Collaborative Denoising Autoencoder for High Glycated Haemoglobin Prediction

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Abstract. A pioneering study is presented demonstrating that the presence of high glycated haemoglobin (HbA1c) levels in a patients blood can be reliably predicted from routinely collected clinical data. This paves the way for performing early detection of Type-2 Diabetes Mellitus (T2DM). This will save healthcare providers a major cost associated with the administration and assessment of clinical tests for HbA1c. A novel collaborative denoising autoencoder framework is used to address this challenge. The framework builds an independent denoising autoencoder model for the high and low HbA1c level, which extracts feature representations in the latent space. A baseline model using just three features: patient age together with triglycerides and glucose level achieves 76% F1-score with an SVM classifier. The collaborative denoising autoencoder uses 78 features and can predict HbA1c level with 81% F1-score.

Keywords: Healthcare, Machine Learning, Deep Learning, Collaborative Denoising Autoencoder, Clinical Data, Diabetes, Type-2 Diabetes Mellitus, Glycated Haemoglobin, HbA1c, KAIMRC dataset.

1 Introduction

The haemoglobin when joined with the glucose within the blood, it forms glycated haemoglobin, referred to as HbA1c [30] [24]. Glycated haemoglobin (HbA1c) is the basis for one of the important blood tests used to indicate the status of glucose levels in the blood [30, 24].

The level of HbA1c is strongly related to the average glucose concentration in the blood and the life span of the red blood cells. The normal red blood cells of the human body can last for two to three months before being reproduced. Hence the level of HbA1c can indicate the average level of blood glucose over the whole period of the life span of the red blood cells [25, 31]. This can provide physicians with an important long-term measure for blood glucose levels [1].

The traditional method of measuring the blood glucose levels is by using the fasting plasma glucose (FPG) test. The FPG test can provide a measure of

short-term blood glucose level but requires the patients to undertake an overnight fasting prior to the test. However, the HbA1c blood test can provide an overall average of the blood glucose level over the preceding two to three months (long-term) and can be taken without the patient having to fast the night before the test. Thus, HbA1c test is an attractive option for both patients and practitioners for measuring glucose levels in the blood [1]. Recent studies have showed that HbA1c test can be used as indicator for diagnosing diabetes (T2DM) especially when combined with vital signs such as Body Mass Index (BMI) [15, 21].

The International Expert Committee (IEC), with members from the American Diabetes Association (ADA), the European Association for the Study of Diabetes, and the International Diabetes Federation [11, 6], recommends HbA1c test to evaluate the adults with a high risk of diabetes [1]. HbA1c levels are also related to chronic complications [10]. The IEC recommends effective clinical intervention for those patients with a HbA1c level of 6.5% or more.

Non-diabetic people with an elevated HbA1c level are also at an increased risk of cardiovascular disease [23, 1]. The HbA1c test helps with predicting which patients are likely to develop T2DM in the future [12]. It also helps physicians decide how frequently patients need to undertake clinical screening for T2DM [12]. The earlier the diagnosis of T2DM, the better chance there is of delaying (and possibly preventing) long-term complications [13].

Research has shown that reducing the HbA1c level can significantly reduce the possibility of developing serious complications for diabetic patients. Lowering the HbA1c level by 1% for diabetic patients can help reduce the risk of developing heart failure by 16%, cataracts by 19%, retinopathy and kidney disease by 25% and death caused by vascular diseases by 43% [34, 18]. Hence, a close monitoring of HbA1c levels is recommended for diabetic patients and also for those with potential for developing diabetes [23].

In this paper, we introduce the first study that employs machine learning models to predict the level of HbA1c using patient's data. The study uses routinely collected data from hospital patients to predict the level of HbA1c. We introduce a novel deep learning based framework to predict the level of HbA1c using a significantly large and unique clinical dataset (KAIMRC dataset). According to the IEC classification of the test level, we formulate the risk of the HbA1c test classification problem as a binary classification problem (patients with less than a 6.5% HbA1c level being coded as low HbA1c, and for 6.5% or more being coded as high HbA1c).

We suggest that the outcomes of this work should encourage more clinical investigations of how far other lab tests may be predictable from the HbA1c level. By predicting high and low levels of HbA1c, we also expect that this work will help reduce the need for HbA1c clinical assessments, resulting in reducing the cost and time needed to perform the test. Finally, and most importantly, it will help identify patients who are at risk of developing diabetes by using their hospital history visit records, and hence planning for preventive interventions.

To the best of our knowledge, there are no studies that have investigated the prediction of HbA1c levels using any form of machine learning by making use

of patient visit data. The main contributions of this paper are: I) introduces a novel collaborative autoencoder framework; II) investigates the use of the routinely collected clinical patient data as predictors for HbA1c levels; III) presents a unique and large dataset that contains the HbA1c level for 14,609 different patient visits.

2 Related Work

With the help of Electronic Health Records (EHR), clinical data has developed into an interesting frontier for machine learning research. In recent years, machine learning models have shown powerful capabilities of analysing and understanding complex clinical data in a variety of medical applications. Autoencoders had several successes in diverse areas of applications, and especially recently with the development of deep variations [2, 14]. In the medical field, autoencoders were mainly used to analyse medical imaging data including: removing the noise [16], data analytics [33], and outlier detection [7, 3].

From a clinical perspective, there have been several studies investigating the trend of HbA1c levels. McCarter et al. [28] studied the association of the HbA1c levels for T2DM patients over clinical variables. Conversely, Nathan et al. [29] were able to demonstrate promising results for calculating clinical variables, specifically, the average glucose level, from the HbA1c levels. Kazemi et al. [22] added complications, such as retinopathy, to the clinical variables to analyse the trend of the HbA1c levels. The above studies used the statistical linear model to achieve this task and the data was mostly collected from diabetic patients. Other work by Rose et al. [32] showed a correlation between the mean blood glucose level and the HbA1c level. The correlation coefficients were found to be between 0.71 to 0.86. However, the result can be significantly affected by the time of day (before or after meals) at which the blood glucose level was measured. A very recent study in 2018 by Wells et al. [36] discussed the use of mathematical equations for HbA1c prediction, obtaining an accuracy of 77% using only non-diabetic patients records.

The above studies used statistical and mathematical approaches to investigate the correlation between HbA1c levels and clinical variables. However, they did not explore the prediction power of the HbA1c levels using machine learning techniques. Our approach investigates the use of a novel deep learning technique to predict the HbA1c level for diabetic and non-diabetic patients using only routinely collected clinical data.

3 Dataset

KAIMRC is one of the leading institutions in health research in the Middle East. The KAIMRC[5] dataset was collected by Ministry of National Guard Health Affairs (NGHA) from three main national guard hospitals in Saudi Arabia[6].

[5] Access to the KAIMRC dataset can be obtained upon an official request to KAIMRC.
[6] Western, Central and Eastern regions of Saudi Arabia.

Table 1. Statistics of HbA1c KAIMRC Dataset

Characteristic	**Overall**
Number of patient visits	13,317
Number of features	78
Number of different health conditions	99
Number of patient visit types	4
Number of discharge types	8

The KAIMRC dataset contains a full history of patients for the period between 2010 and 2015. In addition, it contains 41 million time-stamped lab test readings, such as Blood Urea Nitrogin (BUN), cholesterol (Chol) and Mean Corpuscular Hemoglobin (MCH). It also holds time-stamped data on vital signs, such as BMI and Hypertension. Other complementary features were also collected during each visit, such as visit type (in-patient, or emergency), gender, patient age, service type (such as Cardiology, Neurology or Endocrinology), length of stay (LOS) and discharge type[4].

Predicting the HbA1c level using only general clinical data is very challenging. There are many factors that affect HbA1c level and stability such as improved diet and physical exercises. Changes in patient lifestyle is known to have a significant effect on the level of HbA1c. Furthermore, the significant amount of missing data in most of the medical datasets forms another major challenge. Figure 1 demonstrates the challenge of separating the data between the two classes: high and low level HbA1c, by visualising a two dimensional projection of the data using t-SNE [27].

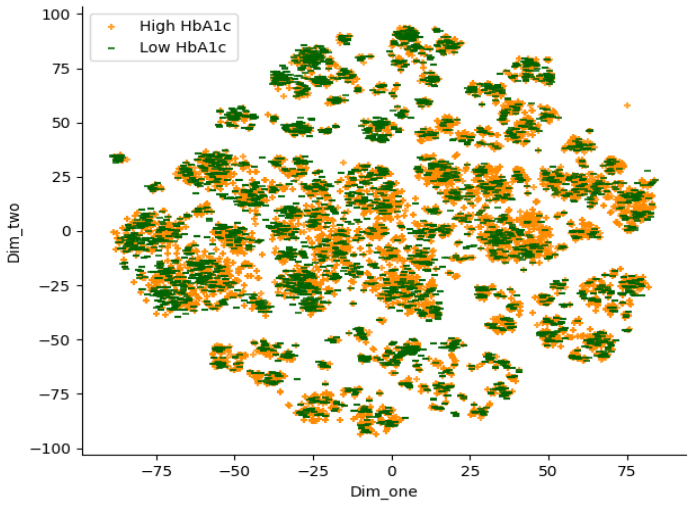

Fig. 1. Projection of the Row Data onto Two Dimensional Space Using t-SNE

3.1 Data Pre-processing

Each patient visit is described by a set of measures. These measures are represented as episodes. Episodes contain the data of irregularly collected vital signs and lab readings. In addition to this, the patient details and visit details (e.g., gender, age, visit type and service provided) are integrated into the episodes. For a patient with an in-patients visit type, only the data for the first day was considered. Cases with values of less than 0.1 of HbA1c are considered to be erroneous readings and have been excluded. This resulted in reducing the dataset size from 14,609 down to 13,317 cases (Table 1).

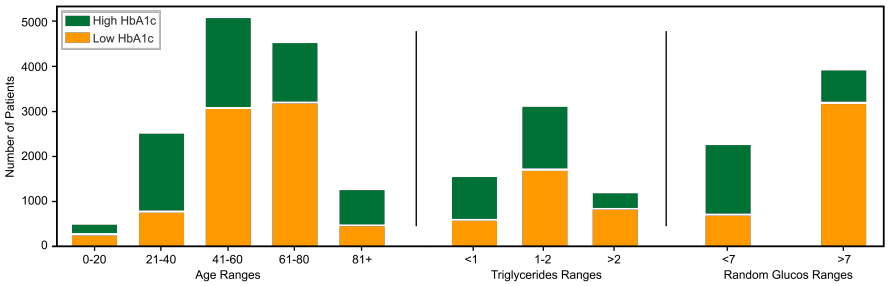

Fig. 2. Classes Distribution over Patients Age, Random Glucose and Triglycerides.

We use 78 features for our analysis: gender, age, service, specialty, visit type and 73 vital signs and lab results. Some features are collected frequently on an hourly basis, such as vital signs. In these cases, the average value for the readings on that day is used instead. 58% of the KAIMRC dataset is labelled as high level: patients with a 6.5 HbA1c level or more, while the remaining 42% are labelled as low level (less than a 6.5). An integer encoding method was used to encode the values of categorical features such as age and gender. Data standardization is used to change the distribution of the features' values so that they are centered on 0 and a standard deviation of 1.

We measured the correlation between the HbA1c level and the 78 features using Pearson Correlation Coefficient (PCC)[8]. The result shows positive linear correlation for 44 features and zero or negative correlation for the remaining 34 features. There are three features, age, Triglycerides (Trig) and Random Glucose (Glur), with correlation between 0.2 and 0.3. Figure 2 shows the class distribution with regards to these three features.

In general, mining clinical data is made difficult by several problems such as missing data, variety of lengths, and irregularity. For instance, the percentage of missing values for Triglycerides and Random Glucose is 54% and 51% respectively. As clinical data is sensitive, we avoided using techniques to interpolate this problem.

4 Methods

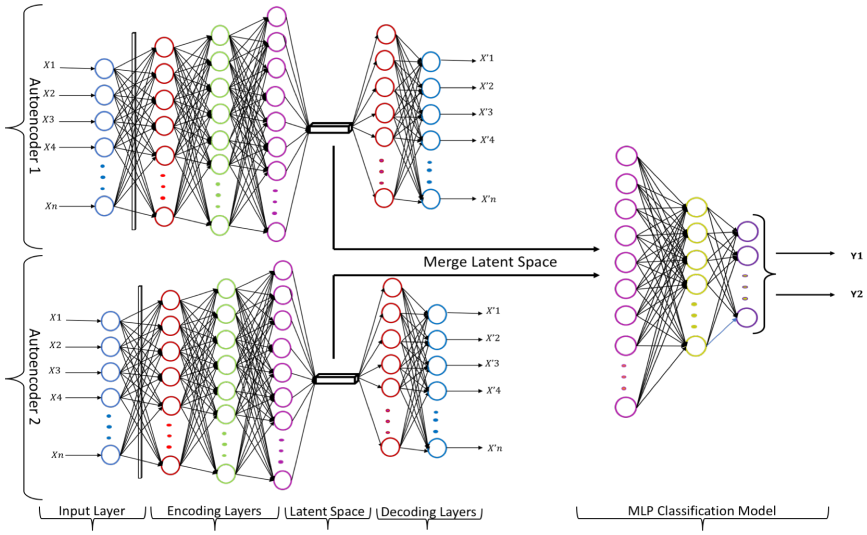

Fig. 3. Proposed Collaborative-Denoising Autoencoders Framework

To increase the separability between the classes, high vs low HbA1c levels, the framework generates new features from each class separately by modelling directly the data that belongs to a given class. This is motivated by the success of pre-training in deep learning models [35, 17], however we use a separate model per class to reduce the within-class noise and increase between-class separability. These two models "collaborate" by combining their outputs together to form the input to a third classification model.

Figure 3 demonstrates the collaborative denoising autoencoders (Col-DAE) framework piloted here. Autoencoder1 models the low HbA1c level class, while Autoencoder2 models the high HbA1c level class. The features of latent space of both models are then merged and fed into the MLP classification model. The MLP model is trained to predict the level of HbA1c. To classify a sample, we feed it to both pre-trained autoencoder models with their outputs merged and fed to the MLP model for prediction.

4.1 Denoising Autoencoders

Autoencoders fall under the umbrella of representative learning with deep neural networks. The goal of an Autoencoder (AE) is to learn an abstract representation of the data presented at its input. The input can be reconstructed from that representation. Hence the desired output of the AE is the input itself [9, 35], making it a completely unsupervised deep learning method.

Given an input x the AE model tries to reconstruct it as r. An AE network consists of an encoder $h = f(x)$ network that transforms x from the input space to the latent space, and a decoder network which does the opposite transformation to reconstruct the original input using the decoder function $r = g(h)$ [26, 5]. The encoder and decoder are implemented as deep neural networks, that are optimised simultaneously using standard stochastic gradient descent algorithms.

The AE's main task is to minimise the reconstruction error between the input x and the reconstructed variable r using loss functions:

$$L(x, g(f(x))) \tag{1}$$

One of the main challenges with training an AE is over-fitting to the training data, also known as the identity function problem [19]. This occurs when the AE cannot extract abstract features from the input and otherwise memorises the data. This can be avoided by reducing the number of units in the hidden layers to be fewer than the number of input units, applying dropouts, or using regularisation. Reducing the size of the hidden layers maps the input to a lower dimensional space (known as the latent space). This forces the network to learn correlations among the input features. The features at the latent space represent a transformed lower dimensional version of the input that conserves its most important information. In addition, even with large hidden layers (larger than the input dimension), the autoencoder can discover important features and structures in the data.

The Denoising Autoencoder (DAE) is an extended version of the basic AE [35]. DAE avoids learning the identity function by trying to reconstruct the input data x from a corrupted version of it, $\tilde{x}$. Decoding the corrupted input requires the network to be able to denoise the corrupted input. This pushes the model towards capturing the important information in the data without modelling the noise. Technically, DAE is trained by minimising the reconstruction error between x and the decoded

$$\tilde{x} : L(x, g(f(\tilde{x}))) \tag{2}$$

Here deep denoising autoencoders are used to model a sequences of patient observations as input $x = (x_1, x_2, ...x_n)$. Mean Squared Error (MSE) is used to calculate the reconstruction error:

$$MSE = \frac{1}{n}\sum_{i=1}^{n}(y - r)2 \tag{3}$$

4.2 Models and Experimental Setup

Our framework (Col-DAE) consists of two denoising autoencoders and one s Multi-Layer Perceptron (MLP) model. The first DAE (Autoencoder1) models the high HbA1c level while the second DAE (Autoencoder2) models the low HbA1c level. Each DAE model has three hidden layers for the encoder, as shown

in Figure 3. Prior to the encoder, an isotropic Gaussian distributed noise is added to the input layer [35]. The number of neurons for the layers in the encoder are 90 , 120 and 130 respectively. Each DAE model consists of two hidden layers for the decoder. The first decoding layer (90 neurons) takes the embeddings in the latent space as an input while the output layer has the same size as the input. Tanh activation function is used in all encoder and decoder layers.

An MLP model is used as the classification model. It consists of three dense layers. The first merges the latent spaces from the two DAEs with 260 neurons (130 from each DAE). The second and third layers of the MLP classification model has 70 and 32 neurons respectifly. Relu activation function is used in both layers and Sigmoid for the output layer used for the two classes prediction.

The DAEs (Autoencoder 1 and Autoencoder 2 in Figure 3) are pre-trained and validated to reconstruct the input using 80% and 10% of the data respectively. The remaining 10% of the data is kept as the test set. The MLP classification model is trained and validated using the training and validation sets along with the associated HbA1c labelled levels. Each test sample is fed to both DAEs and the embedding outputs from both DAEs are merged to form the input vector of the MLP classification model. These tasks (pre-train the DAEs, train the MLP and testing the Col-DAE model) are repeated 10 times using a 10-folds cross-validation approach to ensure that all data points are included in testing the model. The DAEs of the Col-DAE model are trained for 100 epochs using an Adam optimiser with Mean Squared Error as the loss function. The MLP of the Col-DAE model uses same optimiser, loss function and number of epochs for training.

4.3 Comparative Models

We have compared our results against popular base-line models: Support Vector Machines (SVM) and Logistic Regression (LR). We also compare our results to deep learning approaches such as MLP and Autoencoders [26, 20]. We explored all models with different feature sizes (using the top three correlated features, the 44 features with positive correlation and the 78 originally collected). Because deep learning approaches work with high dimensional data, the MLP, DAE and Col-DAE models were not experimented using three features. For the purpose of fair comparison, these models were employed using the same data pre-processing, training and testing techniques used for the Col-DAE model.

In addition to the accuracy, we report F1, F1 Weighted, Recall and Precision measures to evaluate the performance of the proposed models. The Col-DAE model was experimented on using different combination of regularisers, activation functions, dropout rates, learning rates, and optimisers. We only report the results with the best performance as per the reported measures.

5 Results

The performance metrics for predicting the level of HbA1c, obtained using the compared models: SVM, LR, MLP, DAE and Col-DAE with different feature

sizes, are presented in Table 2. All models show better performance when using the 78 features despite the negative linear correlation for 34 features except for DAE models. We report an F1-score of 73.34% and 65.63% F1-Weighted measures for DAE. However, the DAE models show clear signs of over-fitting. The large difference between the two measures is explained by the 79.08% recall and 68.48% precision. This is being ascribed to biased classification behaviour. The DAE model performs the lowest among all models.

The rest of the models (SVM, LR, MLP and Col-DAE) do not show any bias towards any of the classes. The SVM and MLP models with 78 features achieved competitive performance with an F1-score of 78.84% and 79.72%. However, the SVM model achieved promising performance, using three features only, with 76% F1-score.

Table 2. Performance of Classifiers for HbA1c Risk Prediction

Model	Features Size	F1-Score	Accuracy	F1-Weighted	Recall	Precision
SVM	3	0.7609	0.7172	0.7162	0.7724	0.7499
	44	0.7817	0.7292	0.7239	0.8324	0.7370
	78	0.7884	0.7398	0.7356	0.8322	0.7492
LR	3	0.7168	0.6526	0.6476	0.7543	0.6830
	44	0.7394	0.6859	0.6832	0.7648	0.7159
	78	0.7574	0.7113	0.7098	0.7733	0.7424
MLP	44	0.7857	0.7465	0.7456	0.7973	0.7752
	78	0.7972	0.7588	0.7573	0.8146	0.7827
DAE	44	0.7334	0.6650	0.6563	0.7908	0.6848
	78	0.7301	0.6563	0.6445	0.7985	0.6737
Col-DAE	44	0.7974	0.7626	0.7620	0.8032	0.7929
	78	**0.8109**	**0.7760**	**0.7751**	0.8240	0.7987

Table 2 shows that the Col-DAE model using 78 features achieved better results than the compared base-line models, with 81.09% F1-score and 77.60% of accuracy. Figure 4 summarises the 10-folds results of the reported measures achieved by the proposed models. Figure 4 shows small variation between the folds and especially in F1-score which demonstrates the consistency of the Col-DAE's performance. The differences between the obtained F1-scores for Col-DAE with 78 features and the comparative models are statistically significant (p-value is 0.006 with SVM, 0.005 with LR and DAE and 0.028 with MLP).

6 Discussion and Conclusion

Our framework is trained using patient clinical data from patients visiting the hospitals for a variety of health conditions. Despite the large number of missing values, the SVM achieved 76% F1-score using three features. The Col-DAE

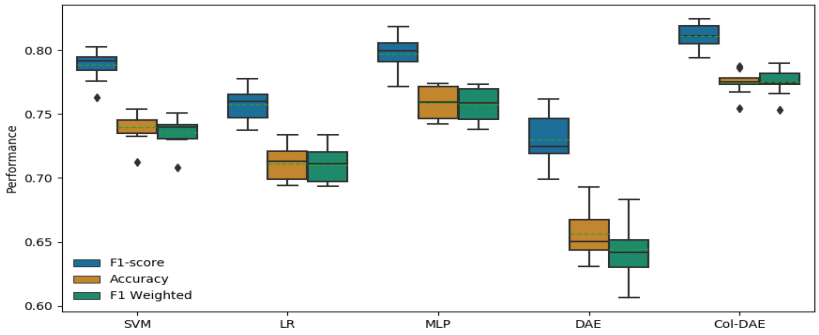

Fig. 4. Box plot of the detailed performance for the proposed models.

outperformed the base-line classifiers and achieved 81% for F1-score using 78 features. Due to the lack of similar studies and related work using machine learning, the accuracy achieved in this paper could not be compared to any previous work. Hence, this forms the baseline accuracy for studies aiming at predicting of HbA1c level in the future.

The outcome of this work is significant for enabling physicians to make preventative intervention decisions in order to successfully manage the risk of high level HbA1c. The replication of this work using other hospital clinical datasets can ultimately help provide improved healthcare services to patients and reduce the cost and time needed to assess the HbA1c test. This can help identifying patients who are at a high risk of developing T2DM, and has the potential to be used as an early warning indicator for developing serious health complications.

We introduced here the collaborative denoising autoencoders (Col-DAE). The framework uses denoising autoencoders to model separately the high and low level HbA1c data. The latent spaces of both models are then merged and passed to a MLP model for decision making. This framework was utilised for a complex classification challenge (HbA1c level prediction from routinely collected clinical data) and has shown very promising results. The framework presented here is a general framework and can easily be generalised for a wide range of applications and for multi-class problems. Future work will study the interpretation of the used features and also investigate the impact of applying different techniques for handling the missing data in KAIMRC dataset.

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