Non-Invasive Glycosylated Hemoglobin Monitoring using Artificial Neural Network and Optimized SVM

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Abstract. The study aims to develop a non-invasive system using sensors and machine learning algorithms to monitor the Glycosylated Hemoglobin (HbA1c) level. The device incorporates a breath analyzer with sensors to determine the amount of humidity, temperature and acetone that a person has exhaled. Artificial Neural Network (ANN), a supervised machine learning algorithm will be used to evaluate and to correlate the measured acetone level to HbA1c level. Based on the result of the neural network regression, temperature, humidity, sensor voltage and sensor resistance are strongly correlated to glycosylated hemoglobin level. The predicted HbA1c level will be classified further into three (3) categories. To classify the 3 categories of HbA1c levels, hyperparameter optimization using support vector machine (SVM) algorithm was performed. Linear kernel function of SVM was the best kernel function based on the results of training with 98.8% accuracy. The trained model was tested also using new or unseen samples. Based on the testing results, the system is 100% accurate.

Keywords: Diabetes Mellitus, Glycosylated Hemoglobin, Artificial Neural Network, Hyperparameter Optimization, Optimized SVM

1. INTRODUCTION

One of the most prevailing diseases in the world and in the Philippines is diabetes mellitus. As stated by the World Health Organization (WHO), diabetes mellitus can be defined as a chronic disease in which insulin disorder triggers a significant rise of blood sugar or levels of blood glucose. WHO is projecting that in 2030, diabetes will be the 7th leading cause of death in the world [1]. Glucose comes from the food eaten by people while insulin is a hormone that is formed by the pancreas that permits cells to utilize glucose for the body to have energy. Diabetes has major two types, insulin-independent diabetes or Type 1 and non-insulin dependent diabetes or Type 2.

Type 2 diabetes or diabetes mellitus (DM) [2][3][4], is defined as a metabolic disorder that employs resistance to insulin that depicts elevated amount of blood glucose. Due to its rising incidence and economic impact related to the treatment of consequential morbidity, the best approach for this is effective management and monitoring. According to the American Association for Clinical Chemistry, there are three traditional ways of measuring the glucose level that are commonly done in the laboratory: fasting blood glucose (FBG), glucose tolerance test (GTT), and determining the amount of glycosylated hemoglobin (HbA1c). The mentioned traditional ways of determining the glucose level are all invasive, expensive, and time-consuming procedures.

According to Qiao et al [5], both types of diabetes could lead to a condition called Diabetic Ketoacidosis. It is a critical condition that occurs when the beta cells that produce insulin are not producing them and the body begins to break down fat as an alternative for energy production, thus resulting to a build-up of acid in the bloodstream called ketones. Experts said that type 2 diabetes patients have cases that need insulin therapy or injection due to uncontrolled diabetes, loss of weight and/or simultaneously diagnosed with other diseases such as hypoglycemia. Uncontrolled diabetes can be identified by an abnormal value of hemoglobin A1c, or glycosylated hemoglobin. The hemoglobin A1c test can provide the patient's average levels of blood glucose for the previous two to three months which can be determined by the physician in-charge.

There are numerous studies conducted to develop a non-invasive and invasive diagnosis of diabetes. Different mediums were used such as blood, urine, saliva, sweat, tears, and breath [6]. All mediums used glucose as biomarkers except for breath which used acetone as biomarker. Breath analysis [7] is a solvent-free, non-invasive, sensitive and convenient method of determining and monitoring diabetic ketosis [5]. Two reviewed studies already used the acetone in breath as a biomarker for determining a persons' blood glucose level using Support Vector Machine (SVM) and Artificial Neural Network (ANN). The said studies aim to determine the amount of blood glucose in a patient and then classify them into Healthy Subject, Type 1 DM, and Type 2 DM [8][9]. Other study used and compare the different machine learning algorithms[10] to develop a predictive model for detecting diabetes [11].

One of the objectives of the proposed work is to establish the relationship of breath acetone to glycosylated hemoglobin. HbA1c or glycosylated hemoglobin is a critical parameter in determining uncontrolled diabetes in Type 2 DM patients. There is a correlation between blood ketones and breath acetone, as well as with urine ketones [12]. This was also supported by the study conducted by Li et al [13] where a positive correlation can be traced with breath acetone and glycosylated hemoglobin, and a clear correlation between the ketone bodies that are present in breath, in blood, and in urine.

Three sensors will be used for the project, three of which are to be attached to the mouthpiece. Those sensors include a gas sensor (TGS822), a pressure sensor (BMP180), and a temperature and humidity sensor (DHT11). These sensors will measure and detect the humidity, temperature, pressure and acetone level exhaled by an individual. These parameters, primarily the ketone present in breath depicted by the acetone level were evaluated and correlated with the percentage of HbA1c or glycosylated hemoglobin. Consequently, the HbA1c value acquired was used to determine the control of the patient with diabetes, either the patient has good control (controlled), poor control (uncontrolled), or uncontrolled diabetes that needs insulin therapy (uncontrolled with insulin dosage). Prediction or calculation of the amount of insulin dosage is not part of this study.

2. GLYCOSYLATED HEMOGLOBIN

2.1. Diabetes Mellitus

Diabetes Mellitus (DM) is a chronic medical issue that generally disturbs the ability of the human body to generate energy from the intake and processing of food. Scientifically, it is considered a metabolic imbalance condition characterized by the instance of having elevated levels of blood sugar over a prolonged period [2].

Generally, the human body processes sugar and carbohydrates by breaking them down to a distinctive type of sugar called glucose. Consequently, glucose is the one responsible in fueling the cells in the human body. However, for cells to accept and process glucose for the purpose of producing energy, insulin, a peptide hormone produced by the pancreas, is needed. With DM, two instances are possible. One is that the insulin made by the body is insufficient for its needs, or another is that the body cannot properly utilize its produced insulin.

2.2. Types of Diabetes Mellitus

Type 1 Diabetes. This type of diabetes often begins in childhood. In this case, there is not enough insulin for the cells because the body attacks the pancreas with antibodies. This results to damage in the pancreas that normally produce insulin.

Type 2 Diabetes. It has the highest prevalence in the types of DM, which accounts for 95% of adults diagnosed with diabetes. Before, this form of diabetes is called adult onset diabetes, because it generally occurs in adults. However, with the present continuously rising cases of obesity in the younger age bracket, even adolescents and younger are developing this kind of diabetes. Thus, type 2 DM being denoted as adult onset diabetes may not be applicable anymore. In this type of diabetes, either the amount of insulin produced is insufficient for the needs of the body, or the body cells form resistance to insulin the body produces.

Gestational Diabetes. It is a form of diabetes acquired by pregnant women. It is usually diagnosed in middle or late pregnancy. In this case, there is a greater risk to the unborn baby than risk to the mother.

2.3. Conventional Methods for Diabetes Mellitus Diagnosis

There are three basic conventional methods or tests for diagnosing diabetes mellitus that are usually performed in laboratories such as Fasting Blood Glucose (FBG), Oral Glucose Tolerance Test (OGTT), Glycosylated Hemoglobin (HbA1c) Test.

Fasting Blood Glucose (FBG). It is an invasive method and the most common in the conventional methods of determining blood glucose, usually done in the laboratory, in which the amount of glucose in the blood is measured after fasting for a minimum of eight hours. It is a test measuring the amount of blood glucose in a specific, single point of time. In fasting, the patient is not allowed to eat or drink anything, apart from a small amount of water during the prescribed time frame [14].

Oral Glucose Tolerance Test (OGTT). An invasive method also, and one of the conventional ways of diabetes detection and evaluation done in two hours in which the patient drinks 75 grams of glucose to challenge the body of the patient in processing the glucose. This method determines the amount of glucose in the blood after fasting for at least 8 hours. The process will include first having a health care professional obtain a blood sample from the patient. Afterwards, the patient will be instructed to drink a liquid that contains glucose. For the case of gestational diabetes diagnosis, blood samples must be taken every hour for 2 to 3 hours. During the fasting in OGTT, elevated levels of blood glucose for two or more blood test during one to three hours typically suggest the presence of gestational diabetes [14].

Glycosylated Hemoglobin (HbA1c) Test. The HbA1c test, an invasive method, is a blood test that shows the average levels of blood glucose over the recent 2 to 3 months. This test can also be referred to as hemoglobin A1C, HbA1C, glycosylated hemoglobin, and glycosylated hemoglobin test. Fasting is not required prior to the administering of the test. Generally, the test is not accurate for people with anemia. This test is also an invasive method to diagnose the diabetes. Table 1 shows the category of HbA1c level.

Table. 1 Category of HbA1c Level

HbA1c Level (%)	Category
<= 7%	controlled
7.1% to 10%	Uncontrolled without insulin therapy/dosage
> 10.1%	uncontrolled with insulin therapy/dosage

In this study, the proponents will utilize the Glycosylated Hemoglobin (HbA1c) test to diagnose the Diabetes Mellitus. The proposed method is non-invasive which will use breath sample as media to measure the acetone biomarker leading to prediction of glycosylated hemoglobin.

3. METHODOLOGY

This section will discuss the data gathering, development of model for glycosylated hemoglobin prediction and model optimization to classify the Type 2 diabetes whether it is controlled, uncontrolled or uncontrolled with required insulin dosage.

3.1. Data Gathering

Fig.1 shows the system flow for the data gathering unit. The unit is composed of temperature and humidity sensor (DHT11), pressure sensor (BMP180), and gas sensor (TGS822). To start the data gathering, the user must blow into the mouthpiece. This mouthpiece is attached to the temperature and humidity sensor and gas sensor. The pressure of the breath sample must be at a constant level. Measurement of acetone in breath requires reliable and accurate measurement device and a well-controlled breath sample [15]. With this, a barometric pressure sensor, BMP180, was utilized to determine the pressure in hectopascal (hPa). Both pressure sensor and temperature and humidity sensor have digital output, so these sensors are directly connected to the raspberry pi.

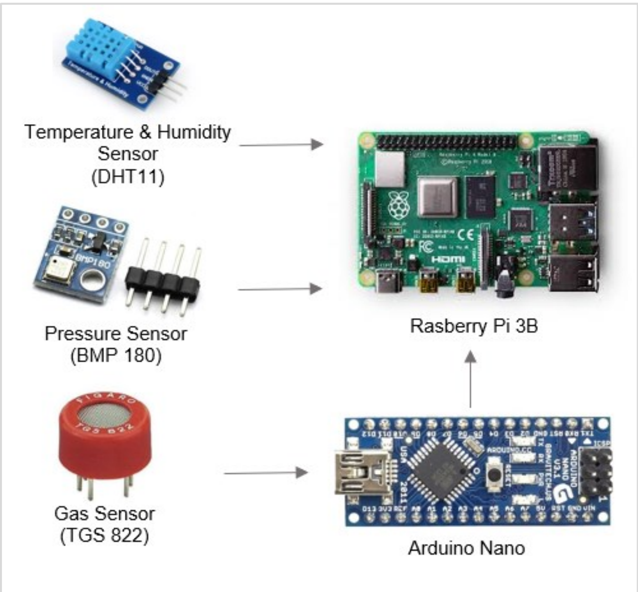

Fig. 1 System flow for data gathering

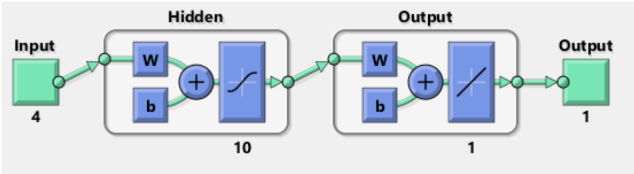

Fig. 2 Graphical diagram of the neural network

On the other hand, TGS822, a gas level sensor with good sensitivity towards acetone and ethanol gases will be used. The gas sensor uses an analog read, so an Arduino nano is used. Pressure sensor is used only to maintain the breath sample at a constant level and will not be included as input during training.

For this study, the dataset is composed of four (4) features such as temperature, humidity, sensor voltage, and sensor resistance with 90 samples (30 – controlled, 30-uncontrolled, and 30-uncontrolled with insulin dosage). This will be the input of the artificial neural network to predict the HbA1c level. Since ANN and SVM are supervised machine learning algorithm, the proponents used the EKF Diagnostic Quo-Lab Analyzer to measure and tag the HbA1c level of the samples.

3.2. Prediction of Glycosylated Hemoglobin using Artificial Neural Network

To predict the corresponding HbA1c level, Artificial Neural Network (ANN) will be utilized using MATLAB. The study used 10 number of hidden neurons during training. ANN [16] [17] fits best when there are several parameters (like temperature, humidity, sensor voltage, and sensor resistance) to be considered in acquiring the accurate output [18].

Fig. 2 shows the graphical diagram of the artificial neural network. As shown the input is composed of four (4) features or characteristics. These features will be fed to the hidden neurons to predict the HbA1c level.

3.3. Classification of Type 2 diabetes based on HbA1c level

After the prediction of HbA1c level, it will be classified further into controlled, uncontrolled without insulin therapy or dosage, and uncontrolled with insulin therapy or dosage. The proponents used support vector machine (SVM) as classification algorithm. SVM has different kernel functions such as Linear, Quadratic, Cubic, Fine Gaussian, Medium Gaussian, and Course Gaussian. Optimizable SVM using classification learner app of MATLAB was utilized during training and validation. The optimizable hyperparameters are kernel function, box constraint level [0.001,1000], kernel scale [0.001,1000], multiclass method [One-vs-One and One-vs-All] and standardize data.

4. EXPERIMENT RESULTS

4.1. Prediction of Glycosylated Hemoglobin using ANN

Prediction of HbA1c level will be done using ANN. The dataset which is composed of 4 input parameters such as temperature, humidity, sensor voltage, and sensor resistance with 90 samples will be fed to the Neural Fitting app of MATLAB. Neural Fitting app will help to select data, create and train the network, and evaluate its performance using mean square error (MSE) and regression analysis. A two-layer feed-forward network with sigmoid hidden neurons and Bayesian regularization as training algorithm was used in this study. Bayesian regularization training algorithm typically requires more time, but can result to good generalization for difficult, small or noisy datasets. The following figures show the training results and performances of the model. Fig. 3 shows the neural network training performance. The best validation performance of the model is at epoch 6 with mean square error (MSE) equal to 2.3363.

Correlation coefficients or Pearson's correlation (R) gives insight if the input parameters or the input features have strong positive or negative relationship with the output. R value equal to positive 1 (+1) means that the input parameters have strong positive linear relationship with the output or target, thus input-output has strong correlation. On the other hand, R value equal to negative 1 (-1) means that the input parameters have strong negative linear relationship with the output or target, thus input-output has strong correlation also. Furthermore, R value equal to zero (0) means that input parameters have no linear relationship with the output or target, thus the input-output has no correlation.

As shown in Fig. 4, the R values are 0.88359 for training and 0.87447 for testing. Both values are greater than 0.5 meaning there is strong correlation or strong relationship between input and output parameters. Thus, the temperature, humidity, sensor voltage and sensor resistance can be used to predict the HbA1c values or level.

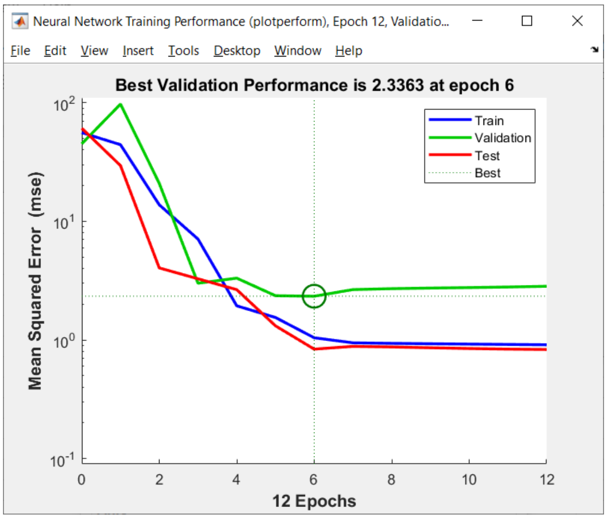

Fig. 3 Neural network training performance

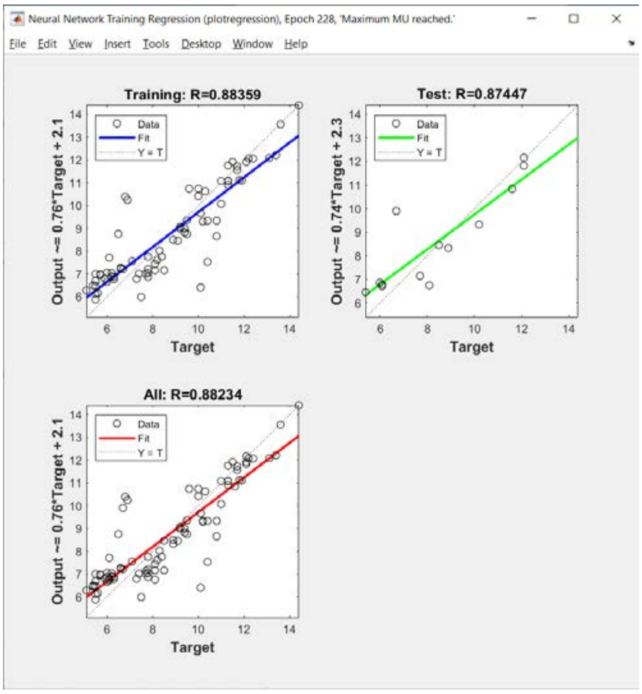

Fig. 4 Neural network training and testing regression

4.2. Classification of Glycosylated Hemoglobin Level

After the prediction of HbA1c level, it will be classified further whether the HbA1c level is controlled, uncontrolled without insulin therapy or dosage, and uncontrolled with insulin therapy or dosage. The proponents used support vector machine (SVM) as classification algorithm. Table 2 shows the results of training using different SVM kernel functions. Based on the results of the training, Linear SVM has the highest classification accuracy equal to 98.8% while Course Gaussian SVM posted the lowest classification accuracy of 81.10%.

Fig. 5 shows the minimum classification error plot using optimized SVM. Hyperparameter optimization using classification learner application of MATLAB will tune the model by selecting different advanced options. The internal parameters of the model or hyperparameters can be fine-tuned, example for optimized SVM, the number of box constraint of an SVM can be changed. For a given model, the application used different combinations of hyperparameter values by using an optimization scheme that seeks to minimize the model classification error to develop a model with the optimized hyperparameters. Based on the plot, the system used a One-vs-One multiclass method, Box constraint level equal to 1.1772 and linear as kernel function.

Table. 2 Training results using different SVM kernel functions

Kernel Function	Training Time (s)	Accuracy (%)
Linear	1.02160	98.80
Quadratic	0.33347	96.60
Cubic	0.26548	96.70
Fine Gaussian	0.27308	82.20
Medium Gaussian	0.27654	88.90
Course Gaussian	0.26685	81.10

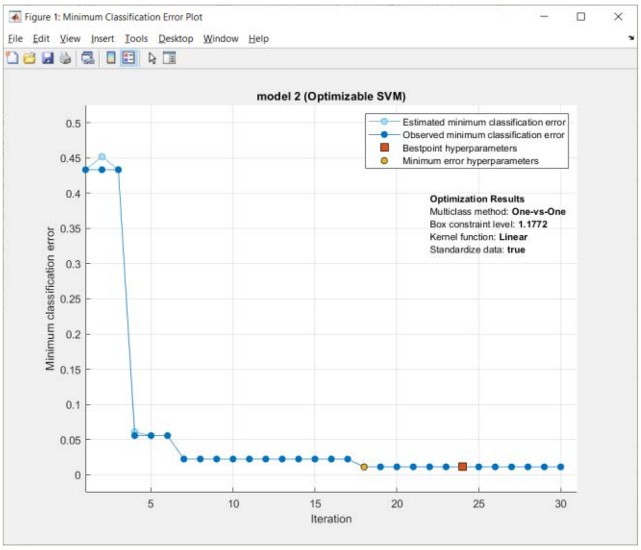

Fig. 5 Minimum classification error plot using optimized SVM

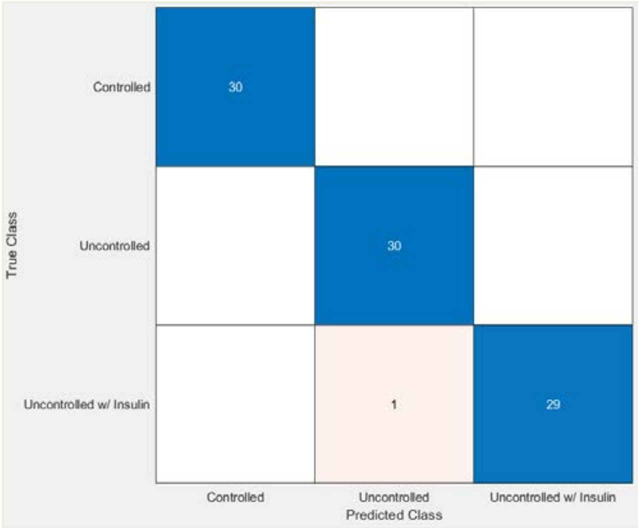

Fig. 7 Confusion matrix of the developed model

Fig. 6 shows the receiver operating characteristic (ROC) curve of the trained model. The ROC curve shows the performance of a classification model at all classification thresholds. This curve plots two parameters such as the true positive rate (TPR) and the false positive rate (FPR). Area under Curve (AUC) ranges in value from 0 to 1. A prediction that is 100% correct has an AUC of 1.0. Since the AUC in this study is equal to 0.99, it means that the model has desirable performance.

Fig. 7 shows the confusion matrix of the developed model. Calculating a confusion matrix can give a better insight if the classification model is correct, that is the true class should be equal to the predicted class. This will show if the model is confused or not during prediction.

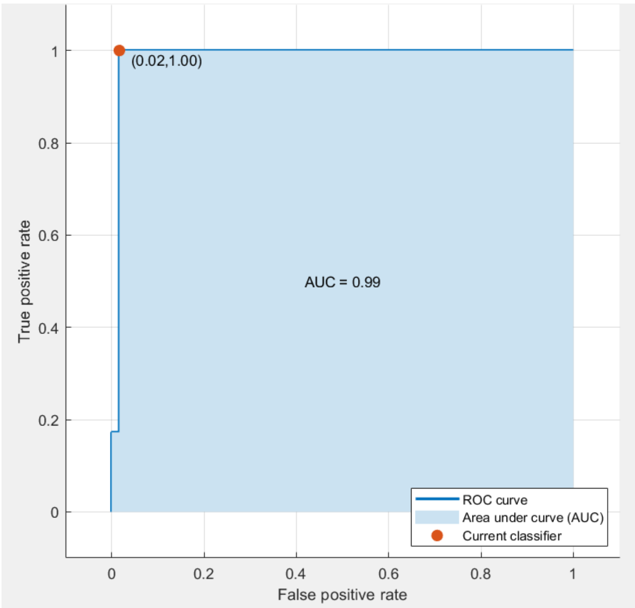

Fig. 6 Receiver operating characteristic curve of the trained model

As shown in the figure, the model has good prediction capability since the model is confused only for one (1) sample whether it is uncontrolled without insulin therapy or uncontrolled with insulin therapy.

Fig. 8 shows the scatter plot of HbA1c level with respect to one of the inputs which is the sensor voltage. As shown, there is a separation between the three (3) classes. This separation is called hyperplane that served as the decision boundaries that help classify the data points. Since there are 3 classes or input features, the hyperplane becomes 2-dimensional plane.

After training, the trained model will be exported to the command window and used to test the new or unseen samples. Thirty (30) samples were used in the testing of the trained model. All classes were properly represented with 10 samples each category. Table 3 below shows the result of testing. As shown, the system is 100% accurate using the unseen samples.

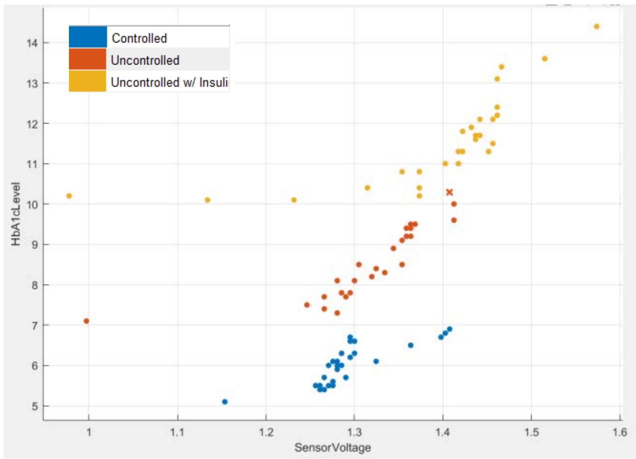

Fig. 8 Scatter plot of HbA1c level vs. sensor voltage

Table. 3 Testing result of trained model using new samples

Temp (˚C)	Hum (%)	Sensor Voltage (V)	Sensor Resistance (Ω)	HbA1c Level (%)	Category	Remarks
29	90	1.309872923	28171.64179	5.2	controlled	successful
28	91	1.285434995	28897.3384	6.4	controlled	successful
29	92	1.363636364	26666.66667	5.7	controlled	successful
26	78	1.28054741	29045.80153	6.2	controlled	successful
29	90	1.270772239	29346.15385	5.9	controlled	successful
27	92	1.270772239	29346.15385	5.6	controlled	successful
29	92	1.246334311	30117.64706	6.9	controlled	successful
29	91	1.300097752	28458.64662	6.8	controlled	successful
29	91	1.363636364	26666.66667	6.2	controlled	successful
25	76	1.319648094	27888.88889	6	controlled	successful
23	68	1.290322581	28750	7.8	Uncontrolled without insulin therapy/dosage	successful
25	57	1.358748778	26798.56115	9.1	Uncontrolled without insulin therapy/dosage	successful
29	91	1.348973607	27065.21739	7.9	Uncontrolled without insulin therapy/dosage	successful
29	92	1.290322581	28750	8.9	Uncontrolled without insulin therapy/dosage	successful
28	93	1.339198436	27335.76642	9.5	Uncontrolled without insulin therapy/dosage	successful
27	91	1.28054741	29045.80153	9.3	Uncontrolled without insulin therapy/dosage	successful
29	92	1.23655914	30434.78261	9.8	Uncontrolled without insulin therapy/dosage	successful
28	92	1.309872923	28171.64179	9	Uncontrolled without insulin therapy/dosage	successful
28	87	1.373411535	26405.69395	7.8	Uncontrolled without insulin therapy/dosage	successful
25	91	1.241446725	30275.59055	10	Uncontrolled without insulin therapy/dosage	successful
29	92	1.451612903	24444.44444	11.3	Uncontrolled with insulin therapy/dosage	successful
28	93	1.373411535	26405.69395	10.4	Uncontrolled with insulin therapy/dosage	successful
29	91	1.456500489	24328.85906	11.5	Uncontrolled with insulin therapy/dosage	successful
29	91	1.402737048	25644.5993	11	Uncontrolled with insulin therapy/dosage	successful
29	89	1.461388074	24214.04682	13.1	Uncontrolled with insulin therapy/dosage	successful
25	93	1.407624633	25520.83333	10.3	Uncontrolled with insulin therapy/dosage	successful
29	92	1.461388074	24214.04682	12.4	Uncontrolled with insulin therapy/dosage	successful
28	92	1.417399804	25275.86207	11.3	Uncontrolled with insulin therapy/dosage	successful
30	92	1.436950147	24795.91837	11.6	Uncontrolled with insulin therapy/dosage	successful
28	89	1.456500489	24328.85906	12.1	Uncontrolled with insulin therapy/dosage	successful

5. CONCLUSION

A non-invasive glycosylated hemoglobin prediction monitoring system intended for type II diabetic patients has been successfully developed. Using ANN, the collected dataset consisting of temperature, humidity, sensor voltage and sensor resistance was used to predict HbA1c level. Neural network regression results show that the 4 input features are highly correlated to the level of HbA1c. The proponents made use of the optimized SVM to further classify the HbA1c level. SVM 's linear kernel function was the best kernel function with 98.80% training accuracy based on the results. The trained model was tested also using new or unseen samples. Based on the results the system is 100% accurate.

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