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A Review of Advances in Modeling and Prediction of Blood Glucose Level in Diabetes Mellitus

O. S. Asaolu[1*], T. A. Fashanu[1], O. A. Fasanmade[2] & N. O. Orieke[1]
[1] *Department of Systems Engineering, University of Lagos, Akoka, Lagos, Nigeria*
[2]*Department of Medicine, Lagos University Teaching Hospital, Idi-Araba, Lagos, Nigeria*
*Corresponding author - asaolu@yahoo.com

Abstract
Diabetes Mellitus as a metabolic disorder is quite intricate to model because it is dependent on several factors; the phenomenon is nonlinear and dynamic in nature. More so, the factors that affect blood glucose level in diabetes mellitus are patient specific. A comprehensive review of advances in modeling and prediction of blood glucose level in diabetes mellitus using mathematical models is provided in this work. This will reveal the extent of research geared towards understanding the physics behind variations in blood glucose level in diabetes mellitus hence, charting the course for future studies.

Keywords: Diabetes Mellitus (DM), Insulin, Blood Glucose Level (BGL), Type 1 Diabetes Mellitus (T1DM)

1.0 Introduction

Diabetes Mellitus (DM) is described as a group of metabolic diseases characterized by hyperglycemia resulting from defects in insulin secretion, insulin action, or both, according to ADA (2004). The pathogenesis and etiology of DM are broad ranging from autoimmune mediated β-cell destruction, genetic defects of the β-cell and insulin action, exocrine pancreas disease to insulin resistance. The classification of DM is based on the pathogenesis. The predominant types of diabetes are the Type 1, Type 2 and Gestational Diabetic Mellitus. Type 1 diabetes accounts for 5 – 10% of those with diabetes and results from autoimmune destruction of the β-cells. Patients that suffer from Type 1 diabetes usually depend on exogenous insulin for survival. Type 2 diabetes accounts for 90 – 95% of those with diabetes and results predominantly from insulin resistance and reduced insulin production. Gestation diabetes occurs in the form of any degree of glucose intolerance with onset or first recognition during pregnancy.

The process of predicting BGL in DM involves identifying the trend in blood glucose variation with respect to the factors that affect BGL such as insulin, meal, exercise, stress level etc. The human glucose metabolism is non-linear and difficult to model, hence the need for a predictive model to replicate the observed trend in glucose metabolism. Mathematical models have been used to predict BGL in DM patients. This include; Auto-Regression (AR), Support Vector Machine/Regression (SVM/R),

Compartmental Model (State Space), Artificial Neural Network (ANN) and Neuro-Fuzzy Networks (NFN).

2.0 Literature Survey

The idea of predicting BGL based on past blood glucose values was suggested in the late 80's and early 90's though the first implementation was by Bremer and Gough (1999). A comprehensive review of advances in modeling and predicting BGL in diabetes is presented. Our review covers the AR, Compartmental (State Space), SVM/R, ANN and NFN models.

2.1 Auto-Regressive (AR) Based Predictive Models

Bremer and Gough (1999) identified the statistical dependence of glycemic data in both diabetic and non-diabetic individuals using the autocorrelation functions (ACF). In their investigation, non-diabetic glycemic measurements exhibit constant sampled mean and variance. More so, the ACF is independent of absolute time hence, showing high degree of stationarity. T1DM patient's glycemic measurements show high degree of non-stationarity with non-constant mean and variance and with ACF slowly decaying to zero. This non-stationary nature of glycemic variation in T1DM patients makes the prediction of BGL complex over time. However, the statistical dependence of the glycemic measurements identified by the ACFs can be exploited in constructing linear models of varying system order in predicting BGL. Sparacino *et al*. (2006) developed an AR model fitted against past glucose measurements provided by continuous glucose monitoring (CGM) in predicting hypo/hyperglycemia episodes in diabetic patients. The results obtained from 13 diabetic volunteers monitored for 48hours show that hypoglycemic episodes can be predicted more than 20 min ahead in time. Sparacino *et al*. (2007) extended their previous work by developing a low order (first order) AR model with time-varying parameters, identified by recursive least squares (RLS) with a constant forgetting factor, to predict glucose with in a time frame of 30 to 45 minutes with sufficient accuracy. The results obtained from 28 T1DM volunteers monitored for 48 hours at a 3 minutes CGM interval showed that 30 minutes crossing of the hypoglycemic threshold can be predicted 20-25 minutes ahead in time. Jaques *et al*. (2007) investigated the feasibility of data driven AR models to serve as the forecasting engine of predictive blood glucose monitoring systems. Their work criticized prevailing development in blood glucose control where continuous glucose measurement and an insulin pump are used to form a closed loop system, as the system cannot prevent BGL from becoming high or low. The model uses AR model of order 10 and the regularized least square methods in training, since the design matrix is generally rank deficient. The Clarke's Error Grid Analysis (CEGA) of results obtained from CGM data collected from nine (9) T1DM patients over a five (5) days period indicated that, for a 30-minutes prediction horizon, individually tuned models yield 97.6 to 100.0% of data in the

clinically acceptable zones A and B, whereas cross-subject, portable models yield 95.8 to 99.7% of data in zones A and B. However, the performance of the model significantly drops as the prediction window increases. The AR model portability from individual to individual showed good correlation suggesting that the results obtained from portable models are not significantly inferior to those obtained with individually tuned models. The ACF of the residual error from the prediction showed that the AR model captured sufficient but not all of the correlations in the glucose model.

Markakis *et al*. (2008) presented a discrete time, non-parametric model of the insulin-glucose dynamic based on the Principal Dynamic Modes (PDM) approach. The model is a different approach to Model Predictive Models (MPC) that generally adopts a parametric approach to modeling the insulin – glucose dynamics: the available input - output data sets are fitted in a pre-determined model structure. The non-parametric nature of the model implies that the structure of the model is data driven. The PDM describes the dynamics of the captured data using a linear filter that reveals peak value, peak time, time constant and system memory. An Auto Regressive model whose order is determined by the A1C is used to predict the future glucose disturbance (e.g. meal etc.) through parameter estimation based on linear least square. The result and accuracy of the model depends on the accuracy of Sorensen's model from which the PDM was derived. Sorensen's model was derived from numerous real data and a number of models have latched on it as a representation of the actual glucose metabolic process such as Parker, Doyle and Peppas (1999), Parker et al. (2000) and Lynch and Bequette (2002). The results of this model demonstrated that insulin-glucose dynamics of a T1DM patient can be captured using data driven non-parametric models in the form of PDM. Blood glucose disturbance can be captured using AR predictive model. PDM – MPC combination can regulate blood glucose in the presence of stochastic noise with BGL not exceeding $\pm 20 mg/dl$ from the basal value.

Eren-Oruklu et al. (2009), developed a third order AR(3) and AR with moving average ARMA(3,1) models, with time varying parameters identified by recursive least squares (RLS), using a forgetting factor μ which could be modulated according to the glucose trend. The inherent inaccuracy of the low order linear model is compensated for by the use of recursive identification of model parameters. In other to quickly capture unprecedented glycemic disturbances the RLS algorithm is integrated with a change detection method that reduces μ when persistent change in model parameters is detected. The ARMA model was selected over the AR model since the model error information is leveraged by the ARMA model structure. The accuracy of the prediction evaluated for the population with type 2 diabetes using CEGA shows that within a prediction horizon of 30mins, in the hypoglycemic range, 92.94%, 5.29%, and 1.77% of the data result where in regions A, B and C respectively. In the normoglycemia range the

values are 91.50%, 7.87%, and 0.63% while in the hyperglycemia range 89.79%, 8.70%, and 1.51% where in regions A, B and C respectively. Finan *et al*. (2009) presented an ARX(3) model with exogenous inputs of ingested carbohydrate and insulin medication to predict blood glucose variation in diabetic patients. They investigated the performance of a non-recursive; recursive and zero-order hold parameter identification for the ARX model. In a 30-, 60- and 90mins prediction window the non-recursive model produce a Root Mean Square Error (RMSE) of 27-, 46-, and 59mg/dl, respectively while the recursive model produced RMSE of 27, 45, and 61 mg/dl, respectively. Test data prediction results obtained indicated that the recursively identified ARX model produced results that were similar but not superior to the non-recursive model. More so, marginal advantage was recorded by the recursive/non-recursive models over the zero-order hold model.

Gani *et al*. (2009), developed an AR(30) model with time-invariant parameters identified by regularized LS on pre-filtered data with CGM as the input variable. The model showed that accurate prediction of subcutaneous glucose can be achieved by smoothing raw CGM glucose data using Tikhonov regularization. This advancement reduced high frequency noise associated with raw CGM data by placing regularity constraints on the noisy signal. However, the resulting smoothed data is unstable and contain unphysiologic coefficients that will cause inaccurate prediction. Applying regularized least-squares technique on the smoothed data produces a stable AR model of order 30 with physiologically plausible AR coefficients. Simulation results indicated that stable and accurate models for near-future glycemic predictions (< 60 mins) with clinically acceptable time lags are attained only when the raw glucose measurements are smoothed and model's coefficients regularized. More so, this model may yield "universal," or "portable," models for glucose concentration predictions as the range of both the smoothing and regularization parameters did not affect the accuracy of the prediction with regards to the nine T1DM patients investigated. Gani *et al*. (2010) further reviewed their previous work on data driven glucose modeling for predicting blood glucose dynamics in Type 1 diabetic patients using AR(30) model with fixed coefficient for different individuals. They investigated the possibility of developing a universal data driven model from a single diabetic patient. This involved the use of same-subject model predictions as a reference for comparisons against cross-subject and cross-study model predictions, which were evaluated using the RMSE and CEGA. The result of this comparison showed that the average cross subject and cross-study RMSEs of the predictions were small and indistinguishable from those obtained with the same-subject models. CEGA results showed that more than 99.0% of the paired sensor-predicted glucose concentrations lay in the clinically acceptable zone A. Shanthi *et al*. (2010) developed a model that combines the use of AR as a linear aggregation of previous glucose values and a moving average model that considers previous variations

in blood glucose values to predict hypo/hyperglycemia episodes in time steps of 10mins, 20min and 30mins. It employs data regularization techniques of Tikhonov presented by Riccardo Bellazzi (2000) as a data preprocessing technique for model stabilization. The results obtained from the study of five (5) diabetic subjects showed that within the prediction horizon of 10-, 20- and 30 minutes the maximum RMSE obtained are 0.9-, 2.7- and 4.2mg/dl respectively.

2.2 Compartmental Model (State Space) Based Predictive Models

Hovorka *et al*. presented an adaptive nonlinear predictive model for maintaining BGL within the normoglycemia range in Type 1 diabetic patients in a fasting condition. The compactmental model consists of sub-models representing the subcutaneous absorption of administered short acting insulin and gut absorption of ingested meal. The predictive performance of this model was compared with data from 15 clinical experiments of T1DM patients. The model produced mean square error of 3.6mg/dl proportional to the prediction horizon of 15 minutes. More so, CEGA shows that 95% and 5% of the model results fall into region A and B of the CEGA respectively for a prediction horizon of 60 minutes. Palerm et al. [17] proposed a state space based approach to diabetic dynamics representation using optimal estimation Kalman filter. The model captures the effect of measurement sampling frequency, threshold level, and prediction horizon on the sensitivity and specificity of the predictions. Optimal estimators are tuned to trade-off false alarm rate with the rate of missed predicted hypoglycemic episodes. Hence, predictions are made using an estimate of the rate of change of the blood glucose, using a Kalman filter that trades off the probability that a measured glucose change is due to sensor noise versus an actual change in glucose, to obtain the maximum likelihood estimate of glucose (and its first and second derivatives). The future blood glucose level is modeled as a function of the current blood glucose level, the rate of change in blood glucose level (i.e. the velocity) and the rate of change of the rate of change in blood in glucose level (i.e. the acceleration).

The acceleration is assumed to vary in random fashion driven by input noise which describes change to the process. In this case, the model given by alarm levels is defined as a function of current and future estimates of glucose, hypoglycemic threshold and prediction horizon. Palerm et al. [18] furthered their previous work with Kalman filter model to predict blood glucose variation using double integration random walk as a prior for glucose dynamics. They further validated the result of their previous prediction algorithm based on the analysis of clinical hypoglycemic clamp data from 13 subjects. For a 30-minute prediction horizon and alarm threshold of 70 mg/dl, the sensitivity and specificity were 90 and 79%, respectively, indicating that a 21% false alarm rate must be tolerated to predict 90% of the hypoglycemic events 30 minutes ahead of time. Furthermore, they revealed that putting a significant weight on the trust in the

measurement means that the estimates will track the sensor signal very closely, even if noisy. Conversely, weighing the model significantly more than the measurement, results in a heavily filtered estimate. Gireesh and Punna [19] reviewed the use of Kalman Filter, AR and feed forward neural networks for glycemic predictive models revealing that the three methods are amiable to predicting blood glucose levels ahead of time.

Stahl and Johansson [20] showed how system identification and control may be used to estimate predictive quantitative models to be used in the design of optimal insulin regimens. The system is divided into three subsystems; (a) Insulin Subsystem (b) glucose Subsystem (c) Insulin-glucose Subsystem. The insulin model used is a second order compartment model for the fast acting insulin. The long acting insulin was modeled using the Berger model which is a non-linear model that introduces the dose dependent dynamics. The fast carbohydrates which are mono- and disaccharides are modeled as second order compartment model. Slow carbohydrates (polysaccharides which need to be digested before they are converted into glucose) are modeled as a fourth order compartment model (linear state space model). They presented the best model as the log-normalized linear model based on subspace based identification and the GTFM-Wiener model, even though they did not meet the 9mg/dl accuracy target within the two hour prediction window. El-Khatib et al. [21] studied the use of MPC in closed-loop artificial pancreas design for Type 1 diabetes control.

Mihalis et al. [22] presented a computational analysis of the dynamics of intravenously infused insulin and blood glucose model that represent most diabetic patients. This model is augmented with glucose disturbance signals that represent the different internal and external factors affecting BGLs in diabetic patients. This work is an improvement on the Diabetic Minimal Model which does not represent endocrine insulin action as used by most models to represent Type 1 DM. The model represents glucose disturbance in an exponential form $\gamma \exp(-kt)$ to represent the different sources of glucose disturbance. It uses Switching Control Strategy (SCS) that switched glucose control between Proportional Derivative Controller (PDC) and Model Predictive Control (MPC). The MPC is suited during meals, when the effects of the bilinear term are significant and disturbance is possible to predict as the exponential models are known. PDC is suited for non-meal (small-scale) disturbances, when the nonlinear effects are limited and disturbance is hard to predict. In conclusion SCS provides a better control of blood glucose level for both severe and non-severe Type 2 diabetic patients, Type 1 diabetic patient and ICU patients. Ahmed and Mahmud [23] developed a PID controller as an artificial pancreas. The PID controller captures the free fatty acid - glucose - insulin dynamics and adjusts the process (diabetic mathematical model) outputs based on the history and rate of change of the error signal. Their results reveal that the response of

the PID controller is not acceptable in the sense of control since the BGL has an oscillation causing a drop in BGL below the basal.

2.3 Support Vector Machine/Regression (SVM/R) Models

Eleni *et al*. [24] investigated the use of SVR and compartmental models of insulin dynamics, meal dynamics, exercise dynamics and continuous glucose measurements to predict BGLs in seven (7) T1DM patients. This multi-parametric investigation involved the collection of subcutaneous CGM readings every 5 minutes; body monitoring system for physical activity consisting of sensors for heat flux, skin temperature, near body temperature, galvanic skin response and a two axis accelerometer; food intake (i.e. type of food, serving sizes and time) and the insulin injections (type, dose and time). The study predicted subcutaneous glycemic level using three compartmental models that is; the meal model, the insulin model and the exercise model. SVR built with a linear kernel function was employed to provide individualized glucose prediction. The use of SVR ensured that the optimization problem is transformed into a dual convex quadratic programming leading to a global minimum. The training datasets were obtained from seven (7) T1DM patients. The SVR was trained individually for each patient using a V-fold cross validation to avoid over fitting. The result obtained from the first approach of the model showed that the average value of RMSE for 15 minutes and 30 minutes predictions is equal to 9.60 mg/dl and 16.23 mg/dl respectively. In both cases, the predicted glucose concentrations exhibit a strong correlation with the measured values (i.e. 0.95 and 0.88). CEGA of this model revealed that 98.86%, 92.54%, 80.02%, 62.91% of the predictions fall into region A, the clinically acceptable range for the 15-, 30-, 60-, and 120 minutes prediction horizon respectively. Hence, as the prediction window increases to 60 and 120 minutes the performance of the model decreases significantly. In other words glucose concentration in patients with Type 1 diabetes can be predicted with a sufficient numerical accuracy in the short-term using SVR.

2.4 Artificial Neural Network (ANN) Based Predictive Models

Raed [25] investigated the performance of feed forward NN model for predicting BGL in diabetic patients. The Levenberg Marquardt NN (LM NN) and the Radial Basis Function (RBF) models were used in the investigation. The LM NN model used in this study consists of a two layer feed forward NN (5 hidden units and 1 output unit) with learning algorithm that starts with incremental error back propagation and gradually switches to conjugate gradient based back propagation for final convergence. Simulation was performed on a set of data from 70 different diabetic patients with the normalized training vector made of; Present Glucose Level (PGL), Short Term Insulin (STI), Mid Term Insulin (MTI), time period and meal. The result of the simulation revealed that the RBF model was good at memorizing the training data, but poorly predicted the future values of glucose. The LM NN model could capture, identify and generalize the insulin/glucose

dynamics of the samples of the 70 diabetic patients used in the training. Mougiakakou et al. [26] investigated the use of a combination of compartmental models and artificial neural networks in predicting blood glucose variation in T1DM children. The training data set was taken from four (4) T1DM children and consists of Continuous Glucose Measurements, insulin intake and meal intake along with the corresponding time. The influences of insulin and meal intake were estimated using a compartmental model with their outputs fed as the insulin and meal intake in the NN training set. Two artificial neural networks consisting of a Feed-Forward NN (FFNN) trained with the back-propagation algorithm with adaptive learning rate and momentum, and a Recurrent NN (RNN), trained with the Real Time Recurrent Learning (RTRL) algorithm were used for the training for comparative purposes. RNN outperformed FFNN in predicting blood glucose level.

Quchani & Tahami [35] researched on the comparative performance of a Multilayer Perceptron (MLP) and the Elman Recurrent Neural Network (RNN) as non-linear models in determining blood glucose concentration using past values of blood glucose, insulin, meal, exercise and stress levels in ten (10) Type 1 diabetic patients. Meal intake was expressed in grams; exercise was expressed as a four step scale, where 1 means doing nothing and 4 expresses heavy exercise; stress was also expressed as a four step scale, where 1 means relaxing and 4 expresses heavy stress condition. Measurement interval was 1 hour. The training inputs were normalized before training and each patient's data was used for training. The result of this comparison shows that Elman RNN outperformed the MLP by a significant value in terms of mean absolute error. Baghdadi and Nasrabadi [28] introduced an NN predictor for BGL using radial basis function. Training input dataset from a single T1DM patient used in the study consists of injected insulin, blood glucose, meal intake, exercise and stress levels covering a period of 77days. Firstly, the RBF NN was trained by all the 19 input variables. After the training the input variable with a low magnitude of weight was eliminated, followed with the training of RBF NN again. The system was split up to make separate predictions of BGL in the morning, afternoon, evening and night periods. The RBF predictive model resulted in a RMSE of 0.0826-, 0.0513-, 0.0373-, 0.0118 mmol/dl for the morning, afternoon, evening and night predictive period respectively.

Scott et al. [29] investigated the predictive accuracy of a neural network model with time lag capability in predicting BGL in T1DM patients. The Neural Network used in this research has hyperbolic tangent hidden neuron to introduce nonlinearity, and a Laguarre neuron that serves to provide the neural network with memory, thus enabling the processing of information in time. The use of time delay component in the NN was articulated to capture the correlation between different input datasets. It uses back propagation algorithm for training, based on gradient descent optimization of the

predicted BGL with reference to a CGM reference. Optimization via genetic algorithm was used to minimize the number of processing elements and inputs into the neural network. Data capture was achieved with the use of an electronic pocket diary developed using C#.Net, for recording BGL, Time of measurement, Insulin dosage(short and long acting), hypo/hyperglycemic symptoms, carbohydrate intake, lifestyle(activities and events) and emotional states. Test populations of 11 to 17 patients were used for training while an additional patient's data was used for the validation. The overall mean absolute difference percent (MAD%) of the model's predictive abilities in predicting BGL for a single unseen patient's record with varying number of patients (11 - 18) used in training within a prediction window of 100mins appears to be relatively consistent throughout, regardless of training set size ranging from 18.7 to 25.8% with an average of 22.7%. However, the overall MAD of the model's predictive abilities in predicting BGL for a multiple unseen patients' record with varying number of patients (11 - 18) used in training within a prediction window of 100mins is not consistent.

Zarita et al. [30] combined Principal Component Analysis (PCA) and Wavelet Neural Network (WNN) with different embedded wavelet families in the hidden layer (Mexican Hat, Gaussian wavelet and Morlet) in predicting BGL in a single diabetic patient. The prediction model was split into four different intervals; morning, afternoon, evening and night, using dataset from a single patient covering a period of 77 days. Each measurement point accounts for; Time of Blood Glucose Measurement, BGL, Dose of Long Acting Insulin, Dose of Short Acting Insulin, Exercise Level and Stress Level, scaled using Z-Score normalization into a mean of 0 and a variance of 1. PCA was used to reduce the 19 input variables to 4 principal components. Amongst the embedded wavelet families, the proposed expert system with Gaussian wavelet in the hidden nodes of WNN produced the lowest Root Mean Square Error (RMSE) for each interval. The Gaussian WNN predictive model resulted in a RMSE of 0.0450-, 0.0348-, 0.0330-, 0.0170 mmol/dl for the morning, afternoon, evening and night predictive period respectively. Scott et al. [31] proposed a feed forward three layer neural network with a predictive horizon of 75mins, and back propagation training algorithm for predicting BGL. The input layer utilizes time, Continuous Glucose Monitoring (CGM) data, Point of Care (POC) glucose test time and results, insulin delivery type (subcutaneous sliding scale or intravenous drip) and units of insulin delivered. The hidden layer was designed to limit the range of neural network inputs to between -1 and +1 for easy processing and trend identification. This work was intended to prevent hypoglycemia (<70mg/dl) and hyperglycemia (>150mg/dl) events from occurring, which are directly correlated to high mortality rate in patients under surgical critical care. The overall error of the prediction model using the patient specific model and the general neural network model are 7.9% and 15.9% respectively. Likewise, the CEGA shows that 95.1% of the

prediction falls in region A for the patient specific model while 69.8% fall into region A for the general neural network model within the prediction window.

Serge et al. [32] considered the problem of developing a NN based blood glucose control system consisting of connected NN's of different architectures. Considering the high complexity of the glucose/insulin metabolism, the individuality of its characteristics, as well as the lack of accurate mathematical models and rules for calculating the required dose of insulin to ensure the maintenance of glucose in the physiological range, the Nonlinear Autoregressive Exogenous (NARX) neural network and the Time Delay Neural Network (TDNN) were used in their model. NARX showed high generalization abilities while TDNN simplified the training procedure. The training data include; blood glucose reading, insulin dose and the amount of absorbed carbohydrate at 10 minutes interval. Relative error of 99.7% for NARX and 73% for TDNN was obtained for the open loop system, while relative error of 99.9% for NARX and 84.4% for TDNN was obtained for the closed loop system. Shanthi and Kumar[33] proposed a blood glucose predictive model of simple feature based feed forward neural network with back propagation algorithm trained with features of input patterns. The data for the prediction of glucose were obtained in three ways which include; cubic spline interpolated self-monitored blood glucose data from 20 diabetic patients, diabetic resource from the glucose project of the University of California San Diego, UCSD [34] and Continuous Glucose Monitoring. The model extracts the feature set of every contributory input variable used in training the neural network and adjusts the learning rate parameter with the weighted values of extracted features. The extracted features which include mean, variance, skewness, kurtosis and approximate entropy help track the underlying variation of the dynamic signal. Hence the recurrent characteristics of blood glucose dynamics can be tracked with a moving window of length 'n' with a step size of 'p'. For every window, the features are computed and passed to the network for learning. The proposed model was able to catch up with glucose dynamics with a root mean square error of 6.3mg/dl within a prediction horizon of 30 minutes. Comparatively, the feature based FNN performed better than the LM NN from previous models.

2.5 Neuro-Fuzzy Network Based Predictive Models

Neuro-Fuzzy Networks have seen huge application in the prediction of the onset of diabetes and prediction of BGL in diabetes management. Boroujerdi et al. [35] exposed this possibility by suggesting the amiability of generating a patient specific knowledge-base, by reproducing the variability observed in the patient's modal blood glucose. Deutsch et al. [36] suggested that due to the high variability and uncertainty of the observed blood glucose data a qualitative means of pattern recognition will be more suitable for analysis and pattern recognition. Kahn et al. [37] supported the idea of deciphering the patient specific blood glucose variation pattern. Ewart and Tibor [38]

proposed a fuzzy means of learning the patterns in the observed blood glucose profile. It entailed the decomposition of the blood glucose profile into a series of "events" (event extraction) during which blood glucose is described as being flat, falling or rising and these events can be interpreted in terms of causal relations between glucose and insulin. Marco et al. [39] proposed an Object Oriented Model (OOM) for the development of a Knowledge Based System (KBS) for blood glucose regulation. The use of OOM allows for structured representation of terminological, assertion and expert knowledge in the form of an object in a domain. The 'state' of an object was defined by an attribute slot and constraint slot. The possible 'events' were formalized by functions slot, events slot, logical properties slot and behavior slot.

Erik et al. [40] developed a software prototype based on neural network, fuzzy logic and expert system to investigate the feasibility of a patient specific blood glucose predictive model for type 1 DM. The system can predicts blood glucose level changes resulting from regimen disturbances and recommends regimen (food, insulin and exercise) changes for compensation. The model produced a mean absolute percent error of 10.5% between actual and predicted BG values from inputs of daily insulin, food, and exercise information for a T1DM test subject. As a result of limited evaluation process and subject sample size no significant validity conclusion could be made for this model. Ghevondian et al. [41] developed a Fuzzy Neural Network Estimator (FNNE) to predict the onset of hypoglycemia considering the serious health implication of hypoglycemia in T1DM patients. The FNNE uses heart rate and skin impedance as system input using a correlation between hypoglycemia, cardiovascular system response and cholinergic sympathetic activity (which is responsible for sweating). Fuzzy inference engine and a multi-layered neural network system with trainable weight matrix are used in transforming these measured physiological parameters into estimated blood glucose levels. Training dataset (group A) was derived by inducing hypoglycemia on six (6) non-diabetic individuals while measuring BGL, skin impedance and heart rate. Validation and Test datasets (group B) were derived by inducing hypoglycemia on six (6) diabetic individuals while also measuring BGL, skin impedance and heart rate. FNNE achieved an overall BGL correlation of 0.983 between groups A and B. The model revealed that hypoglycemia leads to increased heart beat by approximately 21bpm and reduced skin impedance by approximately 111ohms for T1DM patients. Sapna and Tamilarasi [42] investigated the use of data mining in predicting diabetes. They used a neuro-fuzzy system in solving the problem with the application of Genetic Algorithm (GA) which allows for learning and adaptation capabilities. Atlas et al. [43] developed a wireless, fully automated, closed-loop artificial pancreatic system that uses an algorithm based on fuzzy-logic theory (a form of probabilistic logic), a learning algorithm, and an alert module with personalized system setting. The algorithms for alerts integrate information derived from past glucose levels, insulin delivery (time and dose), and

models of insulin pharmacodynamics. Miller et al. [44] presented an automatic learning algorithm for the artificial pancreas system developed by MD logic a leading U.S. provider of High Performance Electronic Health Record (EHR) Solutions.

Vithyatheri et al. [45] proposed a model for diagnosing diabetes mellitus through a combination of Rule Based Reasoning (RBR) and Object Oriented Programming. Fayrouz et al. [46] developed a scalable closed loop glucose regulatory system which can be tuned to each patient. The model is based on the Hovorka Type 1 diabetic patient model and consists of a Recurrent Neural Network (RNN) used as a nonlinear predictor and a Fuzzy Logic Controller (FLC) which is used to determine the insulin dosage required to regulate blood glucose level. A table of fuzzy IF-THEN rules that link the input and output Membership Functions (MFs) is built based on the desired plasma glucose dynamics behaviors. Each rule output is demonstrated using MIN-MAX law and each crisp output is computed using CENTROID defuzzification method. The output of the FLC is scaled according to the sensitivity of the patient. Moshe et al. [47] investigated the performance of the logic based artificial pancreas developed by MD Logic against a sensor-augmented pump treatment, in young T1DM patients at an overnight camp. The investigation revealed a superior performance in the logic based artificial pancreas in the reduction of nocturnal hypoglycemia and tighter blood glucose control. Ahmed and Mahmud [48] developed a fuzzy logic algorithm for implementing an artificial pancreas. The model entailed the fuzzification of two input signals which include the glucose concentration and the rate of change in glucose concentration, and one output of the dose of insulin. In their result, the response of this controller in stage of steady state has kept the BG concentration almost at the basal level, although it has a little overshoot before the steady state.

2.6 More recent research

A personalized blood glucose predictor based on time-series model of historical glucose measurements, pooled panel data regression and pre-clustered information was developed by Juan and Chandima [49] and it performed fairly well. A variant of grammatical evolution model and a tree-based genetic programming model that uses a three-compartment model for carbohydrate and insulin dynamics was formulated by Hidalgo *et al*. [50]. Their model achieved 90% of the prediction within regions A and B of CEGA. The authors of this work established in [51] that the necessary and sufficient conditions to predict blood glucose level in a Type 1 diabetes mellitus patient are: knowledge of the patient's insulin effects and meal effects under diverse metabolic scenarios and the transparent coupling of the insulin and meal effects. A neuro-fuzzy model which performed very satisfactorily with 87.5% and 12.5% of predictions falling respectively in the A & B regions of the CEGA was developed.

3.0 Conclusion

The complex nature of BGL variation in diabetics has received significant attention from different mathematical perspectives. However, there is no uniform dimension for concept description. More so, the blood glucose prediction models are not designed for integration of uninvestigated attributes that contribute to BGL variation in multi-scenario applications. The use of Auto Regressive (AR) models in predicting BGL analyzed using RMSE and CEGA have produced significant results yet the underlying physics behind BGL variation in diabetics is still vague. The use of compartmental models to describe the glucose/insulin dynamics in diabetes has also produced varying definitions to BGL variations. This is compounded by the inherent fuzziness of the glucose/insulin dynamics that is very difficult to define using exact quantities. Hence a much better understanding of the glucose/insulin dynamics in a diabetic patient is needed in order to provide a complete state space model. Support Vector Machine/Regression has seen better application in predicting the on-set of diabetes than in predicting blood glucose level variation. The use of ANN models in predicting blood glucose level has also produce significant successes however; the inability to relate BGL variation to specific activities of a diabetic patient poses a major bottleneck to providing better understanding of the glucose/insulin dynamics in diabetes. The use of the NFN in predicting BGL in diabetic patients has not been well exploited. Much application of NFN models has been seen in predicting the on-set of diabetes and in fuzzy logic controllers for artificial pancreas. However, the inherent vagueness in the glucose/insulin dynamics makes the NFN model amiable to solving this fuzziness and create greater patients' awareness. Hence, it is recommended that more NFN research work geared towards unraveling the fuzzy nature of glucose/insulin dynamics in BGL variation in diabetic patients be undertaken.

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