Using Oral Glucose Tolerance Test and Support Vector Machine to predict Type 2 Diabetes

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**Abstract**

Diabetes is a large healthcare burden worldwide. With increasing evidence that lifestyle modifications and drug interventions can prevent diabetes, early identification of high risk individuals is important for targeted prevention strategies. We present an automatic tool that uses machine learning techniques to predict development of type 2 diabetes mellitus (T2DM). Data generated from an oral glucose tolerance test (OGTT) was used to develop a predictive model based on the support vector machine (SVM). We trained and validated the models using the OGTT data and epidemiological data of 1,496 healthy individuals collected during the San Antonio Heart Study. This study collected glucose and insulin concentrations before glucose intake and at three time points thereafter (30, 60, and 120 minutes). Furthermore, epidemiological information as age, ethnicity and BMI were also a part of the dataset. Using these 11 measurements, we have generated 61 deduced features. The features are ranked and top ten features are shortlisted using Minimum Redundancy Maximum Relevance (mRMR) feature selection algorithm. All possible combinations of the 10 ranked features were used to generate SVM based prediction models. This research shows that information extracted from an individual’s abnormal blood glucose levels has high predictive performance. Significantly, insulin and epidemiological features do not provide additional performance improvement for diabetes prediction. The results of this work inform the identification of parsimonious clinical data that need to be collected for efficient diabetes prediction.. The results of our approach show an average accuracy of 96.46% and a specificity of 80.45% on a holdout set.

Type 2 Diabetes prediction, machine learning, disease risk assessment, San Antonio heart study.

# Introduction

The global incidence of diabetes was estimated at 422 million in the year 2014 and its prevalence among the adult population increased from 4.7 % in the year 1980 to 8.5 % in 2014 [1]. In 2015 alone, an estimated 1.6 million deaths worldwide were attributed to diabetes. In addition, compared to a non-diabetic individual, a diabetic patient is at a greater risk of developing cardiovascular diseases, visual impairment and limb amputations. Due to the substantial socio-economic burdens that are associated with diabetes, its early detection, prevention, and management has become a worldwide top-level health concern. There is experimental evidence that the development of diabetes can be delayed or even prevented provided an individual undertakes a lifestyle change that includes diet management, adopting exercise, and adhering to a pharmacological treatment [2]. The early identification of high risk individuals of diabetes is therefore, essential for targeted prevention strategies [3].

The number of clinical studies aimed at diagnosing the state of diabetes have been growing in number in the last two decades. However, studies that predict the persons who areat risk of developing diabetes are limited. This subject has seen an increased amount of research interest in the last decade [4] and the clinical significance of such predictions largely depend on the type and quality of data collected. There are studies using sociodemographic characteristics such as age, ethnicity, body mass index (BMI) and genealogical information collected through population surveys to assign a probability to an individual having diabetes [5, 6]. Due to the unreliable data collection, such techniques can often be misleading. . The collection of specimen such as blood on the other hand, provides more reliable data and is a first step towards disease prognosis with a deeper clinical insight. In regard to diabetes, the oral glucose tolerance test (OGTT) not only is used to diagnose diabetes, but provides a critical understanding of its future evolution through the beta-cell function and insulin resistance that are widely regarded as the major factors of the development of T2DM. In an OGTT, the blood glucose and insulin levels are measured a regular intervals in a 2-hr period after orally administering a standard dose of glucose [\cite stumvoll\_use\_2000}]. A precursory stage commonly referred to as prediabetes exists before overt T2DM, and is described by an impaired glucose tolerance (IGT). According to the World Health Organization diagnostic criteria, the IGT is defined as having a fasting blood glucose level of <126 mg/dL and a 2-hour blood glucose level in the range of 140-200 mg/dL, measured during the OGTT [\cite{organization\_definition\_2006}]. . Although prediabetes is considered as an intermediate stage in the natural progression of T2DM \cite{defronzo2011assessment}, it has been reported that only 50 % of the subjects diagnosed with IGT developed diabetes within 10 years [7, 8]. Moreover, long-term population studies have also shown that around 50 % of the diabetic patients did not exhibit IGT at any time prior to the diagnosis [9], which suggests that the fasting and 2-hour blood glucose levels in and by themselves cannot accurately determine the future development of T2DM.

In contrast to traditional scientific approaches using population based statistics, ma- chine learning (ML) methods develop models that are trained using large data. ML has been proposed as a viable method for diabetes screening. Barakat et al used socio-demographic information, and point of care measurement form blood and urine to develop diabetes risk models [13]. This approach uses ensemble approach based upon a combination of SVM and random forest. Han et al employed SVM to develop a decision making algorithm for the diagnosis of diabetes [14] which provided an added comprehensibility of the classification mechanism. This approach uses socio-demographic information and glucose levels at baseline and 2h thereafter during an OGTT for ML based diabetes prediction. Investigations to identify individuals at high risk of developing future T2DM include San Antonio Diabetes prediction model (SADPM) [15] where a logistic regression model was constructed using physiological parameters such as systolic blood pressure and cholesterol level. The underlying causes of T2DM in the form insulin resistance and insulin secretion were studied to develop a prediction model in [9]. In another study, multivariate logistic models using the blood glucose values measured in the OGTT were used to predict the future risk of developing T2DM [10, 16].

We hypothesized that features extracted from OGTT data will be able to predict future onset of diabetes. In this paper, we develop a diabetes prediction model by identifying the features computed from the OGTT data that strongly correlate to future diabetes onset. Furthermore, we develop a support vector machine prediction model using these features. For this purpose, we use the OGTT data generated from the population-based, epidemiological study, the San Antonio Heart Study (SAHS) [17, 18].

# Materials and Methods

### San Antonio Heart Study

The San Antonio Heart Study (SAHS) is a population-based epidemiological study that was conducted to assess the risk factors of diabetes and cardiovascular diseases in healthy population [16], [17]. It includes 5,158 men and non-pregnant women of Mexican-American and non-Hispanic white residents of San Antonio, Texas. The age of the individuals at the time of recruitment was between 25 and 64 years. As a part of the data collection, the blood glucose and insulin levels were recorded during the oral glucose tolerance test (OGTT), which measures the body response to a standard 75 g dose of glucose after fasting overnight.

T2DM was diagnosed by a WHO criteria, defining fasting glucose level ≥126 mg/dL or 2-hour glucose level ≥200 mg/dL [19]. Furthermore, all individuals taking anti-diabetic medications was also classified as diabetic [DMI]. All individuals with self-reported cardiovascular event at follow-up, such as heart attack, stroke or angina, were labeled as CVD. Individuals without T2DM or self-reported CVD were labeled as healthy. During the course of the study, a total of 171 individuals developed T2DM with 10 individuals also reporting at least one cardiovascular event. The incidence rate of T2DM for this population was 11.4%. Figure 1 illustrates the blood glucose and insulin values recorded at the baseline, and at 30, 60 and 120 minute after the intake of standardized glucose concentration during the OGTT.

Table 1: The classification of the 1,496 subjects used in this study

|  |  |  |  |
| --- | --- | --- | --- |
| Healthy | DMI | CVD | DMI+CVD |
| 1.281 | 161 | 44 | 10 |
| 85.63 % | 10.76 % | 2.94 % | 0.67 % |

### Preparation of the Data

The dataset included the glucose and insulin values recorded at the baseline, 30, 60 and 120 minute intervals, and ‘healthy’ or ‘diabetic’ label marked in a follow-up encounter. The distribution of these values marked by ‘healthy’ and ‘diabetic’ labels is shown in Fig. 1. The socio-demographic information such as age, ethnicity and body-mass index (BMI) was also part of the dataset. From the glucose and insulin measurements, we computed the slope and area under the curve between all possible pair combinations of readings. In addition, we also calculated parameters such as the insulinogenic (ratio of insulin and glucose slopes between any two time intervals) and Matsuda indices, as defined in [12, 21]. These variables have shown good efficacy of diabetes prediction in previous studies [9, 12], since they characterize the beta-cell function. In total we prepared 61 features for the classification problem and removed the rows that had missing entries, or contained zero or infinite values. The dataset was then partitioned into training and validation sets. As can be observed from the Table 1, the SAHS dataset is intrinsically imbalanced with the class distribution skewed toward the majority class in a ratio of 7.5:1. The minority class of diabetic subjects was defined as the positive class with a label of 1, whereas the majority class consisting of healthy persons was termed as the negative class marked by a ‘−1’ label.

### Machine Learning Framework

We developed a supervised learning scheme in which the classifier output labels were obtained from the follow-up data, and the support vector machine (SVM) technique was used to construct the future diabetes prediction models. The SVM works on the principle of structural risk minimizationin which the goal is to develop a model from the given training data such that it generalizes well to new datasets and minimizes the empirical risk associated with misclassification of samples in the training set [22,23]. For a binary classification problem, the model constructed by the SVM finds a decision boundary or a separating hyperplane which aims to minimize the overlapping between the two classes in the training set. For problems that may not be amenable to linear separation between the two classes, the SVM technique is very attractive due to fact that the input feature space is first transformed to a higher dimension and then a linear boundary is determined, which generally gives better training performance [24].

Let us consider a training data (*x*1, *y*1), (*x*2, *y*3),..., (*xk*, *yk* ) of *k* pairs containing *xi* ∈ R*N* features and the binary classes *yi* ∈ −1, 1. The SVM approach transforms the input features using a nonlinear mapping Φ: *x* f→ φ(*x*) into a higher dimension space R*P* , where in general *P* » *N*. Due to the transformation, the classes can then be separated using a linear decision boundary in the enlarged space. The non-linear SVM classifier F is expressed in terms of the higher dimensional hyperplane,



When the classes may not be completely separable, introducing a slack variable ζ in the higher dimension space R*P* is a common practice which allows for the classifier

250

Healthy Diabetic

200

150

Glucose [mg/dL]

100

50

250

Baseline 30 60 120

*t* [minutes]

200



Healthy Diabetic

150

Insulin [mg/dL]

100

50

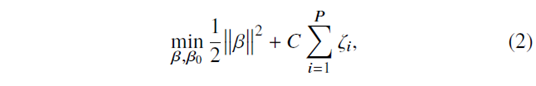
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Baseline 30 60 120

*t* [minutes]

Figure 1: Box plots of glucose and insulin measurements for healthy and diabetic subjects.

output in (1) to be on the incorrect side of the margin. Therefore, in order to find the optimal separating hyperplane that maximizes the distance *M* from the boundary for all the points, and bounds the value of I,*i* ζ*i* and in turn misclassification rate, we introduce the convex optimization problem,

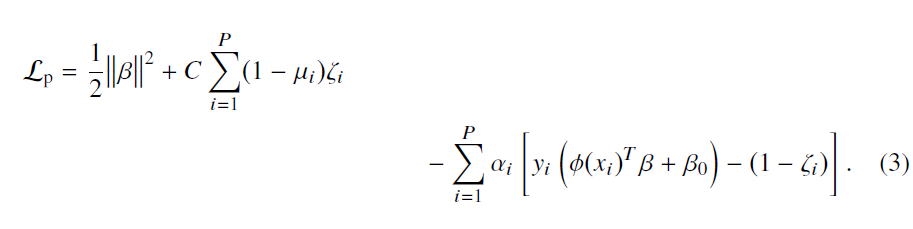


with the nonlinear constraints *yi* (φ(*xi*

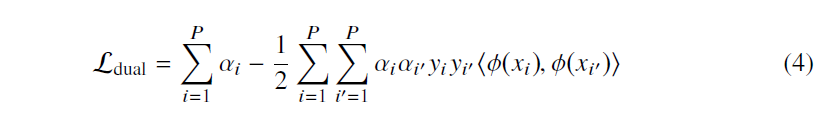
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β + β0) ≥ 1 − ζ*i* ∀*i* and ζ*i* ≥ 0, and the

coefficient *C* is termed as the cost parameter which decides the rigidity of the margin of the classifier. The solution of (2) can be computed using the Lagrange primal objective function [24],



By minimizing Lprimal with respect to β, β0, and ζ*i* , we get the corresponding dual form of the Lagrange function,



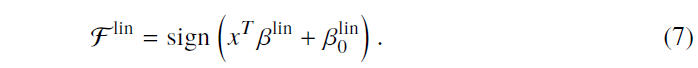
subject to 0 ≤ α*i* ≤ *C* and α*i yi* = 0 and the constraints, ζ*i*, µ*i* ≥ 0∀*i*. The nonzero coefficients α*i* and β0 are determined using (1). As the dimension of the input feature space goes up, the computation of the mapping Φ gets excessive in complexity. With the introduction of a kernel,

K(*x*, *x*,) = <φ(*x*), φ(*x*,)>, (5)

we can compute the inner product on (4) without computing the mapping Φ [25], which becomes computationally expensive as the dimension of the input feature space increased. In this paper, we used the Gaussian radial basis function, as the kernel where σ is a free parameter. During the training, we tuned the values of the parameters *C* and γ through a grid search to obtain the optimal performance of the SVM.

For a linear variant of the SVM, the classifier can expressed without any coordinate

mappings as,



### Feature Extraction

We extracted all the features from the SAHS data acquired at the baseline. The labels (healthy and diabetes) were generated at the 7.5 years follow-up using the current standard of care [\cite{rapid\_rise\_1984\_stern}]. The features used in this study include:

• Raw measurements of blood glucose and insulin concentrations (N = 8)

• Deduced features from measured blood glucose and insulin defined as the slope and area under the curve between all possible combinations of a pair of readings (N = 48)

• The insulinogenic (ratio of insulin and glucose slopes between any two time intervals) and Matsuda indices, as defined in [8], [20], and the homeostatic model assessment of insulin resistance (HOMA-IR), which is calculated as the product of fasting blood glucose and fasting blood insulin divided by 22.5. The HOMA-IR is a reasonable approximation of the insulin resistance which requires a euglycemic insulin clamp experiment which is risky and complicated \cite{ Matsuda1462 }.

• Sociodemographic characteristics such as age, ethnicity, and body mass index (BMI)

In total we extracted 61 features illustrated in Figure 2.

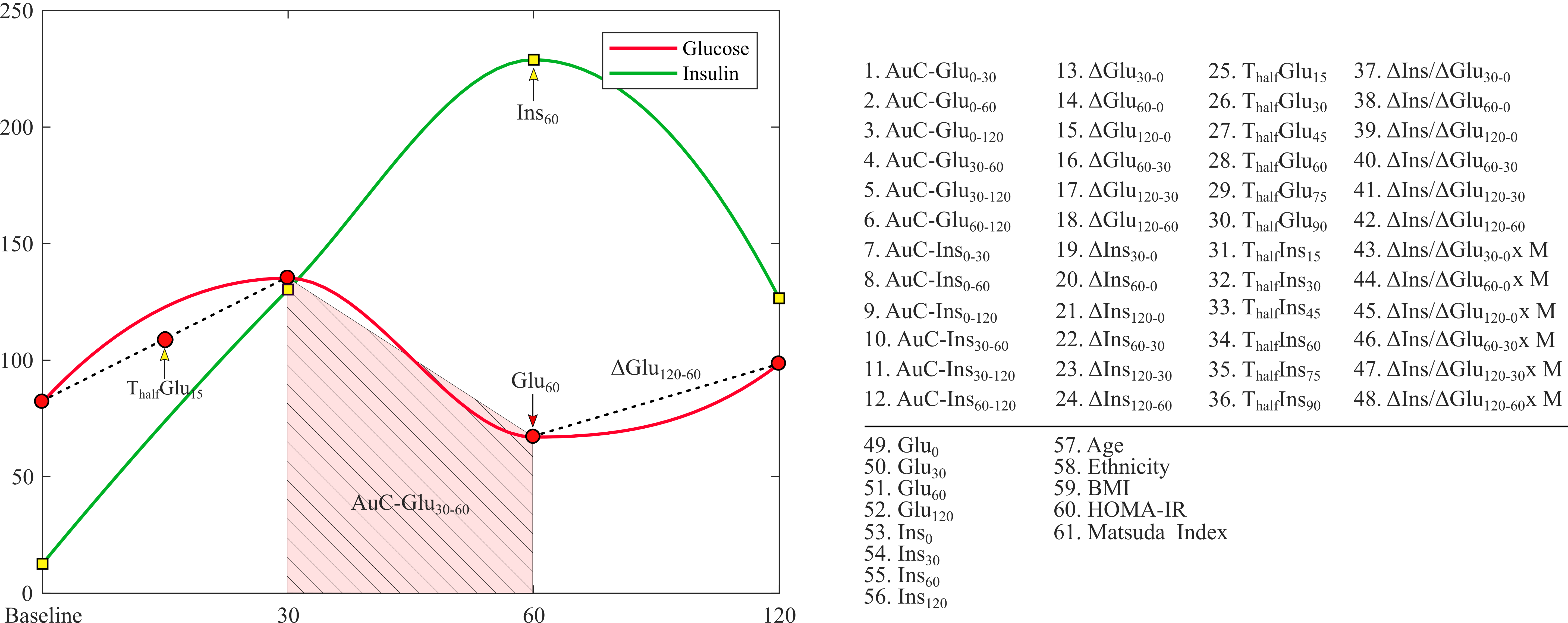
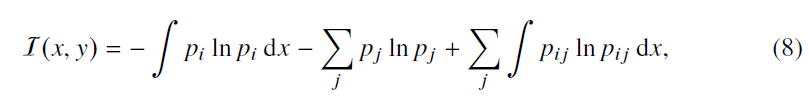


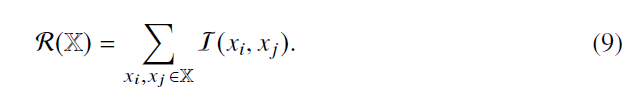
Figure 2: List of all 61 features extracted from the OGTT in this work.

### Feature Selection

Before constructing the SVM model to predict a future diabetes event, we search for the most effective subset of features in terms of relevance to the classifier output. As a first step to achieve this, we selected ten most relevant feature from the 61 available features. This step decreases the computational cost during the model development by reducing the dimensionality of the feature space. To prevent the selection of highly correlated features, which adds to the computational cost of the classifier without necessarily improving the performance [26], we minimize the correlation among the features by minimal redundancy-maximal-relevance (mRMR) algorithm [27]. This algorithm utilize relevance between feature (x as continuous random variable) and the class labels (y as discrete random variable) described in terms of the mutual information, defined as [25]:



where pi , and pj are the probabilities of the random variables x and y taking a particular value xi and yj ∈ (−1, 1) ∀ j respectively. The term pij denotes the joint probability P{x = xi, y = yj }. The three terms in (8) represent the continuous, discrete and joint entropies of the random variables in the respective order. The features that are most relevant to the class label individually yield the maximum I. However, a drawback of pursuing this approach is that the selected features may be mutually correlated, and having a redundant list of shortlisted features only adds to the computational cost of the classifier without necessarily improving its performance. Even more so, the addition of extra features commonly result in the deterioration of the classifier performance [27]. Therefore, an heuristic approach is to keep only a single feature from a correlated set of features that provides similar relevance information, and discard the remaining features from the set X. We follow the minimal-redundancy- maximal-relevance (mRMR) algorithm [28], which selects the features that not only yield the maximal mutual information (8) with respect to the class label, but minimizes the mutual correlation among the features expressed in terms of redundancy R as:



where I follows its definition in (8). By minimizing R, the mRMR framework selects a set of mutually exclusive features that are most relevant to the class label. Here, we first shortlist a set of ten features that are strong predictors of the future development of T2DM, on the basis of yielding maximum I with respect to the diabetic class.

The application of the mRMR algorithm produces the features that are listed in Table

2 that are ranked in order of their relevance. The prefixes *AuC* and *Sl* denote the area under the curve and slope respectively, and the OGTT time interval corresponding to the feature appears in the subscripts.

In the second phase, we constructed SVM models for all 1023 combinations of the 10 ranked features. For each feature combination, the training and validation sets were randomly created 100 times. The best averaged validation accuracy and sensitivity for different number of features is shown in Fig. 3. The x-axis labels represent the feature combinations in which the numbers represent the feature rank as listed in Table 2. For selecting the best feature set, we chose the criteria of maximizing the product of validation accuracy and sensitivity. The combination of four features - AuC-Glu0-120, ΔGlu120-0, ΔGlu120-60 and ΔGlu30-0 yielded the best performance of 0.78. We choose this combination to generate the classification models in the rest of this paper.

Table 2: List of ten most relevant features ranked by the mRMR algorithm

|  |  |
| --- | --- |
| Rank | Feature |
| 1 | AuC-Glu0-120 |
| 2 | ΔGlu120-0 |
| 3 | ΔGlu120-60 |
| 4 | ETHN |
| 5 | ΔIns120-0 |
| 6 | ΔGlu60-0 |
| 7 | ΔGlu30-0 |
| 8 | ΔGlu60-30 |
| 9 | ΔIns120-60 |
| 10 | ΔIns60-0 |

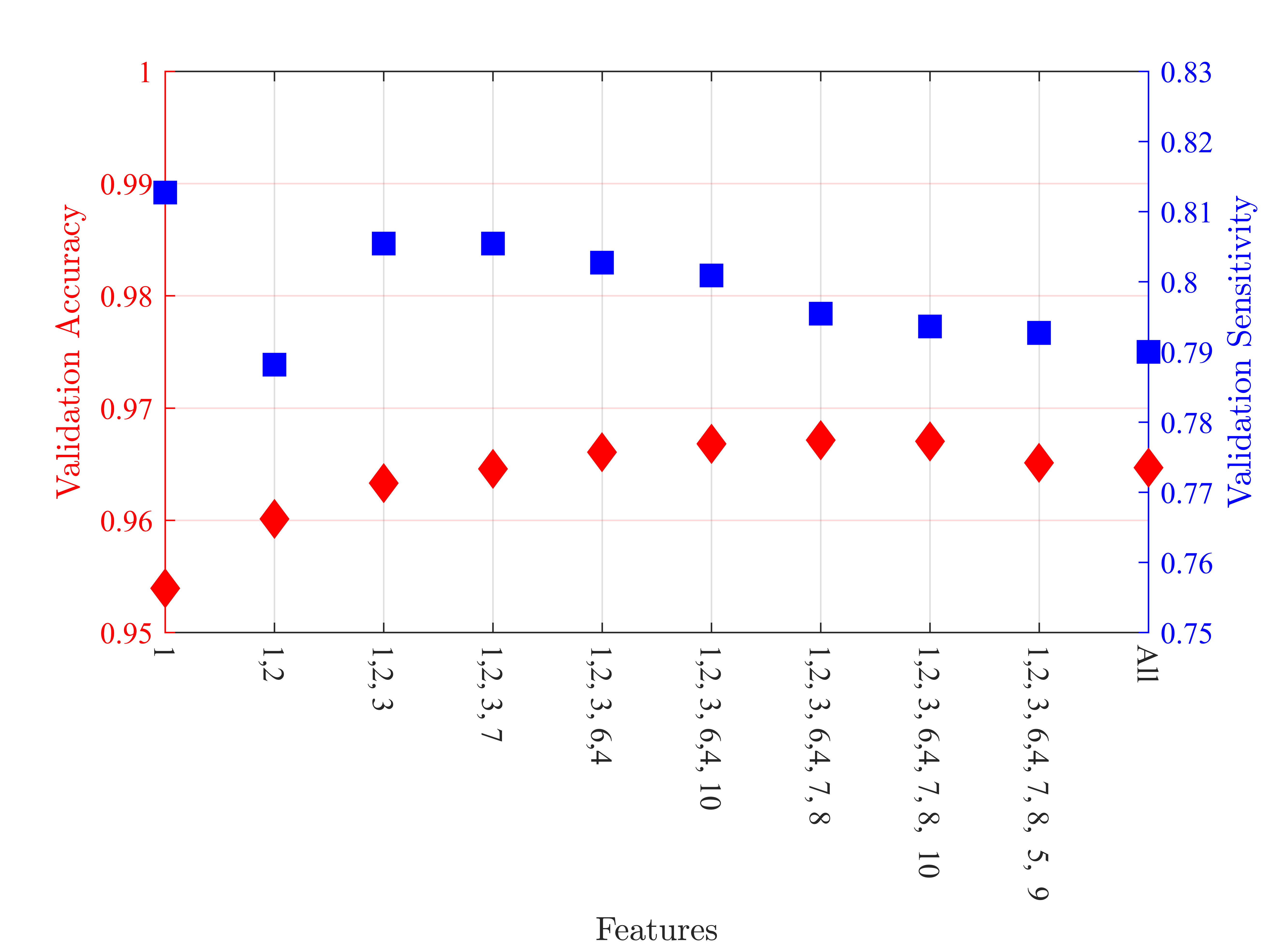


Figure 3: Average performance of the individual features gauged by the accuracy

# Classification

We developed a supervised learning scheme using SAHS data and the labels (healthy, diabetic) obtained at the follow-up. The SVM was used for development of the models for diabetes prediction. As observed in Table I, the SAHS dataset is intrinsically imbalanced with the class distribution skewed toward the majority (healthy) class with a ratio of 7.5:1. We have excluded the 44 CVD entries for potentially wakening the labels as the only way of defining this class was based upon the self-reporting and not on quantitative assessment. for the classification problem and removed the rows that had missing entries or contained zero or infinite values. The dataset was then partitioned into training and validation sets. The minority (diabetic) class was defined as the positive class with a label of 1, whereas the majority (healthy) class was defined as the negative class marked by a label -1. In order to ensure that the model remained unbiased, robust, and generalize well to new data, we performed 10-fold cross-validation during the training, while the training performance was averaged over all 10-folds. All the experiments were carried out using the statistical and machine learning toolbox of Matlab® (version 9.2.0 .556344, MathWorks Inc., Natick, Massachusetts, USA) and the data was normalized prior to the training.

We have compared the performances of a linear and non-linear SVM. In both cases, the optimal hyperplane parameters were assessed through a grid search with a view to maximize the sensitivity. To analyze the influence of class imbalance on the classification performance, we defined the following experiments:

Experiment I: The dataset was balanced with random under-sampling of the majority class, and took 160 instances from each class for the training.

Experiment II: The dataset retained the unbalanced class distribution and randomly sampled 1,200 (out of 1,281 instances) to generate the training set that contained 160 and randomly samples 1,200 instances of the diabetic and healthy classes respectively.

For both the experiments, we used ten most relevant features shortlisted during feature selection procedure. The optimal hyperplane parameters *C* and σ in (2) and (6) respectively were determined through a grid search with a view to maximize the classifier sensitivity defined as, TP/(TP + FN) where TP and FN refer to the number of correctly and incorrectly classified diabetic subjects respectively.

# Results and Discussion

In order to correctly predict the future diabetes subjects, the model was trained to maximize the sensitivity. To train the predictor model, we used four features, all of which were derived from the blood glucose measurements. We used the definition of accuracy as the ratio of number of correctly classified subjects to the total number of subjects, whereas the specificity was the ratio of the correctly classified healthy subjects to the total number of healthy subjects and sensitivity as the ratio of correctly classified diabetic subjects to the total number of diabetic subjects. Table IV presents a comparison of the mean training performance of both the balanced and unbalanced cases of the linear and non-linear SVM classifiers averaged over 100 trials. Notably, the random under-sampling of the majority class lowers the classifier stability as evident in a greater standard deviation (SD). An otherwise comparable performance suggests that the models are not skewed toward the majority class. The optimal hyperplane parameters corresponding to the Matlab arguments ‘BoxConstraint’ and ‘Gamma’, were respectively assigned the values of 1.0 and 6.0. For the linear version of the SVM, an average of 250 and 1,114 support vectors were

Table 3: Mean Training performance of the classifiers

|  |  |  |  |
| --- | --- | --- | --- |
| Method | Accuracy ± SD | Sensitivity ± SD | Specificity ± SD |
| Linear SVM (Balanced) | 78.46 % ± 1.47 % | 77.58 % ± 1.37 % | 79.34 % ± 2.22 % |
| Linear SVM (Unbalanced) | 79.66 % ± 0.45 % | 77.77 % ± 0.84 % | 79.91 % ± 0.45 % |
| SVM-RBF (Balanced) | 78.33 % ± 1.70 % | 78.44 % ± 1.84 % | 78.22 % ± 2.37 % |
| SVM-RBF (Unbalanced) | 78.90 % ± 0.53 % | 78.97 % ± 0.51 % | 78.36 % ± 0.77 % |



Table 4: Validation performance classifiers

|  |  |  |  |
| --- | --- | --- | --- |
|  | Accuracy ± SD | Sensitivity ± SD | Specificity ± SD |
| Linear SVM (Balanced) | 97.18 % ± 1.48 % | 75.91 % ± 12.68 % | 100 % |
| Linear SVM (Unbalanced) | 96.20 % ± 1.94 % | 77.00 % ± 12.08 % | 98.75 % ± 1.35 % |
| SVM-RBF (Balanced) | 97.73 % ± 1.41 % | 80.64 % ± 12.03 % | 100 % |
| SVM-RBF (Unbalanced) | 96.46 % ± 1.40 % | 80.45 % ± 11.50 % | 100 % |
| Two-step Approach [16] | - | 77.70 % | 77.40 % |
| SADPM [15] | 56.329 % | 88.80 % | 52.00 % |



used to construct the hyperplane for the balanced and unbalanced datasets respectively. On the other hand, the corresponding values were 278 and 1,198 for the nonlinear SVM with the RBF as the kernel. It should be noted that the difference in the dimensionality of the hyperplanes between the two variants of the SVM is not large, which indicates that the discriminating power of the features used.

Table 4 displays the mean validation performance of the classifiers. All the trained models were validated on a hold-out dataset randomly replicated 100 times with 11 diabetic and 83 healthy subjects in each replication.. The non-linear SVM classifier in which the class ratio was maintained in the same ratio as the original dataset provided a sensitivity of 80.45%. Although the performance in the case when the classes are balanced is better, the minor improvement does not justify the artificial alteration of the class distribution of the original dataset. The obtained results were also compared to other T2DM prediction models that used the the SAHS dataset. The San Antonio diabetes prediction model (SADPM) [15] used a logistic regression based on a person’s age, gender, ethnicity and the fasting glucose level. The two-step approach used the SADPM to first create a risk score, which was then combined with the 1-hr blood glucose concentration to identify high-risk individuals.

# Conclusion

In this paper, we developed a SVM prediction model to identify the persons that are at an increased risk of developing T2DM in the future. We showed that a high prediction performance can be achieved by extracting information from a person’s blood glucose levels obtained during an oral glucose tolerance test. The accuracy and more importantly sensitivity of the presented classifier show a marked improvement over the previous prediction models that used the same dataset. We also limited the features used to four and all these features were derived from blood glucose levels, thereby reducing the cost and effort involved in clinical procedures, data collection, and model development.

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