-Lead ECGs. In another application of the XGBoost algorithm, in [38] J. Bao et al, used this classification technique to diagnose arrhythmia in patients, based on extensive medical data. In [39], Song, Li and Wang researched mammographic classification, using an XGBoost-based classification algorithm. The XGBoost approach has been gaining popularity in the recent years for machine learning problems.

K. Artificial Neural Networks (ANN)

Artificial Neural Network (ANN) is a commonly used Deep Learning algorithm. ANNs can be used to address problem statements centred around prediction, as well as classification. In our research, we deploy an ANN classifier to the independent variables, in order to predict the outcome of the success of Immunotherapy treatment given to patients. The fundamental inspiration behind the working of ANNs is the human brain. This Deep Learning model imitates the neuron of the human brain, and an intricate lattice of such neurons is created, capable of extremely high performance. The most commonly deployed ANN algorithm is a backpropagation network that performs on a multi-layer, feed-forward neural network.

There are several layers of neurons; these can be of three types, the input layers, hidden layers, and the output layers. The input layer of an Artificial Neural Network consists of feature engineered inputs from the dataset being worked on. The output layer consists of the outputs that are required for the research problem. The hidden layers consist of layers of neurons which aid in the performance of the model, but are weights of the neurons, based on the backpropagation algorithm. Some other variants of neural network models include the Single Layer Perceptron, Multilayer Perceptron (MLP), Recurrent Neural Network (RNN), Convolutional Neural Network (CNN) and the Long Short-Term Memory Network (LSTM).

In [40], Mahima and Padmavati conducted a comparative study of Kernel SVM and ANN classifiers for Brain Neoplasm classification. In [41], S. Kabir et al made use of ANNs to classify female breast tumor types using EIM parameters. In [42], Devi and Rajasekaran used ANNs with a backpropagation algorithm for pancreas image classification. There are several instances of neural networks being used for various problem statements in the healthcare domain; we just listed a few in our research. Neural networks are among the most popular algorithms for solving machine learning problems, particularly concerning biomedical data.

Classifier	Application	References
ZeroR	Anaemia Prediction, Intrusion Detection, Medical Decision Support Systems	Mohammed et al [10], Elekar et al [11], Joshi and Jetawat [12]
RIPPER	Classification of Preictal and Interictal brain states from long term EEG data, Prediction of subarachnoid haemorrhages, Evaluation of Progression of Parkinson's disease, Distributed Multi-Class Rule-Based Classification System	Tsiouris et al [13], Toledo et al [14], Tsiouris et al [15], Govada et al [16]
Naive Bayes	Disease Prediction using Patient Symptoms, Medical Data Classification	Bohra et al [17], Al-Aidaroos et al [18], Langarizadeh et al [19]
Logistic Regression	Autism screening, Interpretation of clinical reports	Thabtah et al [21], Anderson et al [22]
SVM	Prediction of Medical Adherence in Heart Failure Patients, Evaluation of Effectiveness of Medical Data Mining, Performance Evaluation of Dementia Prediction, Comparison of Classifiers for Medical Textual Data Analysis, Brain Neoplasm Classification	Yu et al [23], Janardhan et al [24], Gopi Battineni et al [25], J. S. Raikwal et al [28], Mahima and Padmavati [40]

KNN	Diagnosis of Heart Disease Patients, Prediction and Analysis of Diabetes Mellitus, Comparison of Classifiers for Medical Textual Data Analysis	Mai Shouman et al [26], Iqhal H et al [27], J. S. Raikwal et al [28]
Decision Trees	Prediction of effectiveness of clinical trials of PCOS in women, Prediction of Patient-Controlled Analgesia Readjustment and Consumption	Heping Zhang et al [29], Hu et al [30]
Random Forest	Classification of Medical Data with Feature Ranking, Prediction of Disease Risks from Imbalanced Data, Clinical Risk Prediction	Alam et al [31], Popescu et al [32], Wongvibulsin et al [33]
AdaBoost	Classification of Gene Expression Data, Classification of EEG Motor Imagery	Lu et al [34], Bhattacharya et al [35]
XGBoost	Analysis and Classification of 12-Lead ECGs, Diagnosis of Arrythmia, Mammographic Classification	Raipal [37], J. Bao [38], Song, Li and Wang [39]
ANN	Brain Neoplasm Classification, Classification of Female Breast Tumour types using EIM Parameters, Pancreas Image Classification	Mahima and Padmavati [40], S. Kabir et al [41], Devi and Rajasekaran [42]

Table 2 A summary of machine learning classification techniques used for various medical data classification.

VI. METHODOLOGY: IMMUNOTHERAPY OUTCOME MODELLING

In this section, we present a detailed approach for the prediction of the outcome of Immunotherapy treatment on patients infected with Human Papillomavirus, using Machine Learning classification techniques. As we have previously mentioned, for our comparative analysis, we deploy twelve classic and widely used Machine Learning models for classifying our data. These techniques are as follows:

1) ZeroR
2) Repeated Incremental Pruning to Produce Error (RIPPER)
3) Naive Bayes (NB)
4) Logistic Regression (LR)
5) Support Vector Machine (SVM)
6) Kernel SVM
7) K-Nearest Neighbours (KNN)
8) Decision Trees (DT)
9) Random Forests (RF)
10) AdaBoost
11) XGBoost
12) Artificial Neural Networks (ANN)

ANN is predominantly a Deep Learning algorithm, which is a subset of Machine Learning; this was also used for the evaluation of the effectiveness of Immunotherapy treatment against Human Papillomavirus.

The language for this modelling was Python 3, and it was done using both Anaconda and Google Collaboratory. The data from the UCI Machine Learning repository was converted into a .csv file, cleaned and pre-processed, and uploaded onto the respective Jupyter notebook. The dataset was split into two parts; training data and test data. The split was made through the randomization functionality in Python 3, and 80% of the data was assigned to the training set, and 20% to the test set. The algorithms were run, using a probabilistic, binary classifier, which classified any hypothesis with a probability of 0.5 or more as positive, and any hypothesis with a probability of less than 0.5 as negative.

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The confusion matrix for each result was obtained. Based on these matrices, the performance measures were calculated. For our research, we considered precision, recall, F-measure, and accuracy as measures of "goodness" or performance. A comparative study between the "goodness" of the twelve algorithms was conducted, and their merits were tabulated in a graphical manner and thus analysed.

VII. EVALUATION AND EXPERIMENTAL RESULTS

In order to evaluate the effectiveness of each machine learning classifier that was used in this study, we conducted a wide range of experiments. In the following, subsections, we briefly describe the derived dataset along with the present results and a corresponding discussion.

A. *Evaluation Metric*

To compute the prediction accuracy, the response predicted by the classifier was compared with the true response (i.e., the ground truth), following which we computed the accuracy of all seven classifiers in terms of the following measures of exactness.

1) Precision is a measure of exactness which is defined as the ratio between correctly predicted positives and the total number of values predicted positive by the classifier.

$$Precision = \frac{\mathrm{TP}}{\mathrm{TP+FP}}$$

2) Recall is a measure of exactness which is defined as the ratio of between correctly predicted positives and the total number of true positives and false negatives.

$$Recall = \frac{\mathrm{TP}}{\mathrm{TP+FN}}$$

3) F-measure is a metric that combines precision and recall in a single score, which is the harmonic mean of the precision and recall. [main paper]

$$F - measure = \frac{2*\mathrm{Recall}*\mathrm{Precision}}{\mathrm{Recall+Precision}}$$

B. *Experimental Results and Effectiveness Analysis*

In this research study, we aimed to show the effectiveness of each machine learning based prediction model for individuals with human papillomavirus administered Immunotherapy outcomes. In the section below, we have shown the experimental results of ZeroR, Naïve Bayes (NB), Decision Tree (DT), Random Forest (RF), Support Vector Machine (SVM), K-Nearest Neighbours (KNN), Adaptive Boosting (AdaBoost), Repeated Incremental Pruning to Produce Error Reduction (RIPPER), Logistic Regression (LR), Artificial Neural Network (ANN), Kernel Support Vector Machine (Kernel – SVM) and extreme Gradient Boosting (XGBoost) based immunotherapy outcomes prediction models. The specific details of these classifiers were discussed in the section "Machine Learning classifiers: Background and related work".

For each of the mentioned models, we used the same datasets in order to compare the classification technique in a fair manner.

Classifier	Precision	Recall	F-Measure	Accuracy
ZeroR	0.789	1.000	0.882	0.798
RIPPER	1.000	0.563	0.720	0.611
Naive Bayes	0.889	1.000	0.941	0.889
Logistic Regression	0.938	0.938	0.938	0.889
SVM	0.889	1.000	0.941	0.889
Kernel SVM	0.889	1.000	0.941	0.889
KNN	0.882	0.938	0.909	0.833
Decision Trees	0.929	0.813	0.867	0.778
Random Forest	0.933	0.875	0.903	0.833
AdaBoost	0.929	0.813	0.867	0.778
XGBoost	0.933	0.875	0.903	0.833
ANN	0.889	1.000	0.941	0.889

Table 3: Prediction results using various machine learning classification models

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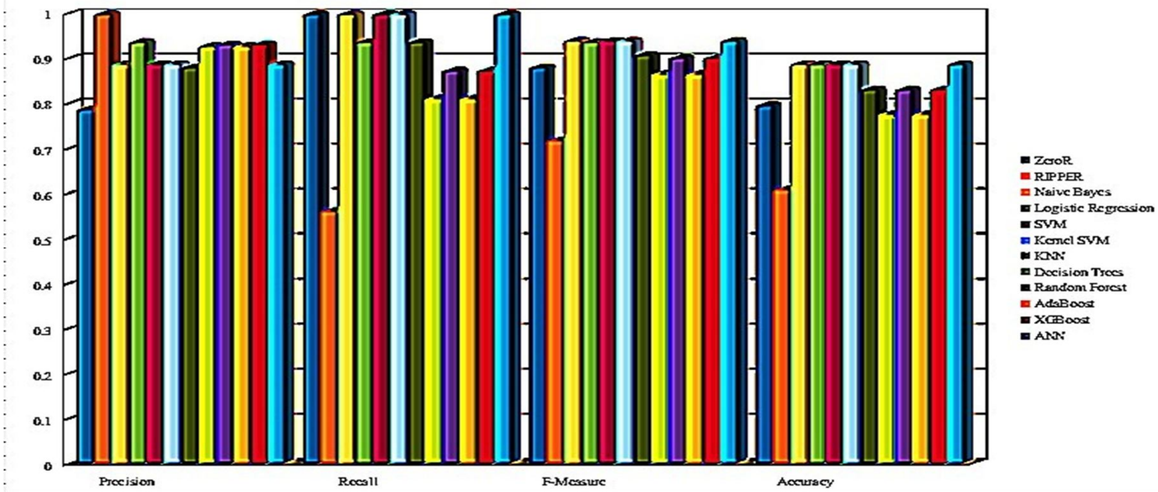

Figure 1: Bar Graph of the effectiveness comparison results for various machine learning classifiers trained on the same data

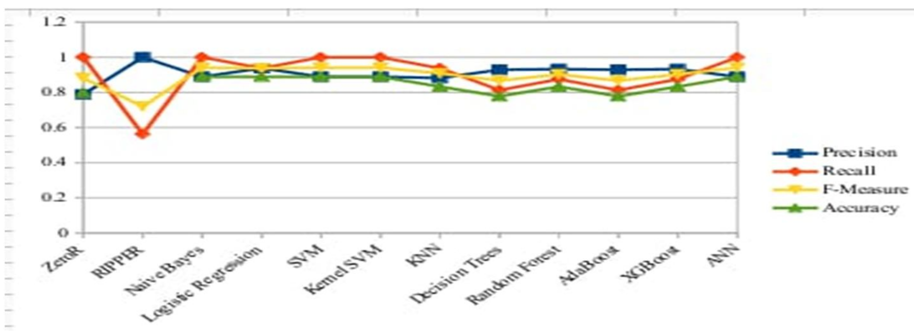

Figure 2: Line Graph of the effectiveness comparison results for various machine learning classifiers trained on the same data

VIII. EFFECTIVENESS COMPARISON

To show the performance of the various Machine Learning classifiers on the dataset, Figs. 1 and 2 show the relative comparison of the performance metrics considered, i.e., precision, recall, f-measure and accuracy. Each classifier is given the same testing and training dataset, in order to ensure a fair evaluation of the classifiers. ZeroR is used as the baseline classifier, compared to which, the Machine Learning classifiers are analysed. Some insights have been noted in the following points.

1) The highest precision was observed in the RIPPER algorithm (100.0%). The baseline classifier, ZeroR has the lowest precision among the classifier (78.9%).
2) ZeroR, Naive-Bayes, SVM and Kernel SVM algorithms performed best in terms of recall (100.0%). The lowest recall was observed in the RIPPPER algorithm (56.3%).
3) Naive-Bayes, SVM, and Kernel SVM algorithms had the highest f-measure (94.1%). The lowest f-measure was observed in the RIPPER algorithm (72.0%).
4) Naive-Bayes, Logistic Regression, SVM and Kernel SVM algorithms had the highest accuracy (88.9%). The RIPPER algorithm had the lowest accuracy (61.1%).
5) All the classifiers considered performed better than the baseline classifier, ZeroR, in terms of precision. Naive-Bayes, SVM and Kernel SVM performed on par with ZeroR when considering recall. No classifier performed better than ZeroR in terms of recall. Naive-Bayes, Logistic Regression, SVM, Kernel SVM, KNN, Random Forest and XGBoost algorithms had a higher f-measure than the ZeroR classifier. Naive-Bayes, Logistic Regression, SVM, Kernel SVM, KNN, Random Forest and XGBoost algorithms performed better in terms of accuracy than the ZeroR classifier.
6) Based on the statements above, it was concluded that SVM is the best classifier for this particular dataset. It performed the best in terms of recall, f-measure, as well as accuracy. For this problem statement, it is evident that the poorest classifier was the RIPPER algorithm, having the lowest recall, f-measure and accuracy.

A. Comparison of SVM with the Baseline Classifier

As shown in Figs. 1 and 2, the values of precision, recall, f-measure and accuracy of the baseline classifier (ZeroR) are relatively poorer than the other classifiers. The reason behind this low value is that the baseline classifier lacks computational intelligence and predicts the predominant class. As the patient demographic and associated variables differ in each medical case, using a baseline classifier is inefficient; it does not take into account the varying nature of patient data and outcomes. A classifier based on SVM resolves this issue, by taking into account each of the patient features and their correlation to the output, and making predictions accordingly.

B. Comparison of SVM with other Machine Learning Classifiers

Being one of the popular Machine Learning based classification techniques, SVM has various use cases. In comparison to newer machine learning algorithms, SVMs are superior, due to their higher performance against limited data. The use of a hyperplane ensures a high accuracy of predictions, as anomalous data is given a lower "say" in prediction, on the basis of how much an outlier it is. Other modern machine learning classifiers like Naive-Bayes, Logistic Regression, KNN, Random Forest, XGBoost and AdaBoost algorithms also provide us with distinct predictions, based on the correlations between patient features and treatment outcome. SVM and Kernel SVM may perform better on this dataset due to the skewed nature of the data. The accuracy of the baseline classifier, ZeroR, was 79.8%, showing an unbalanced proportion of positive outcomes to negative outcomes.

C. Comparison of Machine Learning classifiers with ANN

Since Kernel SVM and SVM algorithms had the same performance, it can be deduced that the hyperplane employed in these algorithms was linear. An interesting observation is that SVM based classifiers performed as well as the ANN classifier, which could be due to the limited size of the dataset. The precision, recall, f-measure and accuracy of the ANN algorithm and SVM based algorithms were the same; from this, we can deduce that they had identical confusion matrices. Our dataset had 90 points of data, which is not enough information to train a Deep Learning classifier, such as ANN. Given the relatively linear nature of the data, the full extent of the intricacies achievable by Deep Learning was not realised, as most synaptic connections in the network were straightforward. Had there been more complexity in the correlations between the features in the output, or a higher volume of data, ANNs would have significantly outperformed the SVM based classifiers for the task of binary classification.

IX. DISCUSSION

The machine learning models that we used to predict the outcome of immunotherapy was tailored to the needs of the respective patients based on the collected data. Initially we employed eleven modern and popular classification techniques ZeroR, RIPPER, Naive Bayes, Logistic Regression, SVM, Kernel SVM, KNN, Decision Trees, Random Forest, AdaBoost and XGBoost. In addition to these models, we have also used Artificial Neural Networks (ANNs). A brief discussion of these techniques is available in the "Machine Learning Classifiers: Background and Related Work"

To predict an individual patient's treatment outcome for warts, we used the following features gender, age, time elapsed before treatment, the number of warts, types of warts, surface area of the warts, induration diameter of initial test as inputs to generate the response to treatment as the output. An additional point that we would like to highlight is that the mentioned machine learning classification plays a vital role in achieving its goal; however, it needs to be noted that raw patient data might not be applicable to build said models. The multi-dimensionality of pre-processing required to be done on raw medical data for prediction and modelling, using the mentioned Machine Learning classification techniques has been discussed briefly in the section titled "Methodology: Immunotherapy Outcome Modelling".

One of the important finding in our research work is that Support Vector Machine based classification models i.e., Support Vector Machine and Kernel Support Vector Machines have shown a high degree of correct prediction.

We observed poor prediction results with the baseline ZeroR classifier, as it simply predicts the predominant class, without the use of a machine learning approach. However, in our research, the ZeroR classifier is used as a baseline for analysis and performance comparison of the various other classifiers. Compared to ZeroR, Naive-Bayes, Logistic Regression, SVM, Kernel SVM, KNN, Random Forest and XGBoost algorithms had higher accuracies. Although Artificial Neural Networks are more popular Deep Learning algorithms, it doesn't give significant results compared to the SVM based algorithms, due to the limited number of samples in the dataset.

X. CONCLUSION AND FUTURE WORK

From our analysis, we concluded that Machine Learning is an effective approach to analyse medical data and predict patient outcome. With the use of Machine Learning techniques, we can suggest optimal treatment methods for patients, to improve the quality of life and patient care. In developing nations such as Argentina, Guyana, India, Brazil, etc., the doctor to patient ratio is relatively low; electronic, telecommunication and computationally intelligent systems and devices can be used to bridge this gap.

We concluded that the best Machine Learning classification technique for our dataset of the success outcome of Immunotherapy treatment for Human Papillomavirus was Support Vector Machine based classification. It outperformed other modern Machine Learning techniques significantly in all performance measures considered, which were precision, recall, f-measure and accuracy.

Due to the highly imbalanced dataset, it was evident that Immunotherapy is an excellent treatment for warts caused by the Human Papillomavirus. The number of positive outcomes of the treatment far outweighed the number of negative outcomes, making Immunotherapy and effective method of treatment for HPV.

Based on our performance comparison of the above-mentioned Machine Learning classifiers, we plan to apply various techniques such as signal processing and Deep Learning, in conjunction with other approaches like Genetic Algorithms to further explore the possibility of integrating Artificial Intelligence with medicine. We would like to explore the use of various Machine Learning algorithms in the future, which can better predict patient outcomes and the course of treatment from medical data, such that each patient receives the optimal care required.

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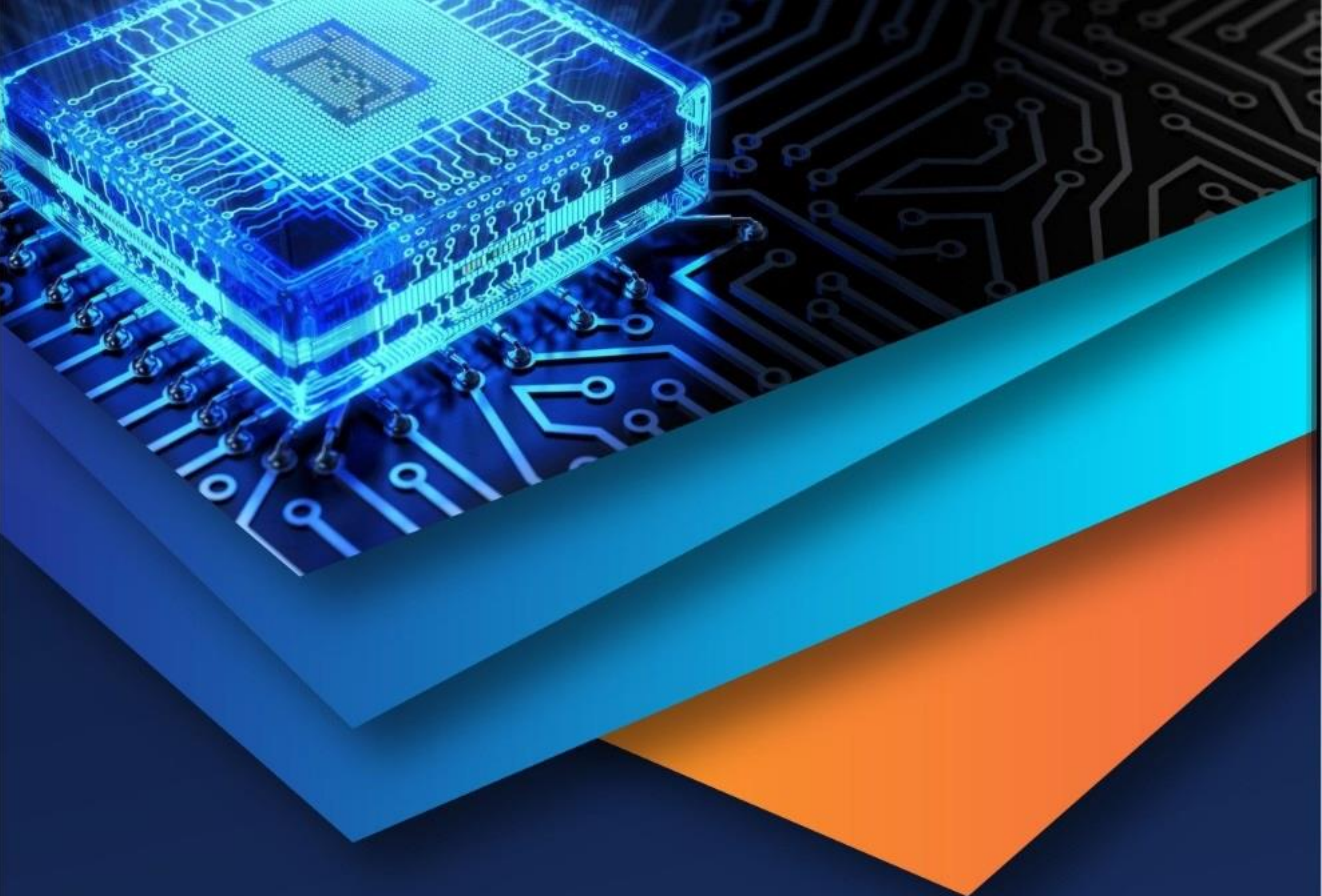

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