Annals of Science and Technology - A, Vol 4 (1): 1-15, 2019

ISSN: 2 544 6320

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ARTICLE

A Coupled Insulin and Meal Effect Neuro-Fuzzy Model for The Prediction of Blood Glucose Level in Type 1 Diabetes Mellitus Patients.

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Received 10th Nov. 2018, Accepted 3rd Feb. 2019
DOI: 10.2478/ast-2019-0001

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Abstract

Diabetes Mellitus is a metabolic disorder that affects the ability of the human body to properly utilize and regulate glucose. It is pervasive world-wide yet tenuous and costly to manage. Diabetes Mellitus is also difficult to model because it is nonlinear, dynamic and laden with mostly patient specific uncertainties. A neuro-fuzzy model for the prediction of blood glucose level in Type 1 diabetic patients using coupled insulin and meal effects is developed. This study establishes 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. The neuro-fuzzy models were trained with data collected from a single Type 1 diabetic patient covering a period of two months. Clarke's Error Grid Analysis (CEGA) of the model shows that 87.5% of the predictions fall into region A, while the remaining 12.5% of the predictions fall into region B within a four (4) hour prediction window. The model reveals significant variation in insulin and glucose responses as the Body Mass Index (BMI) of the patient changes.

Keywords: Blood Glucose Level, Diabetes Mellitus, Neuro-Fuzzy Network, Takagi-Sugeno, Type 1 Diabetes Mellitus

1.0 Introduction

Diabetes is described as a chronic disease that occurs either when the pancreas does not produce enough insulin or when the body cannot effectively use the insulin it produces (World Health Organization, 2013). Diabetes Mellitus (DM) is estimated to affect about 415 million people worldwide (that is 1 in 11 adults) (International Diabetes Federation, 2016). In Africa, Nigeria is the worst hit, with over 4 million people with diabetes (International Diabetes Federation, 2013). This alarming number is on the fast increase daily and in 2012, an estimated 1.5 million deaths were directly caused by diabetes (World Health Organization, 2014). A projection on the global mortality and burden of Diabetes Mellitus (DM) reveals that 80% of the deaths associated with the disease occur in the middle- and low-income countries (Mathers and Loncar, 2006). WHO projects that DM will be the 7th leading cause of death in 2030 (World Health Organization, 2011).

Diabetes Mellitus is of different types however, the most common are Type 1, Type 2 and Gestational DM. In Type 1 Diabetes Mellitus (T1DM) the pancreas undergoes an autoimmune attack by the body itself and is rendered incapable of making insulin (Melissa, 2012). Type 2 diabetes mellitus is characterized by insulin resistance, which may be combined with relatively reduced insulin secretion (Shoback, 2011). Gestational DM is detected during pregnancy and occurs in about 2 to 5% of all pregnancies. Poorly controlled BGL inflicts damaging effects to major organs of the human body. Direct medical implications of overly raised BGL include diabetic ketoacidosis and nonketotic hyperosmolar coma. Long term damages include: Retinopathy, Neuropathy, Nephropathy and Heart diseases which are associated with diseased small and large blood vessels as the case may be.

Presently, there is no cure for diabetes mellitus. This metabolic disorder can only be managed/controlled using oral medication or insulin, depending on the type of diabetes. Proper management of blood glucose level (BGL) in T1DM cannot be achieved without regular measurement. The invasive method of measuring blood glucose is the clinically acceptable means of measuring blood glucose. The finger strip meter and the continuous glucose meter are the most common and they require access to the blood or interstitial body fluid respectively. BGL in T1DM is affected by exogenous insulin, meal, exercise, stress etc. The amount of insulin required in T1DM to correct elevated BGL, depends on the type of insulin used and on the sensitivity of the individual to the insulin. The amount of carbohydrate required for one unit of insulin is given by the Insulin to Carbohydrate Ratio (ICR). The ICR of a patient may change due to; the type of food consumed, body mass index, hormonal balance and fitness level. Exercise is important in improving the lives of T1DM patients as it increases the permeability of glucose in peripheral tissues (Charles, 2002; American Council of Exercise, 2013). Although regular activity is beneficial for all patients, vigorous exercise can cause major disturbances in blood glucose. The glycemic response depends on the type, intensity and duration of the activity, as well as the circulating insulin and glucose counter-regulatory hormone concentrations (Michael and Bruce, 2006).

T1DM patient do not produce insulin hence normal BGL cannot be maintained. Most patients have vague idea of how they expect their BGL to vary after a meal, exercise or insulin injection. Though this is not to be relied upon as patients have slumped into episodes of hypoglycemia or hyperglycemia, it paints a bright picture of a possibility to predict BGL in DM. Hence the need to use an NFN to capture the trend in BGL variation and patient specific responses as it relates to specific activities (e.g. exercise, insulin, and meal) that affect BGL.

The idea of predicting BGL based on past blood glucose values was suggested by Bremer and Gough (Bremer, and Gough, 1999). They identified the statistical dependence of glycemic data in both diabetic and non-diabetic individuals. Sparacino et al., (2007) predicted BGL using first order AR model with time-varying parameters, identified by recursive least squares (RLS) with a constant forgetting factor. They achieved 20-25 minutes′ prediction of hypoglycemic threshold ahead in time. Shanthi et al., (2010) blood glucose level prediction model 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. They obtained maximum RMSE of 0.9-, 2.7- and 4.2mg/dl within the prediction horizon of 10-, 20- and 30 minutes, respectively. Stahl and Johansson (2009) presented a log-normalized linear model based on subspace-based identification and the GTFM-Wiener model for BGL prediction. However, they did not meet the 9mg/dl accuracy target within the two-hour prediction window. Ahmed and Mahmud (2013), developed a PID controller as an artificial pancreas whose outputs are based on the history and rate of change of the error signal. Their results revealed that the response of the PID controller is not acceptable since the BGL has an oscillation, causing a drop in BG level below the basal level.

Zarita et al., (2009) combined Principal Component Analysis (PCA) and Wavelet Neural Network (WNN) with Gaussian wavelet in predicting BGL in a single diabetic patient. 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., (2010) proposed BGL predictive model using feed forward three-layer neural network with a predictive horizon of 75mins, and back propagation training algorithm. 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. Clarke's Error Grid Analysis (CEGA) show that 95.1% and 69.8% of the prediction falls in region A for the patient specific and general neural network model, respectively. Neuro-Fuzzy Networks have seen more application in the prediction of the onset of diabetes and in fuzzy logic controllers for artificial pancreas. Deutsch et al., (1990) 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. Ghevondian et al., (2001) developed a Fuzzy Neural Network Estimator (FNNE) to predict the onset of hypoglycemia using heart rate and skin impedance as system inputs. The model revealed that hypoglycemia leads to increased heart beat by approximately 21bpm and reduced skin impedance by approximately 111ohms for T1DM patients. Moshe et al., (2013) investigated logic based artificial pancreas revealing superior performance in the reduction of nocturnal hypoglycemia and tighter blood glucose control. Ahmed and Mahmud (2013) developed a fuzzy logic algorithm for implementing an artificial pancreas. In their result, the response of this controller in steady state kept blood glucose concentration almost at the basal level, although it had a little overshoot before the steady state.

Juan and Chandima (2016) proposed a personalized blood glucose predictor based on time-series model of historical glucose measurements, pooled panel data regression and pre-clustered personalized regression. Their best performance was a 43-cluster personalized regression that achieved a Root Mean Square Error (RMSE) of 27.458 mg/dl and a correlation coefficient (R^2) of 0.8883. Hidalgo et al., (2017) proposed the use of a variant of grammatical evolution model and a tree-based genetic programming model that uses a three-compartment model for carbohydrate and insulin dynamics. The model achieved 90% of the prediction within regions A and B of CEGA, with 5 – 10% falling into regions D (serious error) and 0.5% in region E (very serious error). Kyriaki et al., (2018) explored the combination of Autoregressive models with exogenous inputs and pharmacokinetic compartment models to predict blood glucose. Clarke's Error Grid Analysis of the model showed that 53.84% of the predictions were in region A in the 4-hour prediction window.

2.0 Coupled Insulin and Meal Effect Neuro-Fuzzy Network Model

2.1 Model Assumptions

The following assumptions are made in formulating the model

1) There is no production of insulin by the T1DM patient.
2) The stress level, activity level, hormonal balance, fat mass index and lean body mass of the patient are fixed and do not affect the Neuro-Fuzzy Network (NFN) training data collected.
3) The effect of the change in age during the period of investigation is insignificant.

2.2 Model Formulation

In other to create patients' awareness to their unique body metabolism a neuro-fuzzy model is formulated. This is based on the proposition that the necessary and sufficient conditions to predicting BGL in a T1DM patient are knowledge of the patient's: 1) Insulin Effects 2) Meal Effects and 3) Transparent coupling of the Insulin and Meal Effects. Insulin Effect refers to the change in BGL for specific metabolic indices because of injected insulin defined by neuro-fuzzy weights (feature extracts). In the same vein, meal effect refers to the change in BGL for specific metabolic indices because of ingested meal defined by neuro-fuzzy weights (feature extracts). Combinations of physiological states that affect BGL variations in T1DM patients define metabolic scenarios. Metabolic index defines specific metabolic values of the physiological states that make up the metabolic scenario, for example Body Mass Index (BMI) of 22.12.

The control variables for the model are:

1) State Variable: Measured BGL $x(k)$ in mg/dl
2) Input Variables: Insulin u_1, Meal u_2, in units (IU) and serving spoon (SS) respectively.
3) Sampling Time: The sampling time (Δt) is the time between successive measurements of the blood glucose level which is one (1) hour.
4) Output: Predicted BGL $x(k+1)$ mg/dl
5) k is the discrete time index
6) Patient's Specifics(Δp): Injection site, Body/Fat Mass Indices, Lean Body Mass, Other Illness etc.

Blood Glucose Level (BGL), $x(k)$

The wide range of variation of BGL in a diabetic patient poses a major bottle neck to NFN training. Hence it is necessary to normalize the BGL. For this research the range of BGL is between 40 to 600 mg/dl since the normal range in healthy individuals is between 70 and 130 mg/dl and the immediate consequences of hypoglycemia (deficiency of glucose is the bloodstream) is more dangerous than that of hyperglycemia (excessive glucose in the bloodstream).

$$\bar{x}(k) = \frac{x(k)}{Max(x(k))} \qquad (1)$$

Insulin Injection, u_1

Insulin effect is modeled as a function of insulin injection u_1, current BGL, sampling time and patient's specifics. This captures the uniqueness of the patient's reaction to injected insulin. The injected insulin u_1 is a scalar function g of the insulin type T and quantity Q injected.

$$u_1 = g(Q,T) \qquad (2)$$

Given that u_1 is injected, the insulin effect on the BGL $I(k)_{u_1}$ given by the function f_1 is

$$I(k+1)_{u_1} \propto f_1(u_1,\ x(k),\ \Delta t,\ \Delta p)$$

$$I(k+1)_{u_1} = K_1 f_1(u_1,\ x(k),\ \Delta t,\ \Delta p) \quad (3)$$

$$\bar{I}(k+1)_{u_1} = \frac{I(k+1)_{u_1}}{Max(I(k+1)_{u_1})} \quad (4)$$

Meal Intake, u_2

Meal effect is modeled as a function of meal intake, current BGL, sampling time and patient's specifics. The ingested meal u_2 is a scalar function m of the meal type M and quantity Q ingested

$$u_2 = m(Q, M) \quad (5)$$

Given that u_2 is consumed, the meal effect on BGL $I(k)_{u_2}$ given by the function f_2 is

$$I(k+1)_{u_2} \propto f_2(u_2,\ x(k),\ \Delta t,\ \Delta p)$$

$$I(k+1)_{u_2} = K_2 f_2(u_2,\ x(k),\ \Delta t,\ \Delta p) \quad (6)$$

$$\bar{I}(k+1)_{u_2} = \frac{I(k+1)_{u_2}}{Max(I(k+1)_{u_2})} \quad (7)$$

Fuzzification of State and Input Variables

BGL variation is fuzzified using the Trapezoidal Membership Function (MF) while insulin, insulin effect, meal and meal effect are fuzzified using the Triangular MF as given in equations (8) and (9) respectively.

$$\mu_F(\bar{u};\ \alpha,\beta,\gamma,z) = \begin{cases} 0, & \bar{u} \le \alpha \\ \frac{\bar{u}-\alpha}{\beta-\alpha}, & \alpha < \bar{u} \le \beta \\ 1, & \beta < \bar{u} \le \gamma \\ \frac{\gamma-\bar{u}}{\beta-\bar{u}}, & \gamma < \bar{u} \le z \\ 0, & \bar{u} > z \end{cases} \quad (8)$$

Where $\bar{u}$ is the in situ variable of interest, α,β,γ are projections of the vertices of a trapezium to its base (representing the in situ values of $\bar{u}$), from left to right.

$$\mu_F(\bar{u};\ \alpha,\beta,\gamma) = \begin{cases} 0, & \bar{u} \le \alpha \\ \frac{\bar{u}-\alpha}{\beta-\alpha}, & \alpha < \bar{u} \le \beta \\ \frac{\gamma-\bar{u}}{\beta-\bar{u}}, & \beta < \bar{u} \le \gamma \\ 0, & \bar{u} > \gamma \end{cases} \quad (9)$$

Where $\bar{u}$ is the in situ variable of interest, α,β,γ are projections of the vertices of a triangle to its base (representing the in situ values of $\bar{u}$), from left to right.

The MFs for the state and input variables are given in Table 1

Table 1: In situ State and Input Variables Fuzzification Ranges

State Variable	**Min**	**Max**	**Hypoglycemic**	**Normal**	**Hyperglycemic**
BGL(mg/dl)	40*	600**	40, 40, 66, 72	66, 72, 120, 138	120, 180, 600, 600
Input Variable	**Min**	**Max**	**Type**	**Low**	**Medium**	**High**
Insulin(u_1) (IU)	0	40	Biphasic Human Insulin	0, 0, 10	0, 10, 20	10, 40, 40
Insulin Effect ($I(k)_{u_1}$) k = 1, 2, 3,4	0	-120	Biphasic Human Insulin	0,0,-60	0,-60,-120	-60,-120,-120
Meal (u_2)	**Min**	**Max**	**Type**	**Small**	**Medium**	**Large**
Meal(u_2) (SS)	0	5	Rice	0, 1, 3	1, 3, 5	3, 5, 5
Meal Effect ($I(k)_{u_2}$) k = 1, 2, 3,4	0	180	Rice	0, 0, 90	0, 90, 180	90,180, 180

N/B: unit of meal size = serving spoon (SS); Units of Insulin and Meal Effect = mg/dl

* Hypoglycemic BGL set to avoid prolonged stay of the patient in the hypoglycemic range

** Maximum Hyperglycemic BGL that can be measured by the One Touch glucose meter used for the experiment

$$F = \{\bar{x} | \mu_F(\bar{x})\} \ for\ \bar{x} \in X \quad (10)$$

Where X is the universe of discourse and $\mu_F(\bar{x})$ is the degree of membership of object $\bar{x}$ in the fuzzy set F and it is a real number that lies between $[0, 1]$. Each of the control variables represents a universe of

discourse. The control variables are each fuzzified to have a three-member fuzzy set (set 1, set 2 and set 3). Hence the fuzzification process is generically represented in equation (11). The span of each fuzzy set is dependent on the nature of the universe of discourse and its members.

$$F \in \{set1, set2, set3\} \quad (11)$$

The fuzzification of the BGL is given in Fig 1.

Formulation of the T-S Model Rule Bases

The Takagi-Sugeno Neuro-Fuzzy Network (T-S NFN) for the investigation of insulin, meal and insulin/meal effects are modeled as a discrete piece-wise linear system with discrete time variable k such that,

The insulin effect consequent part of the T-S model

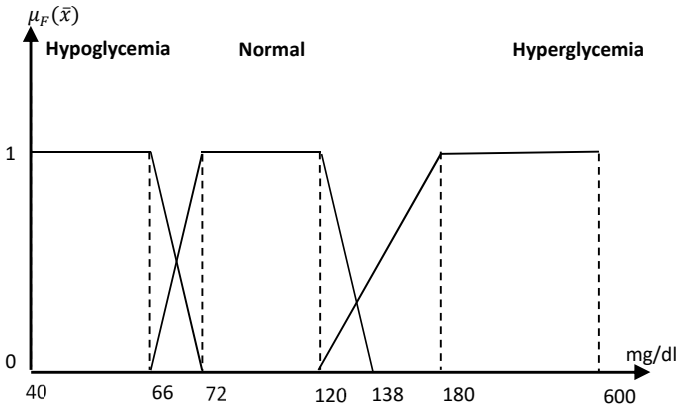


Fig 1: Fuzzification of in situ BGL

rule base is modeled as a function of proportionality

$$\bar{I}(k+1)_{u_1} \propto f_1(u_1, \bar{x}(k), \Delta t, \Delta p) \quad (12)$$

The corresponding consequent part of the meal effect rule base is;

$$\bar{I}(k+1)_{u_2} \propto f_2(u_2, \bar{x}(k), \Delta t, \Delta p) \quad (13)$$

The meal/insulin effect which represents the coupling of the meal and insulin effects is;

$$\bar{x}(k+1) \propto f\left(\bar{x}(k), \bar{I}(k+1)_{u_1}, \bar{I}(k+1)_{u_2}\right) \quad (14)$$

where $k = [1, 2, \dots, N]$ and N is the number of samples taken.

A separate rule base is generated for each investigation; hence there are three (3) rule bases, **RB1**, **RB2** and **RB3** for the insulin effect, meal effect and insulin/meal effect respectively. **RB1** and **RB2** are composed of 9 rules each while **RB3** is composed of 27 rules. The rules represent different experiences of the T1DM patient. Given that the maximum discrete time of the input variables' effect on BGL variation is **z,** then the *jth* rule is of the form:

BGL VS Insulin Rule Base (RB1)

R_j: IF

$x(k)$ is ${F_1}^j$ **AND** u_1 is ${F_2}^j$

THEN

FOR k = 0, 1, … , z

$$\bar{x}(k+1) = \bar{P}_A \bar{x}(k) + \bar{P}_B f_1(u_1, \bar{x}(k), \Delta t, \Delta p)$$
$$\bar{I}(k+1)_{u_1} = \bar{x}(k+1) - \bar{x}(k) \quad (15)$$

Where $\bar{P}_A, \bar{P}_B$ *are state and input matrices respectively multipled by the output of* $\boldsymbol{RB1}$, $j = 1, 2, \dots, 9$; F = fuzzy variable; $\bar{P}_A = \sum_{j=1}^{9} \sigma_j P_{A_j}$; $\bar{P}_B = \sum_{j=1}^{9} \sigma_j P_{B_j}$

BGL VS Meal Rule Base (RB2)

R_j: IF

$x(k)$ is ${F_1}^j$ **AND** u_2 is ${F_3}^j$

THEN

FOR k = 0, 1, … , z

$$\bar{x}(k+1) = \bar{Q}_A \bar{x}(k) + \bar{Q}_B f_2(u_2, \bar{x}(k), \Delta t, \Delta p)$$
$$\bar{I}(k+1)_{u_2} = \bar{x}(k+1) - \bar{x}(k) \quad (16)$$

Where $\bar{Q}_A, \bar{Q}_B$ *are state and input matrices respectively multipled by the output of* $\boldsymbol{RB2}$, $j = 1, 2, \dots, 9$; F = fuzzy variable; $\bar{Q}_A = \sum_{j=1}^{9} \sigma_j Q_{A_j}$; $\bar{Q}_B = \sum_{j=1}^{9} \sigma_j Q_{B_j}$
$\sigma_j = \frac{\mu_j}{\sum_{j=1}^{9} \mu_j}$; $\sum_{j=1}^{9} \sigma_j = 1$.

BGL VS Insulin/Meal Rule Base (RB3)

R_j: IF

$x(k)$ is ${F_1}^j$ **AND** $I(k+1)_{u_1}$ is ${F_4}^j$ **AND** $I(k+1)_{u_2}$ is ${F_5}^j$

THEN

FOR k = 0, 1, … , z

$$\bar{x}(k+1) = \bar{A}\bar{x}(k) + \bar{B}\bar{I}(k+1)$$
$$\bar{y}(k) = \bar{C}\bar{x}(k) + \bar{D}\bar{I}(k+1) \quad (17)$$

Where A_j, B_j, C_j, D_j *are discrete time subsystem matrices,* $\bar{I}(k+1) = \left[\bar{I}(k+1)_{u_1}, \bar{I}(k+1)_{u_2}\right]^T$,
$j = 1, 2, \dots, 27$, F = fuzzy variable.

Given a current state vector $x(k)$ and an input vector u the T-S fuzzy model infers $\bar{x}(k+1)$ as;

$$\bar{x}(k+1) = \sum_{j=1}^{27} \frac{\mu_j (A_j \bar{x}(k) + B_j \bar{I}(k+1))}{\sum_{j=1}^{27} \mu_j}$$

$$\bar{y}(k) = \sum_{j=1}^{27} \frac{\mu_j (C_j \bar{x}(k) + D_j \bar{I}(k+1))}{\sum_{j=1}^{27} \mu_j} \quad (18)$$

$\mu_j = min_{i=1}^{(n-1)} {\mu_j}^i(x, u_i)$ is the minimum of the MF for the fuzzy rule j, and ${\mu_j}^i(x)$ is the MF of the fuzzy term ${F_i}^j$ for control variable x, $j = 1, 2, \dots, 27$, n is the total number of input and state variables.

The overall fuzzy system model can be simplified as

$$\bar{x}(k+1) = \bar{A}\bar{x}(k) + \bar{B}\bar{I}(k+1)$$

Where $\bar{A} = \sum_{j=1}^{27} \sigma_j A_j$; $\bar{B} = \sum_{j=1}^{27} \sigma_j B_j$; $\bar{C} = \sum_{j=1}^{27} \sigma_j C_j$; $\bar{D} = \sum_{j=1}^{27} \sigma_j D_j$ $\sigma_j = \frac{\mu_j}{\sum_{j=1}^{27} \mu_j}$; $\sum_{j=1}^{27} \sigma_j = 1$;

The overall system is nonlinear since $\bar{A}$ is a function of σ_j and σ_j is a function of $\bar{x}(k)$ the state variable.

Since the system output is the same as the future state (i.e. predicted BGL):

$$\bar{y}(k) = \bar{x}(k+1) \qquad (20)$$

$$\bar{y}(k) = \bar{C}\bar{x}(k) + \bar{D}\bar{I}(k+1) \qquad (19)$$

Hence, the *j-th* rule for **RB3** simplifies to

R_j: **IF**
$x(k)$ is ${F_1}^j$ **AND** $I(k+1)_{u_1}$ is ${F_2}^j$ **AND** $I(k+1)_{u_2}$ is ${F_3}^j$
THEN
FOR k = 0, 1, … , z

$$\bar{x}(k+1) = \bar{A}\bar{x}(k) + \bar{B}\bar{I}(k+1) \qquad (21)$$

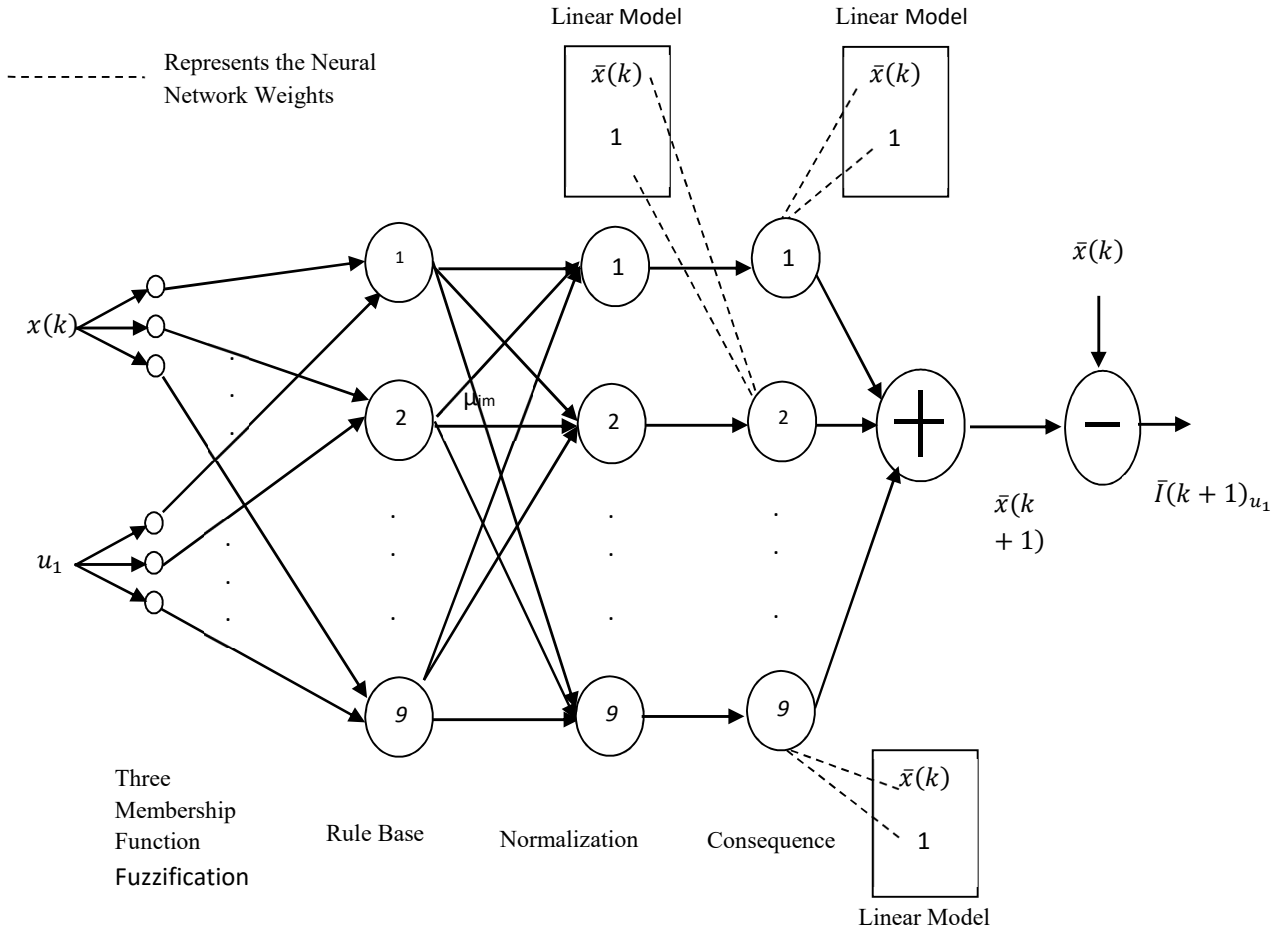


Figure 2a: Insulin Effect Based NFN Model for the prediction of BGL in T1DM Patients

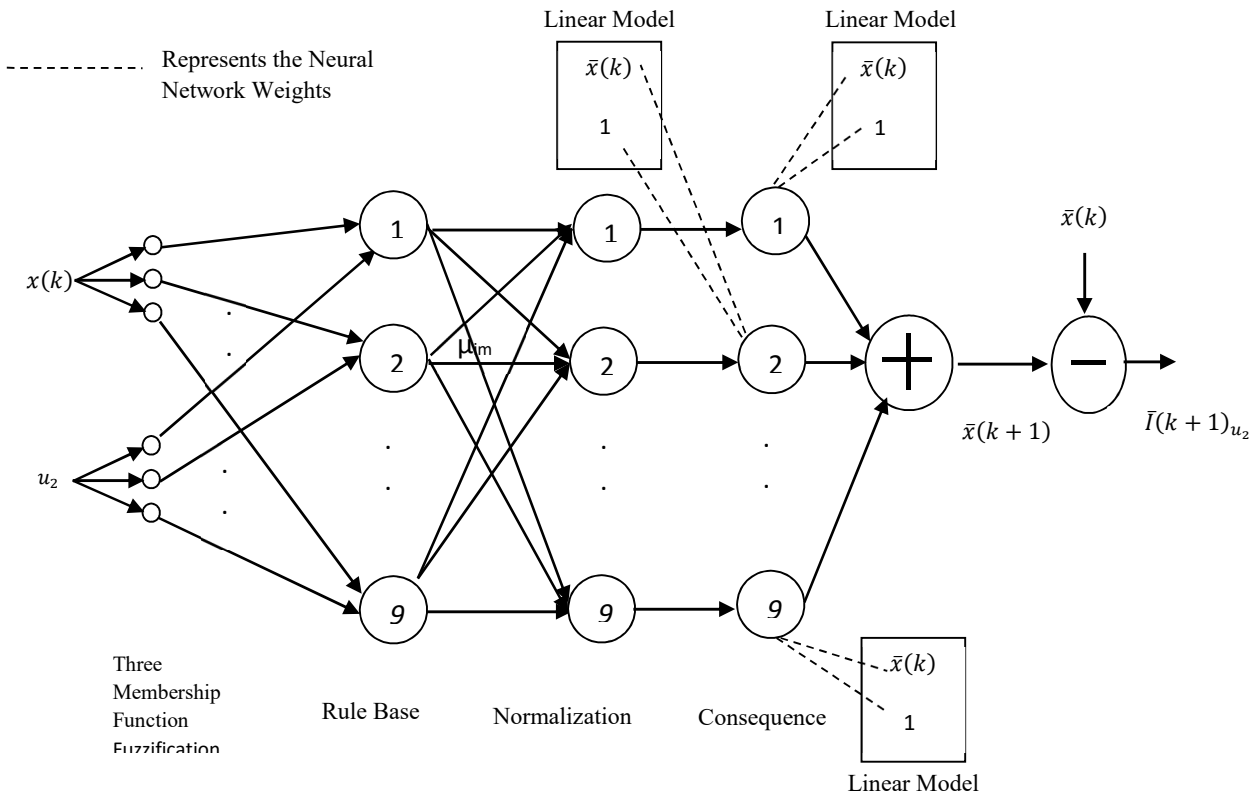


Figure 2b Meal Effect Based NFN Model for the prediction of BGL in T1DM Patients

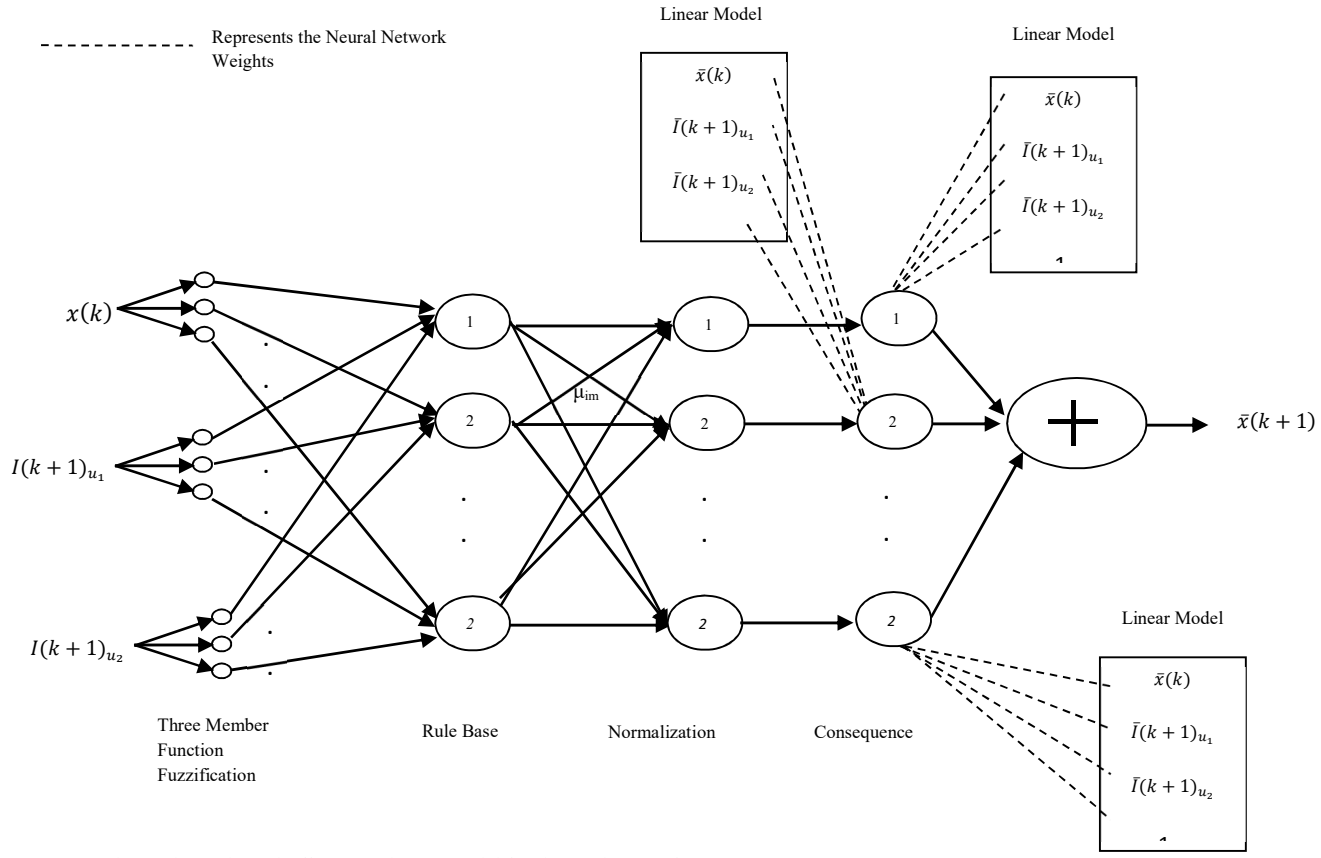


Figure 2c: Couple Insulin and Meal Effect Based NFN Model for the prediction of BGL in T1DM Patients

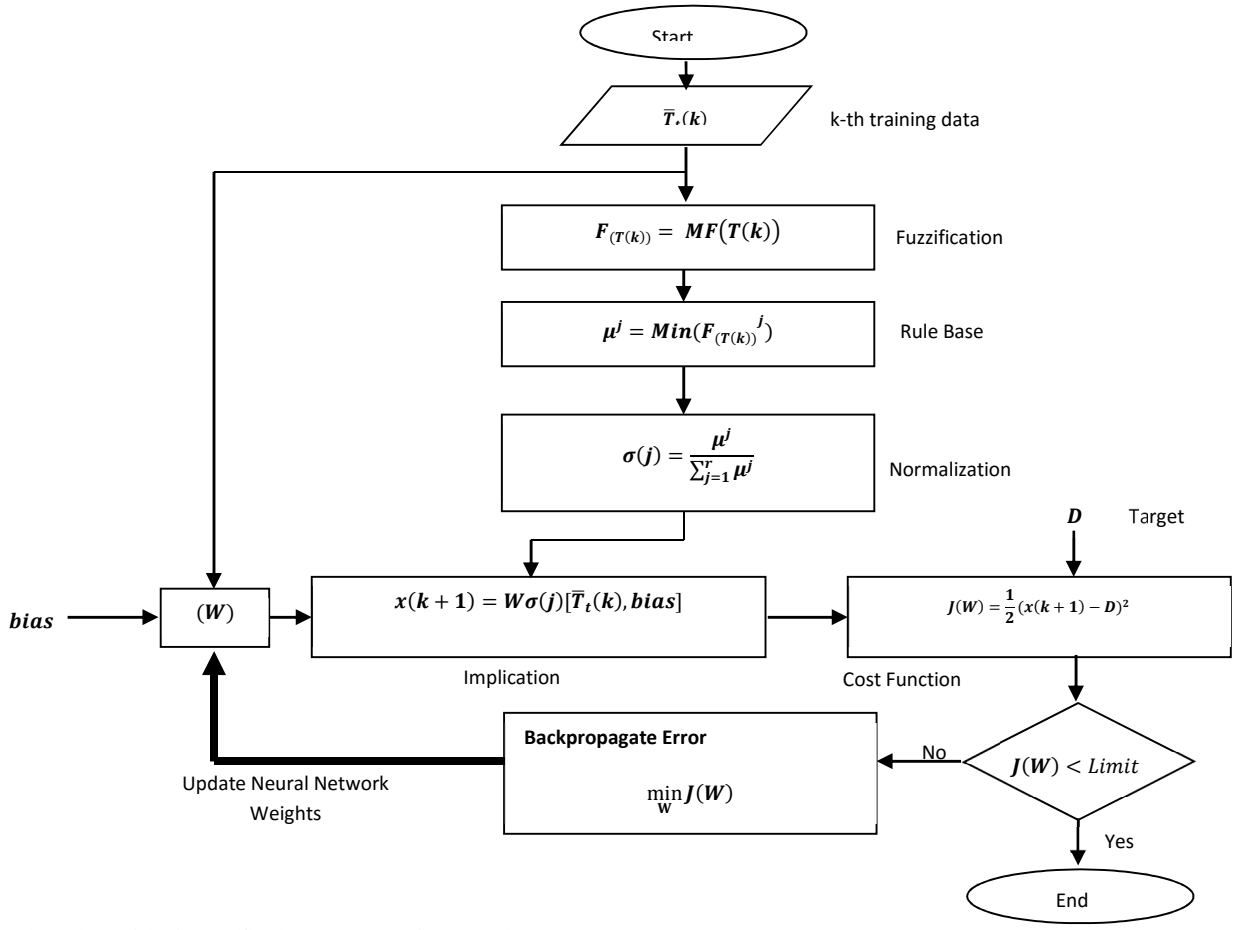


Fig 3: Flow Chart of the forward/back propagation of training data set in T-S NFN

Parameter Identification

In identifying the parameters $\bar{P}_A, \bar{P}_B, \bar{Q}_A, \bar{Q}_B$, $\bar{A}$ and $\bar{B}$, the fuzzy neural network is trained using least square error function and back propagation algorithm. Hence the three (3) rule bases are formulated in the form;

BGL VS Insulin Rule Base (RB1)
R_j: **IF**
$x(k)$ is $F_1{}^j$ **AND** u_1 is $F_2{}^j$
THEN
FOR k = 0, 1, … , z

$$\bar{x}(k+1) = p_{1j}\bar{x}(k) + p_{2j}$$
$$\bar{I}(k+1)_{u_1} = \bar{x}(k+1) - \bar{x}(k) \quad (22)$$

BGL VS Meal Rule Base (RB2)
R_j: **IF**
$x(k)$ is $F_1{}^j$ **AND** u_2 is $F_3{}^j$
THEN
FOR k = 0, 1, … , z

$$\bar{x}(k+1) = q_{1j}\bar{x}(k) + q_{2j}$$
$$\bar{I}(k+1)_{u_2} = \bar{x}(k+1) - \bar{x}(k) \quad (23)$$

BGL VS Insulin/Meal Rule Base (RB3)

R_j: **IF**
$x(k)$ is $F_1{}^j$ **AND** $I(k+1)_{u_1}$ is $F_4{}^j$ **AND** $I(k+1)_{u_2}$ is $F_5{}^j$
THEN
FOR k = 0, 1, … , z

$$\bar{x}(k+1) = w_{1j}\bar{x}(k) + w_{2j}\bar{I}(k+1)_{u_1} + w_{3j}\bar{I}(k+1)_{u_2} + w_{4j} \quad (24)$$

The weights w_{1j} ,…, w_{4j} are weights of the NN which is trained using the input-output data collected from the T1DM patient. They represent the vague experiences of the patient as he/she carries on his/her day to day activities. More so, the trained weights p_{1j} and p_{2j} represent insulin effect on BGL while the trained weights q_{1j} and q_{2j} represent meal effect on BGL.

2.2 Prediction of Blood Glucose Level

Let the NFN trained weights for patient's specific meal/insulin effect feature extraction be $\boldsymbol{W_T}$

Let the inputs (BGL, insulin effect, meal effects and bias) on which prediction is based be $[\bar{p}_{11}, \bar{p}_{21}, \bar{p}_{3\,1}\mathbf{1}]$.

Given that there are $'l'$ rules, let the result of the triggered rules because of the input be

$$H_T = \begin{bmatrix} \sigma_{11}\bar{p}_{11} \\ \sigma_{11}\bar{p}_{21} \\ \sigma_{11}\bar{p}_{3\,1} \\ \sigma_{11} \\ \vdots \\ \sigma_{l1}\bar{p}_{11} \\ \sigma_{l1}\bar{p}_{21} \\ \sigma_{l1}\bar{p}_{3\,1} \\ \sigma_{l1} \end{bmatrix} \quad (25)$$

Hence the predicted output Y_p is given as

$$Y_p = W_T H_T \quad (26)$$

Choice of Training Scenario

The metabolic activities of T1DM patients are affected by their general state of health. Thus, defining the indices of the general state of health of the patient as metabolic scenarios, different training windows are built. These metabolic scenarios span a myriad of indices which include stress, exercise, injection site, body mass index, fat mass index etc. The training windows are chosen to capture the contributory effect of the metabolic indices to the variation in blood glucose level in T1DM.

Robustness and flexibility of the coupled insulin and meal effect BGL predictive model, lies in its modularity. This is achieved using insulin and meal effect rule bases (**RB1** and **RB2**) that span the metabolic scenarios. Insulin/meal rule base (**RB3**) transparently couples **RB1** and **RB2** making **RB3** independent of the specifics of the insulin and meal variables, but on their apparent effects. Hence, **RB3** is quite robust and flexible and spans the metabolic scenarios that have been used in the training. As a result of this design, **RB3** learns the diverse experiences of the T1DM patient while **RB1** and **RB2** are updated as new metabolic scenes arise.

2.3 Results, Observations and Discussions

The insulin, meal and insulin/meal effect models were implemented using MATLAB 2012a. A 31-year-old male T1DM patient, who has been diabetic for 17 years was recruited for this study with the approval of Lagos University Teaching Hospital Research and Ethics Committee. Patient's BMI ranged between 22.42 to 23.55. The training dataset was gathered under normal living condition to capture patient's real-life experience. Blood glucose readings were taken using a One Touch blood glucose monitor. Patient's exogenous insulin injection site is the thigh. Polished rice was considered in this study for meal effect investigation because it is the most staple food in Nigeria. Every reference to rice in this study specifically refers to polished rice.

Figures 4a to 4h show the differences in insulin and meal effect of the T1DM patient for different body mass indices. Figures 4a and 4b show drops in BGL for the metabolic index of BMI 22.42 and 23.32 respectively, when 10IU of Biphasic Human Insulin was administered. The average rate of BGL drop was 36.25mg/dl per hour for metabolic index of *"BMI 22.42"* while it was 32.5mg/dl per hour for metabolic index of "*BMI 23.32*" from a hyperglycemic BGL of 180mg/dl. This shows that the rate of BGL response to insulin increases with decreasing BMI. More so, figures 4c and 4d show drops in BGL for the metabolic index of BMI 22.42 and 23.32 respectively, when 30IU of Biphasic Human Insulin is administered. The average rate of BGL drop is 63.75mg/dl per hour for metabolic index of *"BMI 22.42"* while it was 52.5mg/dl per hour for metabolic index of *"BMI 23.32"*, from a hyperglycemic BGL of 280mg/dl. Figures 4a and 4c show that at constant BMI the average rate of drop in BGL increases as the dose of administered insulin increases.

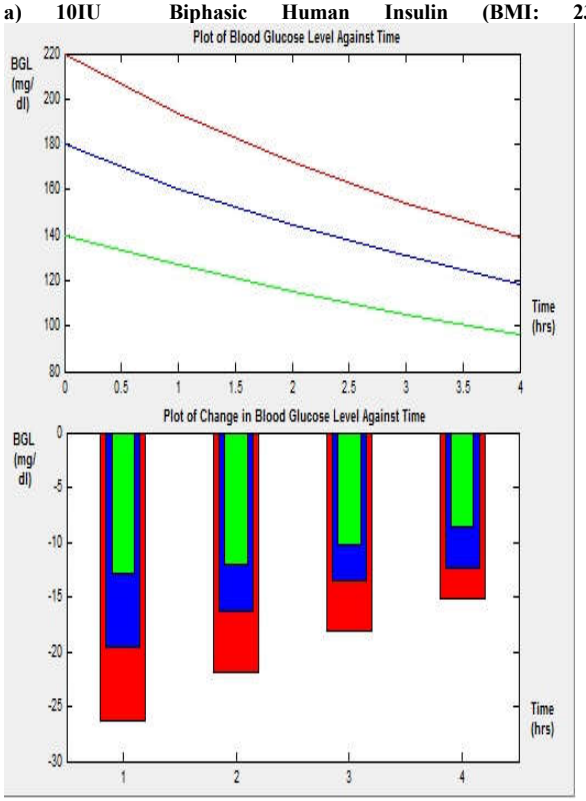
Comparing Figures 4e and 4f show BGL rising at an average rate of 45mg/dl per hour for the "*no meal/ BMI:23.32*" condition and at of 33mg/dl per hour for the "*One(1) Serving Spoon(SS) of rice/BMI:23.32*" condition. The absence of food and insulin in the blood stream result in significant rise in BGL as given by the positive gradient of 45mg/dl per hour. This can be attributed to internal glucose production. **Hence, it is not advisable for a T1DM patient to skip medication**. Figures 4g and 4h show the Meal Effect for "*Three (3) SS of rice/BMI:23.32*" and "*Five (5) SS of rice/BMI:22.42*" conditions respectively. The average rise in BGL is 45mg/dl per hour for the "*Three (3) SS of rice/BMI:23.32*" condition while it is 60mg/dl per hour for the "*Five (5) SS of rice/BMI:22.42*" condition. This shows that BGL response to meal has a positive gradient. It is obvious from the findings that insulin and meal effects change as the body mass index of the investigated T1DM patient change.

Coupling the obtained insulin and meal effects to predicting BGL variations showed promising results in reproducing the same effect as seen in the training data. It also extrapolates future responses. The training data was collected for a period of two (2) months. A stratified holdout procedure with captured dataset randomly split into 70% for training and 30% for testing was used in this study. The NFN T-S model was trained for 100000 epochs, with a neural network weight adjustment step size of 0.03. The performance of the NFN T-S model on BGL prediction was assessed using new sets of measurements that were not used during training. The performance of the NFN T-S model is summarized in Table 2.

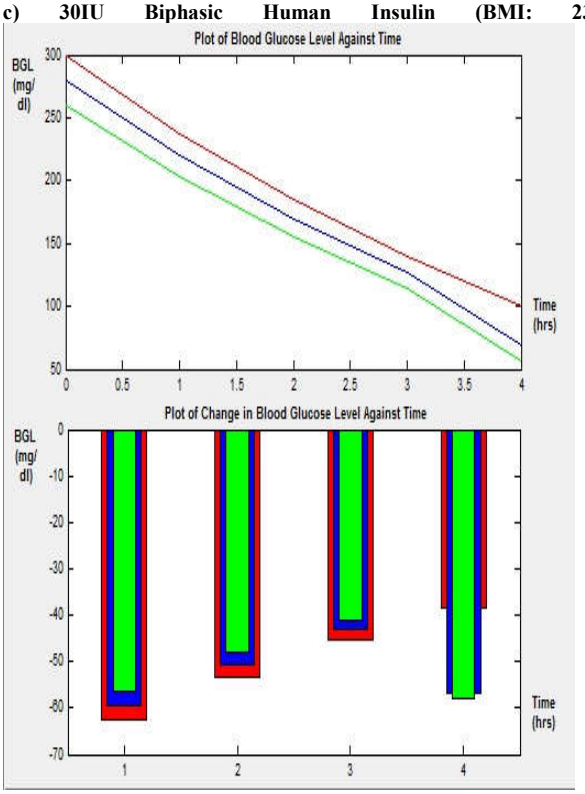
The Clarke's Error Grid Analysis (CEGA) of the performance of the NFN T-S model in predicting BGL in the T1DM patient is given in Figure 5. 87.5% of the predictions fall into region A, while the remaining 12.5% of the predictions fall into region B within the 240 minutes prediction horizon. No predictions fall into regions C, D and E hence; all the predictions are within the clinically acceptable range.

Table 3 shows performance comparison of the coupled insulin and meal effect neuro-fuzzy model with previous predictive models.

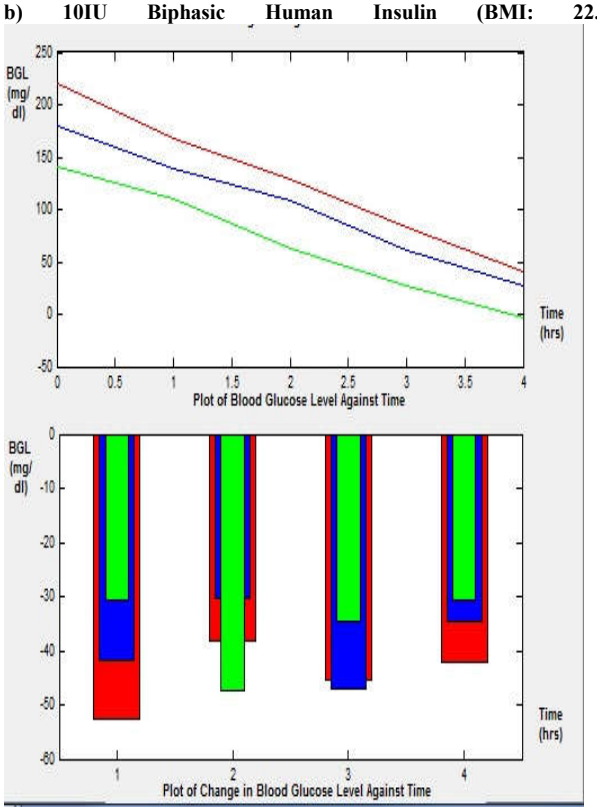
a) 10IU Biphasic Human Insulin (BMI: 23.32)



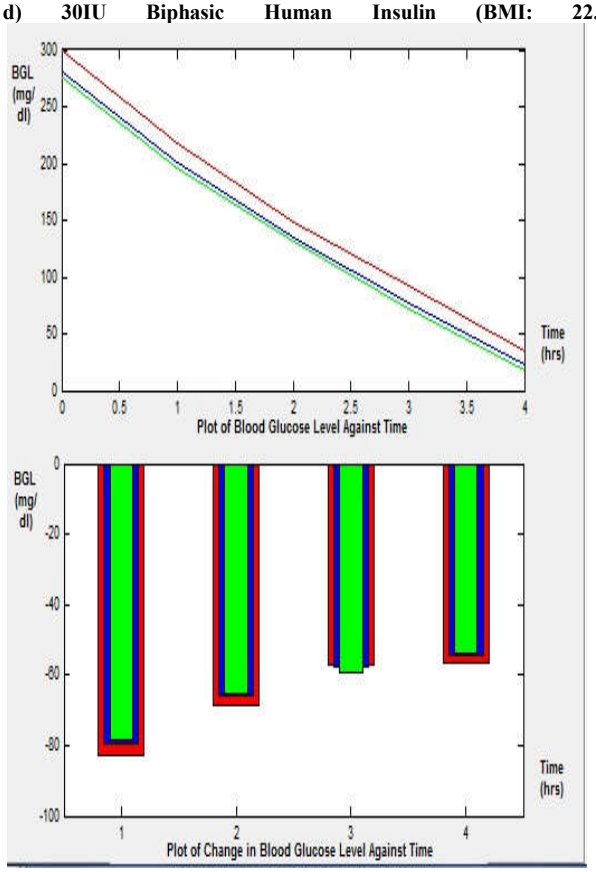
c) 30IU Biphasic Human Insulin (BMI: 23.32)



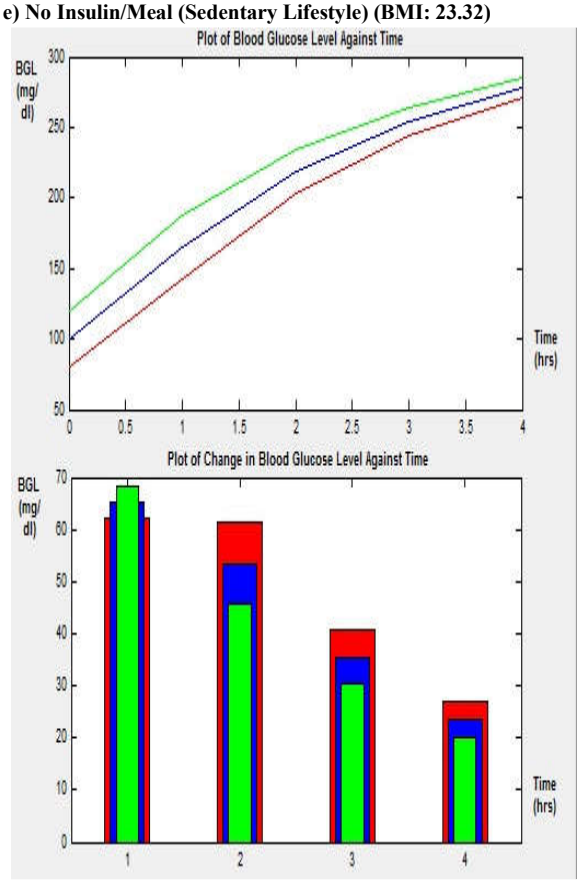
b) 10IU Biphasic Human Insulin (BMI: 22.42)



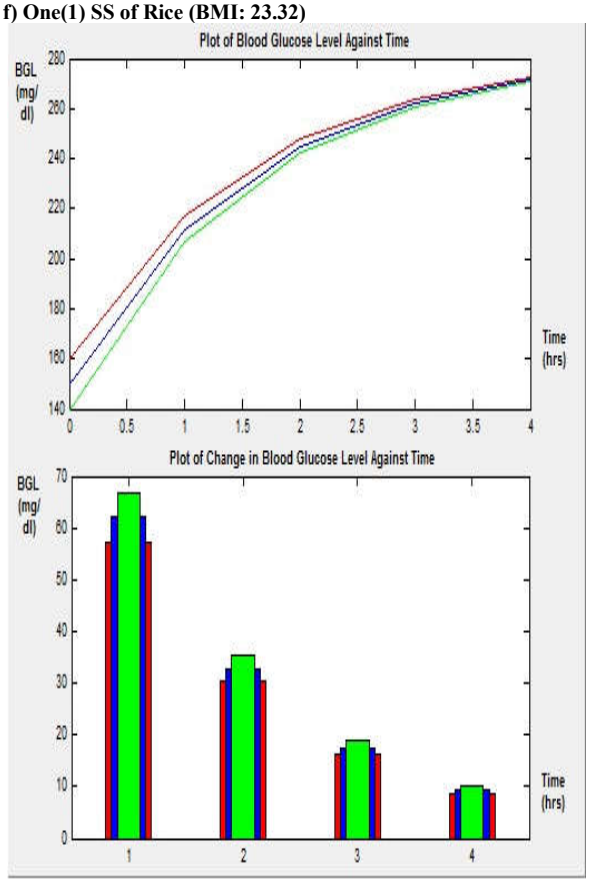
d) 30IU Biphasic Human Insulin (BMI: 22.42)



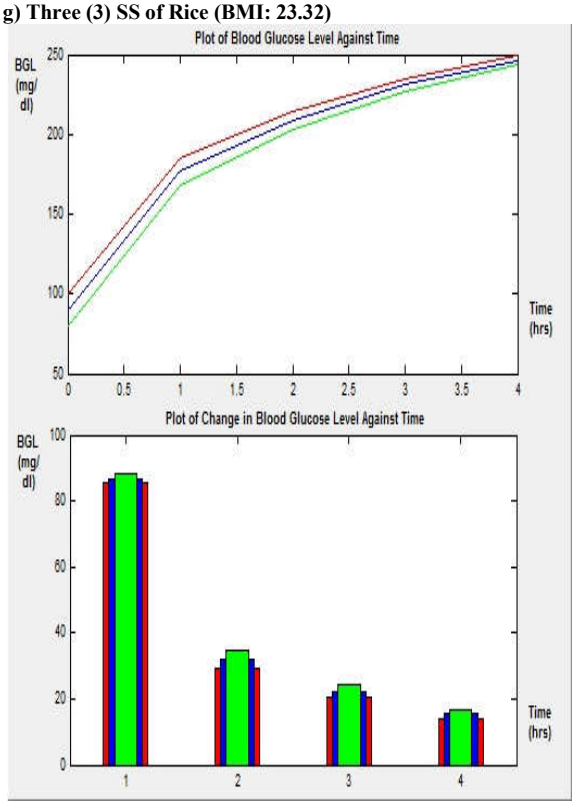
e) No Insulin/Meal (Sedentary Lifestyle) (BMI: 23.32)



f) One(1) SS of Rice (BMI: 23.32)



g) Three (3) SS of Rice (BMI: 23.32)



h) Five (5) SS of Rice (BMI: 22.42)

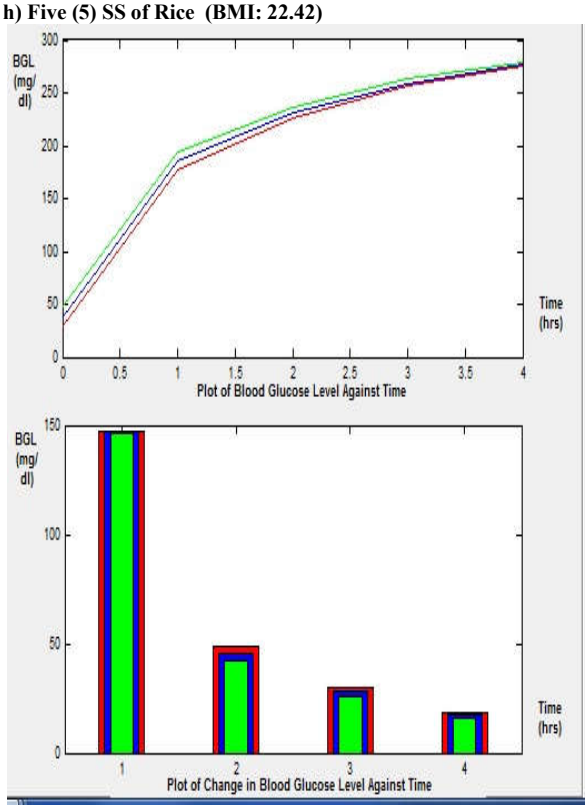


Fig 4: Plots of insulin and meal effects at different metabolic indices

Table 2: Performance Analysis of NFN T-S model on BGL prediction under different conditions

Day 1		Day 2		Day 3		Day 4	
BMI: 23.32		BMI: 23.32		BMI: 22.42		BMI: 22.42	
Insulin: 30IU		Insulin: 10IU		Insulin: 30IU		Insulin: 30IU	
Meal: 3		Meal: 1		Meal: 1		Meal: 5	
IBGL: 123		IBGL: 210		IBGL: 301		IBGL: 231	
MBGL	PBGL	MBGL	PBGL	MBGL	PBGL	MBGL	PBGL
190	193.2	229	216.8	266	270.6	286	288
115	128.3	175	199.2	219	218.7	272	248.7
77	86.1	187	174.7	103	133.4	217	189.9
52	45.6	152	148.8	42	48.8	125	90.9

IBGL: Initial BGL(mg/dl) is BGL before administration of insulin/meal; MBGL: Measured BGL(mg/dl) is hourly measured BGL after administration of insulin/meal; PBGL: Predicted BGL(mg/dl) is NFN predicted BGL; Meal(Serving Spoons); 1 Serving spoon of rice= 50g

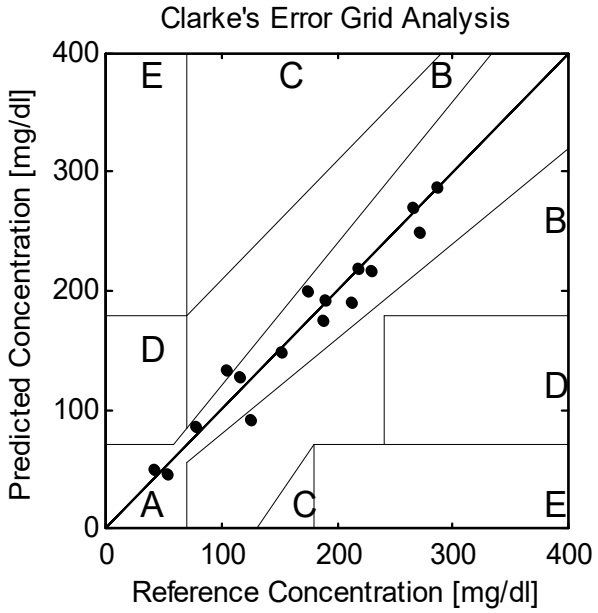


Figure 5: Clarke's Error Grid Analysis of the performance of the Coupled Insulin/Meal Effect NFN BGL predictive model

3.0 CONCLUSION

The model developed establishes the fact that BGL variations in T1DM patients can be decoupled into manageable entities of feature extracts (neuro-fuzzy network weights) describing the insulin and meal effects for specific metabolic scenarios. The transparent coupling of the insulin and meal effects can predict BGL variations for both known and uninvestigated scenarios. The feature extracts defining the insulin and meal effects depend on the prevailing metabolic indices which include; body mass index, activity level, stress level, injection sites etc. However, the transparent coupling of the insulin and meal effects is unaware of the prevailing metabolic indices.

The achievements made by the NFN T-S model in predicting BGL on limited training show very positive indication that predicting BGL variations for T1DM patients using neuro-fuzzy network is viable. Its performance on limited training is comparable to the achievements seen in the Auto Regressive, Compartmental (State Space), Support Vector Regression and Artificial Neural Network Model. The introduction of the concept of insulin and meal effect for diverse metabolic scenarios provides a novel means to explaining the variability in BGL experienced by T1DM patients. This will further enhance patients' awareness to how their day to day activities affect their BGLs. Robustness and flexibility of the model lies in its modularity. This is achieved through the use of **RB1** and **RB2** that span the metabolic scenarios. Hence, **RB3** which is the coupling of **RB1** and **RB2** is quite robust and flexible spanning the investigated metabolic scenarios. As a result of this design, **RB3** learns the diverse experiences of the T1DM patient while **RB1** and **RB2** are updated as new metabolic scenes arise.

Table 3: Comparison of Couple Insulin/Meal Effect NFN with Previous Models

	Description	Coupled Insulin/Meal Effect Neuro-Fuzzy Model	Zarita et al., (2009)	Scott et al., (2010)	Eleni et al., (2011)
1	Model	Combination of Neuro-Fuzzy Network models	Combination of Principal Component Analysis and Wavelet Neural Network	Feed forward three layer neural network	Support Vector Regression and Compartmental Model
2	Participating Patients	One(1)	One (1)	One (1) patient specific, Five(5) general model	Seven (7)
3	Attributes	Current BGL, Insulin injection, Meal, Patient specific attributes such as BMI, Injection Site, Stress and Exercise	Time, Insulin, Meal, Exercise, Stress	Time, CGM data, POC glucose test time/ results, Insulin delivery type/ dosage	Insulin/meal/exercise dynamics, CGM
4	Concept	Insulin Effect, Meal Effect, Coupled Insulin/Meal Effects all in mg/dl	No Concept Definition	No Concept Definition	Insulin/Meal/Exercise dynamics
5	Prediction Partition	Metabolic Indices and Time of the day	Time of the day	Not explicitly defined	Not explicitly defined
6	Accuracy	87.5% and 12.5% in regions A and B respectively of CEGA in 240 minutes prediction horizon	Measured in RMSE of 0.045mmol/dl and no reference to CEGA	95.1% and 69.8% predictions in CEGA region A for patient specific and general models respectively	98.86%, 92.54%, 80.02%, 62.91% of predictions in CEGA region A for 15-, 30-, 60-, and 120 minutes
7	Prediction Horizon	240 Minutes	Not Specified Explicitly	75 Minutes	15-, 30-, 60-, 120 minutes
8	Multi-Scenario Application	Applicable in Multi-Scenario Environment	Restricted application	Highly Restricted application	Restricted application

Contributions to Knowledge

1. This study established that glucose/insulin dynamics of a Type 1 diabetic patient can be decoupled into manageable entities of neuro-fuzzy feature extracts describing the insulin and meal effects for specific metabolic scenarios.

2. Furthermore, this study established that coupling of the insulin and meal effects can effectively predict blood glucose variations in T1DM patients.

For further research work, it is recommended that clinical investigations be carried out for more metabolic conditions which include different meals, exercise levels, stress levels, sites of insulin injection, meal and insulin effect offset etc. It is also recommended that more training data should be collected to enhance the performance of the NFN T-S based BGL prediction model.

Acknowledgement

The authors acknowledge the management, staff and participating patients of Lagos University Teaching Hospital for their assistance in conducting the study.

Statement of Human and Animal Rights

The researcher team obtained approval from the Ethics Committee of LUTH hence consenting patients freely participated in the monitoring and recording of their BGL and other variables at different times under various scenarios for the study.

Authors Contribution

Conception: NOO; Design: NOO, OSA, TAF and OAF; Execution: NOO and OAF

Interpretation: NOO, OSA, TAF and OAF; Writing the paper: NOO, OSA and TAF

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