CONTINUOUS BLOOD GLUCOSE MONITORING, BLOOD GLUCOSE LEVEL PREDICTION AND INSULIN SUGGESTION FOR DIABETIC TYPE 1 PATIENTS OR ARTIFICIAL PANCREAS (AP)

Author

Muhammad Asad

00000119210

MS-15(CSE)

Supervisor

Dr. Usman Qamar

Department of Computer Engineering College of Electrical and Mechanical Engineering National University of Sciences and Technology Islamabad

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Author
MUHAMMAD ASAD
00000119210

A thesis submitted in partial fulfillment of the requirements for the degree of
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Thesis Supervisor:
DR. USMAN QAMAR

Thesis Supervisor's
Signature:_____

DEPARTMENT OF COMPUTER ENGINEERING COLLEGE OF ELECTRICAL & MECHANICAL ENGINEERING NATIONAL UNIVERSITY OF SCIENCES AND TECHNOLOGY, ISLAMABAD
FEB 2019

In the name of Allah most beneficent most merciful

وَلَا يُحِيطُونَ بِشَيْءٍ مِّنْ عِلْمِهِۦٓ إِلَّا بِمَا شَآءَ

And they
can't encompass any
thing from His
knowledge, but to
extend He wills
[2:255]

Declaration

I certify that this research work titled "*Continuous Blood glucose monitoring, blood glucose level prediction and insulin suggestion for diabetic type 1 patients or artificial pancreas"* is my own work. The work has not been presented elsewhere for assessment. The material that has been used from other sources has been properly acknowledged/referred.

Signature of Student

Muhammad Asad

2018-NUST-Ms-Soft-15

Language Correctness Certificate

This thesis has been read by an English expert and is free of typing, syntax, semantic, grammatical and spelling mistakes. The thesis is also according to the format given by the university.

Signature of Student
Muhammad Asad
Registration Number
00000119210

Signature of Supervisor
Dr. Usman Qamar

Copyright Statement

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Dedicated
to

To my Parents, family, friends and Advisors

Abstract

Diabetes type 1 is a chronic disease which is increasing at an alarming rate throughout the world. Studies reveal that the complications associated with diabetes can be reduced by proper management of the disease by continuously monitoring and forecasting the blood glucose level of patients. In the recent past, numerous researches have been carried out to monitor blood glucose level which suggests the quantity of insulin i.e. artificial pancreas. ***Objective:*** *The prior prediction of blood glucose level is necessary to overcome the lag time for insulin absorption in diabetic type 1 patients.* ***Method:*** *In this research, we use Continuous Glucose Monitoring (CGM) data to predict future blood glucose level using the previous data points. We propose optimal nonlinear autoregressive neural networks. We compared optimal feedforward neural network with optimal nonlinear autoregressive neural networks for blood glucose prediction 15-30 minutes earlier for diabetic type 1 patients. We validate the proposed model with 2 diabetic patients using their 24 hours blood glucose level data.* ***Results:*** *In the prediction horizon (PH) of 15 and 30 minutes, improved results have been shown for minimal inputs for blood glucose level of a particular subject. Root Mean Square Error (RMSE) is used for performance calculation. For optimal feedforward neural network, the RMSE is 0.9984 and 3.78ml/dl and for the optimal nonlinear autoregressive neural network it reduces the RMSE to 0.60 and 1.12 ml/dl for 15 min and 30 min prediction horizon respectively for subject 1. Similarly, for subject 2 the optimal feedforward neural network, RMSE is 1.43 and 3.51ml/dl which is improved using the optimal autoregressive neural network to 0.7911 and 1.6756 ml/dl for 15 min and 30 min prediction horizon, respectively.* ***Validation:*** *We further validate our proposed model using UCI machine learning datasets and it shows improved results on that as well.* ***Conclusion and Future work:*** *The proposed optimal nonlinear autoregressive neural network model performs better than the feedforward neural network model for these time series data. In the future, we intend to investigate a greater collection of patients, and other factors of BGLs.*

Key Words: *CGM (Continuous Glucose Monitoring), Blood glucose prediction, Prediction Horizon (PH), feedforward Artificial Neural Network (FFANN), Nonlinear Autoregressive Neural Network, Diabetes, Machine learning and Automatic Insulin Delivery Advisor (AIDA)*

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CHAPTER 1

INTRODUCTION

With time the number of diabetic type-1 patients is increasing rapidly worldwide. Type 1 diabetic mellitus is one of the types in which no insulin is produced because of the absence of beta-cell. To control an equilibrium glucose-insulin level we need a closed-loop feedback system, including the prediction of glucose level and a controller for insulin infusion using Artificial Pancreas (AP). There are a plethora of factors which plays a vital role in insulin-glucose balance such as meal, time, physical activities, psychological problems, stress or diseases. For this reason, it is very hard to predict an accurate blood-glucose level [6]

Some of the other identified limitations are: sensors' accuracy, while pervading into subcutaneous tissue (SC), the delay in action of insulin, the delay in estimating level of glucose using CGM i.e. Continuous Glucose Monitoring, while measuring the interstitial fluid and, in last, those models are lacking which mainly includes emotional factors and physical activity in other limitations. A reliable model is the one which not only understands the physiology of patient but also resolves some external disturbances i.e. exercise, noise, stress and unannounced meals among other factors.

Machine learning algorithms and their respective applications have become the most popular in predicting BG. This popularity requires an updated review of the establishment of recent trends while modeling the strategies. This is done for both; the APs controllers' next generation and the application which are in development's initial stage, for example, short-term prediction-based BG event alarms and personalized decision systems.

There are many CGM systems available in the market most of which require minimal invasion system. There are always some distortion and a delay of about 10-20 minutes in the systems.

It is always difficult to continuously monitor the blood-glucose and suggest insulin instantly. The insulin requires some time to start its action. It is suggested to predict the blood glucose time beforehand. A glucose predictor improves the continuous glucose monitoring system by prediction blood glucose level in specific PH. Different machine learning techniques are used to predict blood-glucose level by feeding features e.g. continuous blood monitoring, meal, exercise and disease history [1] [4] . A comprehensive investigation of the selected studies leads to identify four major areas i.e. Machine learning techniques (8 studies), MPC (6 studies), PID (2 studies), mixed (6) and others (2 studies). Most frequent techniques are model predictive controllers (6), neural networks (4), fuzzy systems (6) and genetic algorithms (3). ANN is especially recommended for such a nonlinear problem which is hard to solve using other mathematical techniques with good accuracy. For these reasons, neural network techniques have been used in the past for predicting glucose levels [15]

A Neural Network Model (NNM) is a group of neurons simulated on a computer. These are the mathematical models for processing information. NNMs are nonlinear models which adapt their behavior based on inputs (external/internal). Because of the non-linearity and adaptive behavior, NNM is best suited for prediction of glucose level in a particular PH [14]

1.1 Background

Diabetes mellitus, commonly known as diabetes is a metabolic and chronic disease characterized by the absence or low production of insulin associated or not with deficient action of it in the organism. Our body cells need energy to survive and keep working and the insulin is important for making that happen. Insulin is a hormone that allows the cells to use glucose (sugar) for energy from the food that we eat. Diabetes has three different types [3].

1.1.1 Type I diabetes mellitus (T1DM)

Is caused by an autoimmune reaction where the body's defense system attacks the cells that produce insulin. The reason for this is not fully understood. Pancreas, which is the organ responsible for the production of insulin, in people with type I diabetes does not produce any quantity making the person insulin dependent. T1DM develops most commonly among younger people [3].

1.1.2 Type II diabetes mellitus (T2DM)

There is a deficit in the production of insulin and resistance to it, which means that the body requires a larger quantity for the same amount of glucose. This is the most common type of diabetes representing 90% of diabetic people worldwide [3].

1.1.3 Gestational diabetes

During pregnancy women who develop a resistance to insulin and consequent high blood glucose are considered to have gestational diabetes. It is suspected that hormones produced by the placenta are responsible for the block of the action of the insulin. After the birth this type of diabetes disappear. Nonetheless, the baby has a higher lifetime risk of obesity and developing T2DM [4].

Nowadays, the diabetes diagnosis is made through blood tests, which involve drawing blood at a health care facility and then send the sample to a laboratory for analysis for better accuracy when compared with traditional glucose measuring devices like finger-stick devices. There are three tests that can be made to make a proper diagnosis which is the following:

- A1C test,
- Fasting Plasma Glucose (FPG)
- Oral Glucose Tolerance Test (OGTT) [3]

1.1.4 Complications

There are symptoms associated with the glucose level on the blood. A person is on a hypoglycemia state when the glucose level is below 70 mg/dl and if it is ignored it can lead to unconsciousness, permanent brain damage or death. If it is above 200 mg/dl two hours after eating or greater than 126 mg/dL when fasting, the subject is considered to be in a hyperglycemia state, which can conduct to cardiovascular disease, blindness, kidney failure or damage, nerve damage, etc. Taking into consideration all problems associated with diabetes, it is considered a serious health problem that should be treated to prevent further body damage.

1.2 Motivation

Today's lifestyle is full of advantages but also filled with disadvantages. Due to the improvement of the living life, changes in diet, less sport and other factors, the global incidence of diabetes is increasing rapidly. Regarding the costs of treating diabetes complications, it was proven that it costs more than 2 times the cost of controlling the blood glucose level. Many people already consider it the 21st century disease. World Health Organization2 classified diabetes as one of the 10 top causes of death between the year 2000 and 2012. In 2013, 382 million people worldwide had diabetes. By the year 2035 it is expected that 592 million people will be living with this disease, which corresponds to an increase of 55% [2] and it is expected that in 2030 diabetes will be the 7th leading cause of death. Since that there is still no cure for diabetes and people who are or will be suffering from this pathology need to control it in order to prevent health complications, it is essential to create systems, devices, etc. that helps them in their daily life [5].

1.3 Objective and Contribution

Diabetes type 1 is a chronic disease which is increasing at an alarming rate throughout the world. Studies reveal that the complications associated with diabetes can be reduced by proper management of the disease by continuously monitoring and forecasting the blood glucose level of patients. In the recent past, numerous researches have been carried out to monitor blood glucose level which suggests the quantity of insulin i.e. artificial pancreas. The prior prediction of blood glucose level is necessary to overcome the lag time for insulin absorption in diabetic type 1 patients. In this research, we use Continuous Glucose Monitoring (CGM) data to predict future blood glucose level using the previous data points. We propose optimal nonlinear autoregressive neural networks. We compared optimal feedforward neural network with optimal nonlinear autoregressive neural networks for blood glucose prediction 15-30 minutes earlier for diabetic type 1 patients. We validate the proposed model with 2 virtual subjects using their 24 hours blood glucose level data. These two case studies have been compiled from AIDA i.e. the freeware mathematical diabetes simulator.

1.4 Outline

The rest of the paper is organized as follows: In Section 2 presents related work, section 3 contains the model/method and performance of BGL prediction, while section 4 illustrates the results and analysis, and lastly, the paper is concluded in section 5.

1.5 Summary

In this chapter, diabetic type 1 disease, its management and better techniques are proposed for glucose-insulin level using closed-loop feedback system, including the prediction of glucose level and a controller for insulin infusion using Artificial Pancreas (AP). All the factors which play a vital role in insulin-glucose balance such as meal, time, physical activities, psychological problems, stress or diseases. For this reason, it is very hard to predict an accurate blood-glucose level [6]

Some of the other identified limitations are: sensors' accuracy, exercise, noise, stress and unannounced meals among other factors.

Machine learning algorithms and their respective applications have become the most popular in predicting BG. This popularity requires an updated review of the establishment of recent trends while modeling the strategies. This is done for both; the APs controllers' next generation and the application which are in development's initial stage, for example, short-term prediction-based BG event alarms and personalized decision systems.

A comprehensive investigation of the selected studies leads to identify four major areas i.e. Machine learning techniques (8 studies), MPC (6 studies), PID (2 studies), mixed (6) and others (2 studies). Most frequent techniques are model predictive controllers (6), neural networks (4), fuzzy systems (6) and genetic algorithms (3). ANN is especially recommended for such a nonlinear problem which is hard to solve using other mathematical techniques with good accuracy. For these reasons, we used neural network techniques for predicting glucose levels [15]

CHAPTER 2

LITERATURE REVIEW

In this research work, we have conducted two literature reviews. First one on glucose-insulin regulation or artificial pancreas (AP) and second one is on blood glucose level prediction. The first literature review is for overall Artificial Pancreas (AP), which includes blood glucose level prediction, estimating insulin and injection of insulin. After conducting first literature review, we restricted our research area to only Blood glucose Level (BGL) prediction and conducted a second literature review for only prior blood glucose level prediction. Both the literature reviews, its summarizations and facts and figures are given below.

2.1 Glucose-insulin regulation Literature review

The scope of this review is restricted to journal publications found between 2015 and 2018. The main search criterion was blood glucose monitoring and insulin suggestion or artificial pancreas.

2.1.1.1 Review Protocol

Development of a review protocol comprises 4 discrete steps namely: inclusion and exclusion criteria, search process, quality assessment, and data extraction and synthesis as recommended by Kitchenham [65] for SLR.

2.1.1.2 Inclusion and Exclusion Criteria

Only journals published from 2015 to 2018 are considered for inclusion. Parameters defined for inclusion criteria are a) Continuous blood glucose monitoring and insulin suggestion for diabetic type 1 patients. The dataset (real and virtual), Model used, the accuracy and performance and future work for further research b) Selected research work must belong to these databases: IEEE, SPRINGER and ELSEVIER. c) Included research work must be

results oriented. In comparison to inclusion criteria, exclusion criteria eliminate researches published before 2015 along with those researches with weak validation methods.

2.1.1.3 Search Process

This process is based on search terms which are defined in. The resulting number of researches were filtered from 2015-2018. Represents the main steps of our search process (Figure 2.1).

2.1.1.4 Quality Assessment Checklist

This checklist has been developed to validate the selected research in accordance with the guidelines by [65] It comprises of following steps: 1) Include the researches from authenticated databases 2) Include the studies where outcomes are validated in proper way 3) Include the latest studies as much as possible. The aforementioned quality points ensure the reliable outcomes of this SLR.

2.1.1.5 Data Extraction and Photosynthesis

This subsection refers to the selection of relevant information from 24 researches.

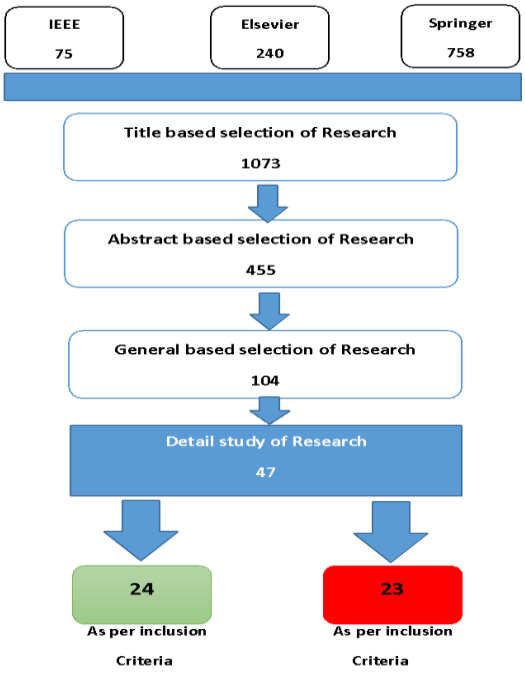

Figure 2.1: Search process

2.2 Models and techniques used in glucose-insulin regulation

This section provides a brief explanation of the highlighted techniques used for continuous blood glucose monitoring and insulin prediction for a diabetic type 1 patients or for the artificial pancreas. The following are techniques and datasets used in the literature for glucose-insulin regulations.

2.2.1.1 ANN

Artificial Neural Networks or Connectionist Systems are vague computing systems. These systems used biological neural networks which are based on brains of animals. Such systems usually learn how to perform any tasks by analyzing examples instead of being programmed in accordance with rules of the specific task [61]. More detail discussion is provided in next section.

2.2.1.2 MPC

MPC is responsible for applying explicit constraints on the insulin delivery rate for the calculation of control. Secondly, it is a generic framework which includes the effect of exercise, daily body functions, and meals. Furthermore, it is also capable of possessing many objectives i.e. from Set-Point Tracking which is supposed to be the target, to the zone. A zone can be defined as "control to the range" [46] [52].

2.2.1.2 System Identification

In the first stage the MPC is trained with NN. The NN learning is dependent on the error. Shown in Figure 2.2. The neural networks is shown in Figure 2.3.

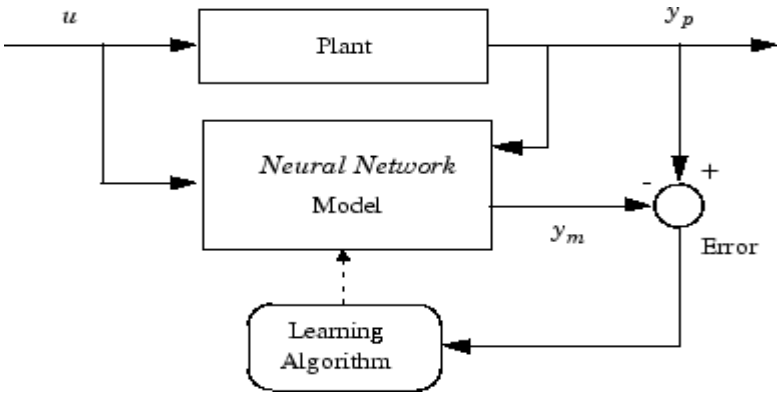

Figure 2.2: System Identification

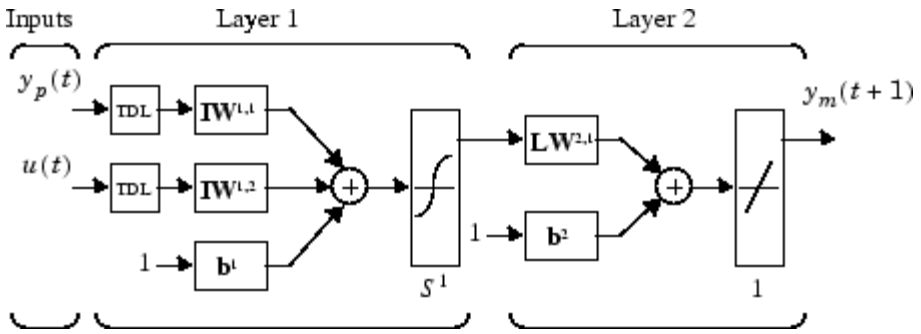

Figure 2.3: Neural Network

2.2.1.2 Predictive Control

The second step is training the complete controller with plant attached. The complete predictive controller is shown in Figure 2.4.

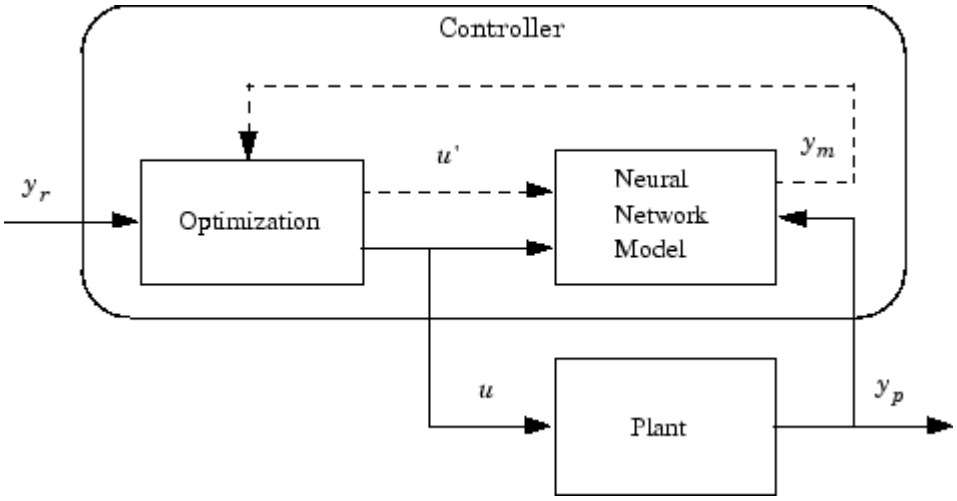

Figure 2.4: Predictive controller

2.2.1.3 PID

PID stands for the Proportional Integral Derivative controller. It is also known as three-term controllers. It basically works on a feedback mechanism of the control loop and this is being used on a large scale in industries' control systems. Moreover, it is also used by many other applications which require continuous modulated control. The PID controller is responsible for continuously calculating error value e (t). This error value is actually, a difference between a measured PV i.e. Process Variable and a desired SpP i.e. SetPoint. Later, it applies correction in accordance with the derivative, integral and proportional terms. These terms are denoted by D, I and P respectively [62].

2.2.1.4 Fuzzy Systems

Fuzzy systems work with a many-valued logic which owns truth values of the variables. These values can be any real number from range 0 to 1. It is usually supposed to handle partial truth concept. This concept is that the truth value may lie between completely false and the completely true. In Boolean logic, by contrast, the variables' truth values can only be the integer values either 0 or 1 [51] [54]

2.2.1.5 Genetic Algorithms

Genetic algorithm is basically a method for solving both unconstrained as well as constrained optimization problems. Such problems are based on usually those selections which are being made naturally, particularly, a process which helps in driving biological evolution. Genetic algorithm repeatedly helps in modifying a population of any of individual solutions [52] [58]

2.2.1.6 Optimization

Optimization is basically about finding the minimum values of the mathematical functions. It can be used for the evaluation of tradeoffs in design, for assessing the control systems and for finding the patterns in data. Optimization problem usually works in the sequence of few steps i.e. first reducing the problem to simple problem then adding again the complexity in the gradual period and, in last, each newly made problem is solved in turn and its solution is used by the next problem as guidance [52]

2.2.1.7 Real Data

One type of data used is "Real Data". Real data is the data which is gathered from the real world instead of generating it by oneself, it is collected through the real objects. Here, in this study, real data would be the one collected about patients from some actually existed hospital.

2.2.1.8 Virtual Data

Another type of data is “Virtual Data”. Virtual Data, as indicated by the name, does not rely on real objects. It is usually generated through some machine or simulator. Simulators, generally, used for generating virtual subjects in this study are UVA/Padova Simulator and AIDA etc. [44] [45]

2.2.1.9 UVA/Padova Simulator

UVA-PADOVA Type 1 Diabetes Simulator works on meal challenges by including a 300 population in subjects of silico i.e. 100 children, 100 adults, and 100 adolescents. A model parameter vector, extracted randomly from an adequate joint parameter distribution, is used to represent each virtual subject [44] [45]

2.2.1.10 AIDA

AIDA is software that helps in simulating various dosage of insulin and adjustments of diet. The AIDA is responsible for creating the learning environments which helps in training and communicating intuitive thinking while dealing with any such adjustments [47]

The following tables summarizes the complete literature review in tables to answer all the research questions mentioned in section 2.3 for future work for my research.

Table 2.1: Keywords

Sr. no	Search term	Operator	IEEE	Elsevier	Springer
1	Continuous glucose monitoring Insulin prediction	AND	2	40	74
2	Artificial pancreas	AND	30	63	340
3	CDSS Insulin prediction	AND	4	7	34
4	Proportional integral derivatives Artificial pancreas	AND	8	75	88
5	Mode predictive controller Artificial pancreas	AND	22	25	52

6	Closed loop systems Artificial pancreas	AND	9	30	170

In the above Table 2.2, it summarizes the number of results for each key word. We used both AND and OR operator to search for the related research papers for this systematic literature review. The above Table 1, is helpful in answering the research questions in section 2.4.

2.3 Glucose-insulin regulation Literature review summary

This section summarizes all the research paper in a Table 2.3. It give a clear idea of the method used, tool which is used to implement the method. Results of each method and what can be done in future work.

Table 2.2: Summarization of all the papers and its future work

Source	***Objective***	***Method***	***Accuracy/Results***	***Future work/challenges***
[42]	Developed a novel scheme for MPC that can be applied to AGC.	pharmacokinetic and dynamics (PBPK/PD)model - MPC	MARD : 10%–14%	NON
[43]	Making it single day centric	Bayesian method	$R^2 = 0.962 \pm 0.027$.	Can be extended to week/month variability
[44]	Individualize model to avoid inter-subject variability	MPC, Nonlinear Time-Variant Mode, Linearized Average Model	--	--
[45]	A rapid model development strategy for new subjects is proposed using	-autoregressive models with exogenous inputs (ARX) -MM	The prediction accuracy new method is comparable to that for subject-	-Try with other algos e.g.Kalman filter. -predicting future glucose l

	the idea of model migration for online glucose prediction		dependent modeling method for some cases.	
[46]	To lower the energy consumption of the AP by reducing controller updates	An event-triggered model predictive controller (MPC)	event-triggered MPC operating a mere 25.88% of the time in comparison with a standard MPC	Extending the event-triggering mechanism to self-triggering methods to enable the CGM to be the 'driver' instead of the controller.
[47]	-Reduce the percentage of time in hypoglycaemia -Improve the percentage of time in euglycemia	run-to-run (R2R) approach	→±30% sensitivity	Can be further improved
[48]	A model to relate subcutaneous insulin delivery and carbohydrate intake to continuous glucose monitoring over 12 weeks	A compartment model comprised of five linear differential equations	38-79% for insulin sensitivity and 27-48% for time-to-peak of insulin action	The model could be implemented in an *in-silico* testing
[49]	Fully automated glycemia controller of T1D in both fasting and postprandial phases	model-free intelligent proportional-integral-derivative (iPID)	iPID detects meals and reacts faster to meal perturbations as compared to a classic PID	improve the computation of the intelligent part of iPID

[50]	For two days	linear differential equations and a simple identification algorithm	--	An effective assessment of how the model impacts the performance of glycemia regulation using model-based algorithms are subject to further investigation.
[51]	Improve the accuracy, applicability, interpretability, and interoperability of these systems (CDSS).	-knowledge-fuzzy inference - ontology reasoning - fuzzy analytical hierarchy process (FAHP)	The resulting system is more accurate, interpretable, dynamic, and interoperable	- Enhancements can be appended to extend its functionality. -other medical domain. -using sentiment analysis for social media
[52]	dual-hormone artificial pancreas (AP)	MPC	--	Further studies using a larger population will be required to validate this result
[53]	For chronic clinical disorders requiring continuous long-term medication	-Gaussian controller with state estimation (SMGC/SE) is proposed, whose gains dynamically vary with respect to the error signal -Kalman filter approach	shows an enhanced performance under various physiological conditions and wide range of disturbances	Real-time implementation
[54]	Optimization: high accuracy and interpretability	- Fuzzy system - Rule Base (RB)	PID data set=84% accuracy BDD data set=99% accuracy	Other optimization methods such as Particle Swarm Optimization (PSO) could be investigated.

		-Reinforcement learning(RL) -Genetic Algorithm(GA)		Future works may take advantage of type-2 fuzzy sets for assessing and improving the performance of the proposed system.
[55]	we propose a novel adaptive fuzzy integral sliding mode control scheme for BGL regulation	-novel adaptive fuzzy integral sliding mode control	Superiority over (PID and MPC) and sliding mode control	-NON -Other Novel algorithms can be tried.
[56]	Individualized models	Novel Linear model : black box and grey box identification	Improved performance	Identification approaches for identifying linear models of real patients by relying on pre-filtered data through the retrofit procedure described in, which can substitute the MA filter.
[57]	Case-based reasoning (CBR)	fuzzy ontology-based CBR	Accuracy =97.67%.	-non
[58]	MPC approach with integral action, called Integral MPC (IMPC), for AP systems is proposed.	Integral MPC (IMPC)	--	Future developments involve the individualization of the weight qv, of the parameter λ and of the time variant set point ysp. The development of an automatic procedure to tune these values is under study.

[59]	model would be required which permits the future evolution of blood glucose to be estimated	-genetic algorithm -minimal model -rPSO - Nelder–Mead algorithm	80% accuracy	-individualized glucose model -enhance the accuracy
[60]	Optimization	5 Machine learning algorithms are compared	Grey wolf optimization gives best results: 96% accuracy	Enhance and cure diabetes by slowly situating the ability of the digestion system. -can be further improved
[61]	Developing an individualized and adjustable algorithm for real-time closed-loop control.	ANN for BGL prediction NN-MPC for insulin dose prediction	-For ANN the RMSD=.074-.083 -For NN-MPC the accuracy is 90% overall	To improve the performance, one can also consider complementing MPC with (Reinforcement learning)RL
[62]	To minimizes the glucose level in small estimate possible time with minimum insulin dose	-Cuckoo Search Algorithm (CSA) -Fuzzy logic -Neural networks -rule base	Takes 80mins to get Normal GL. Where in healthy person it is 60-120min	Further, CSA-FPID may be explored on more rigorous models which include complete dynamics of real diabetic patients.
[63]	To adjust the parameters of a proportional derivative controller using the so-called safety auxiliary feedback element loop	-support fuzzy adaptive system -hybrid PID	Overall: 93.75% - reduction in hypoglycemic episodes has occurred, from 65 to 27 -Hyperclycemia has been reduced from 9.19 to 5.62%	more complex adaptive systems based on some performance index rather than heuristic rules could be applied to refine the tunings of a given controller

	for type 1 diabetic patients			
[64]	-reduce the number of inputs in the training	ANN	RMSE: 15=6.43 ml/dl 30= 7.45	ANN needs to be evaluated in a large amount of patients over a long period

Table 2.3: Tools

Tool	**Number of researches**	**Research identification**
Matlab	11	[42] [43] [46] [53] [54] [55] [56] [57] [60] [62] [63]
Weka	1	[52]
Others	12	[44] [45] [47] [48] [49] [50] [51] [52] [58] [59] [63] [64]

The above Table 2.4 summarizes the tool used in each research papers. It can be helpful in selecting the research tool for our research. Table 3 was useful in answering the research questions in section 2.4.

Table 2.4: Features used

Feature	**No. researches**	**Research identification**
GCM	3	[46] [48] [50]
Insulin	22	[42] [43] [44] [45] [45] [46] [48] [49] [50] [52] [52] [54] [55] [56] [57] [58] [59] [60] [61] [62] [62] [64]
Carbohydrate	19	[42] [43] [44] [45] [45] [46] [48] [49] [50] [52] [52] [55] [56] [58] [59] [60] [61] [62] [64]
Food intake	6	[50] [55] [59] [60] [61] [64]
Exercise	17	[42] [43] [45] [46] [48] [49] [50] [52] [52] [55] [58] [59] [60] [61] [62] [62] [64]
Disease	16	[42] [45] [48] [50] [51] [52] [54] [55] [57] [58] [59] [60] [61] [62] [62] [64]

The above Table 2.5 summarizes the features used in each paper. It gives a better idea, which feature is used in a particular paper. Table 4 was useful in answering the research questions in section 2.4.

Table 2.5: Key Terms in Papers

Key terms	No. researches	Research identification
CGM	17	[42] [44] [45] [45] [46] [48] [49] [50] [52] [55] [56] [58] [59] [60] [61] [62] [64]
MPC	14	[42] [44] [45] [46] [49] [52] [55] [56] [58] [60] [61] [62] [62] [64]
T1DM	11	[42] [43] [45] [45] [46] [49] [50] [55] [56] [61] [62]
AP	12	[44] [45] [46] [48] [50] [51] [52] [52] [54] [55] [56] [59]
CDSS	02	[51] [57]
Closed loop systems	01	[55]
PID	02	[49] [62]

The above Table 2.6 summarizes all the keywords used in the papers in a table form. It is helpful in answering the research questions in section 2.4.

Table 2.6: Methods used in each paper

Sr.no	Methods	Number of research	Research identification
1	MPC	6	[42] [44] [45] [52] [58] [61]
2	Bayesian method	1	[43]
3	ARX	1	[45]
4	Run-to-run(R2R)	1	[46]
5	Compartmental model	1	[48]
6	PID	2	[49] [62]
7	Fuzzy systems	6	[51] [54] [55] [57] [62] [62]
8	Ontology reasoning	2	[51] [57]
9	Reinforcement learning	1	[52]
10	Genetic Ago(GA)	3	[52] [59] [60]
11	ANN	3	[61] [62] [65]
12	Other	5	[50] [52] [56] [59] [60]

The above Table 2.7 summarizes all the methods used in the selected research papers for glucose insulin regulation or blood glucose level prediction. Similarly, the following Table 7 gives an overview of datasets used in the selected research papers.

Table 2.7: Real and virtual dataset used

Status	Number	Research identification	availability
Real dataset	06	[48] [51] [54] [57] [59] [65]	0
Virtual dataset	15	[42] [43] [44] [45] [46] [49] [52] [52] [55] [56] [58] [60] [61] [62] [64]	1
Other	3	[45] [50] [62]	0

The above Table 2.8 gives a clear idea of the availability of datasets for diabetic patients. Table 7 was useful in answering the research questions in section 2.4.

2.4 Research Questions

This section described the research questions made for this systematic literature review. The following are the research questions.

Research Question 1: What are the main issues and possible solutions related to artificial pancreas modeling reported in researches from 2015 to 2018?

Research Question 2: Which are the most frequent machine learning techniques used for blood glucose level prediction?

Research Question 3: What are other techniques used for Artificial pancreas (AP)?

Research Question 4: What are the significant tools available for the modeling of Artificial Pancreases (AP)?

Research Question 5: Is the AP/insulin-glucose regulator mature enough to be used as real-time devices?

Research Question 6: What is the relation between the accuracy and prediction horizon?

2.4.1 Answers to research questions.

This section answers all the research questions. Based on these research questions answers we conducted a second literature review only on blood glucose level prediction. The following are answers to the research questions.

Answer of Research Question 1: One of the main issues is the availability of data set. As shown in Table 2.7, no data set is available. Anyone who wants to do research no diabetic patients, he/she has to generate his own dataset. The second problem is, recording all the

features. As seen in, none of the research work has used all the features which affect blood glucose level. It has a huge impact on results.

A single universal dataset with all the features should be created for research purpose with the collaboration of all the researchers worldwide and should be publicly available for research purpose.

Answer of Research Question 2: As shown in Table 2.5 and Table 2.6, most frequent techniques are model predictive controllers (6), neural networks (4), fuzzy systems (6) and genetic algorithms (3).

Answer of Research Question 3: Table 2.5 and Table 2.6 illustrates that other techniques used are MPC (6), PIC (2) and others (7). Some of the researches have used multiple methods.

Answer of Research Question 4: As shown in Table 3, the tool which is mostly used is Matlab (18). It has all the required libraries which can easily be utilized.

Answer of Research Question 5: From Table 2.2**.** Results and future work, it can be illustrated that it is not mature enough to be used as a completely autonomous system. Because, there is a lot of variabilities; in individual, environment, activities, and diseases etc. Even for the individualized system, once have to monitor some features of the system.

Answer of Research Question 6: Table 2.2 Illustrates that accuracy and prediction horizon have inverse relates. If we increase the prediction horizon, the accuracy decreases. On another hand, when we decrease the prediction horizon, the accuracy increases.

Based on the above literature review and research questions, we conducted another literature review only on blood glucose level prediction.

2.4 Blood glucose level prediction Literature review

Based on Prior blood-glucose level prediction is very useful for management of diabetes therapy. Continuous Glucose Monitoring (CGM) information could be used to predict future blood glucose levels in order to prevent hypoglycemia/ hyperglycemic events and which can be used as input for Artificial Pancreas (AP) for completely autonomous glucose-insulin regulation. In this field, neural network (NN) has proved its efficiency, performance, and reliability. In this part we review different forms of neural networks used on different size of datasets, containing different features, and real and virtual datasets for blood glucose level prediction in a specific prediction horizon (PH). The study provides brief of the methodology

of each study and how it is contributing towards this domain. It also highlights the advantages of the methods used in past and how they can be improved to get high accuracy and precision for blood glucose level prediction. This study is helpful in opening a gateway for new researchers to identify the future need and to carry out their research in that direction. The survey discovers all the neural network techniques used for blood glucose prediction in different prediction horizon (PH).

2.4.1.1 Inclusion-exclusion criteria

2.4.1.2 Publisher

Following are the research publishers considered for this research.

- IEEE
- Elsevier
- Springer
- ACM
- PubMed

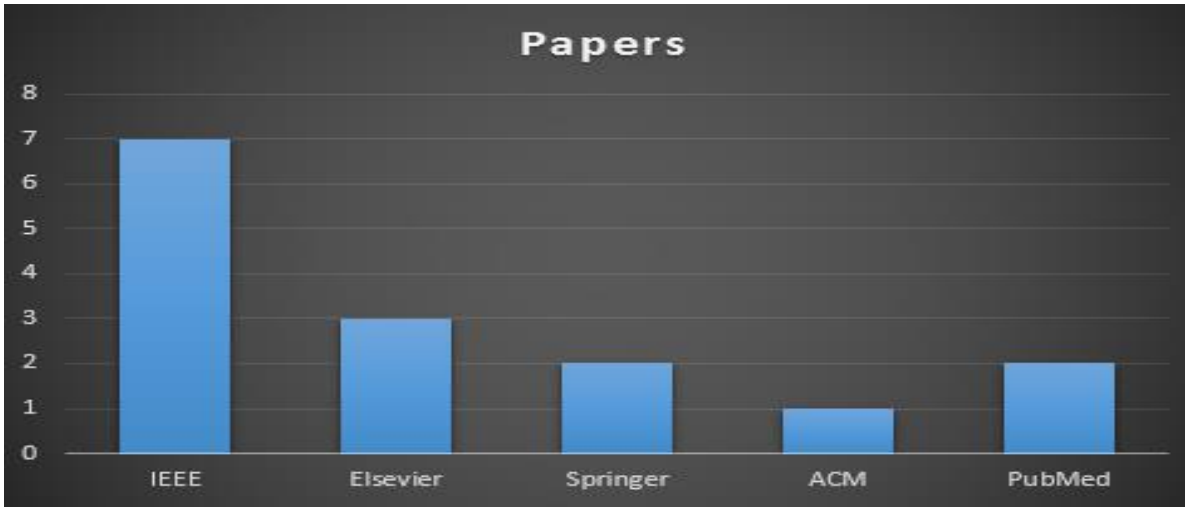

Figure 2.5: Papers Selected from Scientific Databases

2.4.1.3 Subject relevance

I selected research work that is only relevant to my research context. It is related to the title I selected. I rejected irrelevant researches those do not belong to the title.

2.4.1.4 Recent research

Figure 2.6 shows the number of papers selected per year .Most of the papers are from 2011 which is 5 in number.

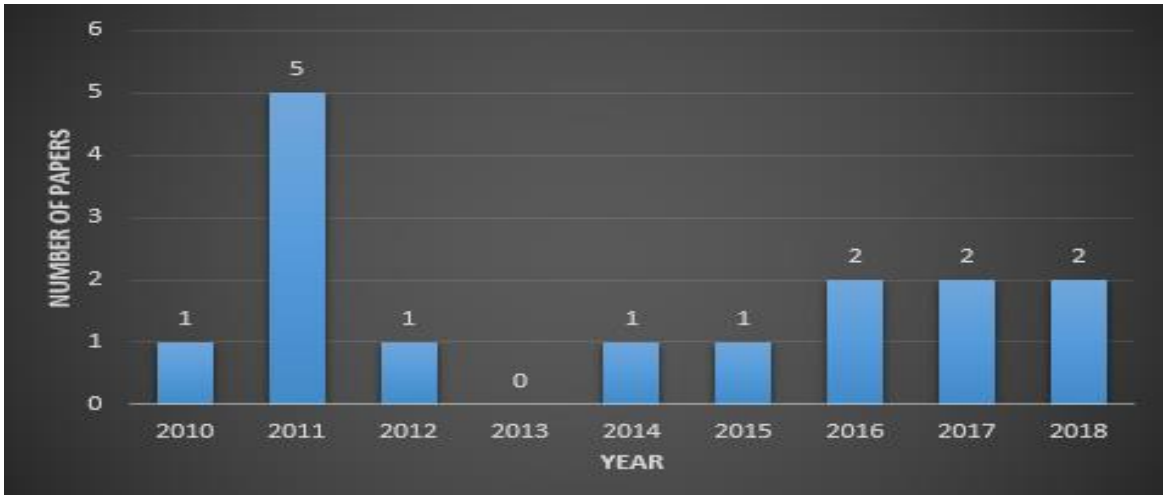

Figure 2.6: Papers selected per the year 2010-18

2.4.1.5 Repetition

Only papers with new and unique research are considered. Those representing same methodology or models are excluded.

2.4.1.6 Quality Assessment

The papers selected form the above databases have certain quality factors that were devised before carrying the research

2.5 Related Work on Neural Networks for BGL prediction

This portion summarizes the studies selected for blood glucose level prediction review. It provides brief of the methodology, data set used and results of each paper.

In this [1] paper, a **Recurrent Neural Network (RNN)** was trained on data, acquired from the CGM device. The trained RNN was used to predict the blood glucose level (BGL) in four different prediction horizons (PH); 15, 30, 45 and 60minutes. The result obtained from the RNN was compared with the Feed Forward Neural Network model (FFNNM). The performance evaluation was done using RMSE, Normalized Prediction Error (NPE) and FIT values. It was concluded that the RNN perform better than FFNN.

In this **[2]** article, a comparative analysis was done between **Multilayer Neural Networks** with hidden layers containing perceptron and decision tree algorithms IDE and J48. The analysis was performed on data obtained from the Pima Indian diabetes mellitus dataset. The analysis was performed using WEKA. It was illustrated that J48 perform better than a multilayer neural network.

In this [3] contribution, a novel calibration model was developed using derivative signals and **Backpropagation of Neural Networks** using a machine learning technique. The technique was applied on spectral data collected from a near-infrared spectrometer in range 2100nm to 2400nm. The performance was evaluated using root mean square error (RMSE), standard error of prediction (SEP), and regression coefficient (R2) terms. The result of the new model was better than previous models.

Tuo et al **[4]** presented a new model for the prediction of blood glucose level. The **Echo State Neural (ESN)** because of it superb results in chaotic time series forecasting. An optimized version of ESN was developed. The optimization was performed using leakage integral neurons and ridge regression learning algorithm. The performance evaluation was done using root mean square error (RMSE), Time gain (TG) and the Continuous glucose-error grid analysis (CG-EGA). The RMSE was less compared to Extreme learning Machine and Back Propagation algorithm under identical conditions. The results illustrated that ESN is more feasible and have high accuracy compared to other models in the experiment.

In this **[5]** paper, **Artificial Neural Network (ANN)** was used for precise blood glucose level (BGL) prediction 15 minutes in advance for diabetes mellitus. Real data from 12 patients by CGM to train the ANN. The performance was evaluated for each of the patient using Root Mean Square Error (RMSE), Sum of Squares of the Glucose Prediction Error SSGPE and the average of the Relative Error (e). The results illustrate that the model can be used to easily identify the hyperglycemia or hypoglycemia in a diabetic patient in 15 minutes horizon.

Bamgbose et al **[6]** presented a closed loop integrated control system is developed to control the glucose-insulin level. The main purpose was to develop a real-time control system for diabetic Type 1 patients. A neural network (NN) was used to predict the amount of glucose using input features. The output of this neural network was used as input of the proportional integral controller (PIC). AIDA, a free diabetic simulator was used to generate the desired data. The performance was evaluated using the root mean square error (RMS). For future

work, the same system can be implemented for data variables including stress and exercise variables. The results of the system can be improved using optimization techniques.

In this **[7]** article, the **Neural Network model** is combined with a **First-order polynomial extrapolation algorithm**. This combination gave both the linear and non-linear components of the glucose regulatory system. The purpose of the system is to develop an algorithm for short-time and considering meal information. The method was applied on 20 simulated and 9 real Abbott FreeStyle Navigator datasets. The result was compared with the neural network. The result illustrated better performance for the new proposed model.

Georga et al **[8]** combined **Extreme Learning Machine (ELM)** with feed-forward neural networks (FFNN) for training the only hidden layer of the FFNN. The model was applied on a large dataset of real clinical data of type 1 patients. The PH was 30 minutes. High accuracy of ELM and its fast learning capability compelled the researcher to use it for blood glucose level prediction (GBLP). As the continuous blood glucose data are sequential, an online sequential ELM kernels (KOS-ELM) was motivated. This paper used glucose, carbohydrates, insulin, and exercise variables. The results showed that the proposed model performed better than the previous models.

Ali et al [11] proposed a novel **Artificial Neural Networks** for continuous blood glucose level prediction of type 1 diabetes mellitus patients. The data was collected from 13 patients for training and testing. Four different prediction horizon was considered; 15, 30, 45 and 60 minutes. The results illustrate an adaptive, high-performance real-time implementation. The main contribution of this research is to reduce the number of inputs in the training and an optimal number of neuron in the hidden layer while training for better results. This research work presented better results than any previous work done till now. The further system can be evaluated for a large number of patients.

In this [12] article, a novel **Wavelet Neural Network** has been proposed. The tuning of WNN is done using fuzzy C-mean (FCM) model which used novel similarity feature. The feasibility is checked via a real-world problem such as blood glucose level prediction. The performance is measured using a mathematics measure; Root Means Square Error (RMSE). The proposed model has improved the accuracy to 100% comparing to the previous models which were 87%.

Zecchin et al **[13]** contributed a novel **Jump NN architecture** is used for short-time with PH (prediction horizon) of 30minutes. The algorithm is tuned on previous data and tested on the rest of the data. The results are compared with the other NN network techniques used, using RMSE, TG, and EOSE. This framework has added meal information as well. The system, in general, can be used for other time series and can add physical activity.

In this [14] contribution, a **Feed-forward Neural Network** is proposed for blood glucose level prediction 75 minutes beforehand the required time. This NNM has a different design that suits it best for real-time prediction. For performance measurement, it uses RMSE (root mean square error), MAD (mean absolute difference) and CEGA (Clarke Error Grid Analysis). The only issue in this experiment is the overestimation of hypoglycemic extremes that is because of a smaller number of hypoglycemic events. This method reduces lag time. Further improved n accuracy can help to make individualized models.

In this [15] paper an online glucose prediction system is developed by continuously monitoring the blood glucose level. The prediction is made using Machine learning techniques the **Artificial neural network model (ANNM)**. The input to this neural network model is provided form 2 commercial continuous glucose devices 20min before. Total 25 patients were used using two different BGM systems in real time. The accuracy is illustrated using RMSE. It has taken into account four different PH; 15, 30, 45 and 60 minutes. The results showed that the proposed model has more accurate results than previous ARM model. The proposed model has no delay as well.

Table 2.8: Feature sets used in researches

Authors/Ref	**Year**	**Features**
Bamgbose et al [6]	2017	Weight(wt) renal threshold of glucose(rtg) creatinine clearance rate(ccr) hepatic insulin sensitivity(sh) peripheral insulin sensitivity(sp) initial plasma insulin level(pb) initial blood glucose level(g0) sampling time(ts)

		Sampled blood glucose levels: g1, g2, g3, g4, g5 carbohydrate intake: m1, m1t, m2, m2t, m3, m3t Infusion boluses by the insulin pump u1, u2, u3, and u4.
Robertson et al [7]	2011	Time(h) BGL (mmol/L) Meal (grams of carbohydrates) Short-acting insulin Long-acting insulin Input vectors Current time step Prediction
Zecchin et al [8]	2012	Meals Carbohydrate intake
Georga et al [10]	2015	Age BMI Descriptive Statistics of Glucose Dataset Average s.c. Glucose Concentration (mg/dl) Hypoglycemic Values Hyperglycemic Values physical activity monitor food intake (i.e. type of food, serving sizes and time) Insulin regime (i.e. type of insulin, injection dosage and time) Carbohydrates
Ali et al [11]	2018	blood glucose level
Ong et al [12]	2016	Glucose level acting insulin Food intake Exercise Stress
Zecchin et al [13]	2014	CGM Data

Pappada et al [14]	2011	insulin bolus Glucose value Meal intake lifestyle emotional factors

The above Table 2.9, illustrates all the features used in each paper. Most prominent are glucose level, meal, and weight. But none of the paper has used all the required features which are affecting blood glucose level. For a completely autonomous and accurate artificial pancreas, we need all the features affecting blood glucose level.

2.6 BGL prediction literature review summary

The following table summarizes all the research paper in a table. It give a clear idea of the method used, tool which is used to implement the method. Results of each method and what can be done in future work.

Table 2.9: Summarization of all the research paper

source	***Method***	***Tool***	***RMSE***	***Contribution***	***Future work***
[1]	RNN:	MATLAB	15min:0.14 30min:0.42 45min:0.84 60min: 1.32	Better results than the NN model and SVR model	Can be improved for 60 minutes
[2]	--	Weka	--	The accuracy of GL prediction improved	Accuracy Can be further improved by optimization
[3]	--	MATLAB	--	Improved	Can be further improved by applying more complex machine learning models
[4]	OESN	MATLAB	Average (mg/dL) ESN=16.32 OESN=15.9 ELN=19.64 BP=28.77	excellent performance in chaotic time series forecasting	It can be further improved by applying different optimization techniques
[5]	Optimizatio (ANN)	MATLAB	6.43 (mg/dL)	--	Can be used on large data set for more than 12 patients for better accuracy

[6]	NN	MAT LAB	5.9 mg/dL	integrated control system	-Implement the same system with stress, exercise variables included. -Can be improved further with the optimized approach
[7]	Elman recurrent (ANNs)	MAT LAB	0.15±0.04 mmol/L	--	-broader range of AIDA cases -real-patient data -factors influencing BGLs.
[8]	NN and a first-order polynomial extrapolation	MAT LAB	NN-LPA=9 Mg/dl NNPG=11.1 Mg/dl AR(1)=20.4 Mg/dl	Meal details	-information on time and dosage of insulin injections -optimized
[9]	NN	MAT LAB	NN-LPA: 9.7 NNPG: 13.4 Poly(1):19.4 Mg/dl	-short-term -meal infor	More features can be added -optimization can be applied
[10]	-ELM -FFNN	MAT LAB	ELM: 9.3 mg/dL K-ELM: 6.1 mg/dL OS-ELM: 13.3 mg/dL KOS-ELM: 8.5 mg/dL	-online -large data processing	further evaluation can be done
[11]	ANN	MAT LAB	15=6.43 mg/dL 30=7.45 mg/dL 45=8.13 mg/dL 60=9.03 mg/dL	-reduce the number of inputs in the training -optimal number of neuron in hidden layer while training	-ANN needs to be evaluated in a large amount of patients over a long period -Use NARX
[12]	- WNN -DOS-FCM	MAT LAB	RMSE= .6465 mmol/dl	Accuracy improvement	DOS-FCM can be used for optimizing the weights duding learning of WNN
[13]	jump NN	MAT LAB	17.6mg/dl	-Meal info -online -short-time	-Can be used for other time series - physical activity feature can be added

[14]	feed-forward neural network model (NNM)	C#	43.9mg/dL	-to reduce lag time	-for individualized model -autonomous system by further improvement -overestimation of hypoglycemia
[15]	artificial neural network model (NNM)	MAT LAB	15min=10 mg/dL 30min=18 mg/dL 45min=27 mg/dL	-Improved accuracy -online glucose prediction	sudden changes are not detected (intrinsic/extrinsic) - different sampling rates and different noise variances

Table 2.10, summarizes the data set used for these 15 research papers. There is both real and virtual dataset used but the problem is none of that used dataset is publically available for further research work. The only one available with 768 subjects have not the required features Equation 2.1 for further work. The virtual dataset can be generated but those are not as reliable for testing with real patients. The sampling rate varies from 5minutes to 90minutes. The prediction horizon varies from 15minutes to 60minutes.

Table 2.11 Dataset used in the research papers

Source	***Data set***	***Availability***	***Samples***	***Sample size***	***Prediction horizon(PH)***	***Real /virtual***
[1]	Gaurdian® Real Time CGM system	NO	9patients	every 5 minutes	15, 30, 45, 60 minutes	Real data
[2]	Pima Indian diabetes mellitus data set	YES	768 patients	--	--	--
[3]	spectral data	NO	90 spectra	--	---	--
[4]	Hospital data	NO	8 patients	--	15 min 45 min 60 min	Real data

[5]	Hospital data	NO	14 patients	15min	15min	Real data
[6]	AIDA diabetes simulator	NO	2,100 sample	90 minutes	--	Virtual
[7]	diabetes simulator, AIDA	NO	28 datasets	---	15, 30, 45, and 60 minutes	Virtual
[8]	Real data and UV/Padova data	NO	20 datasets,	--	30min	Real and virtual
[9]	Real and UVa/Padova Type-1 Diabetic Simulator	NO	5 patients	--	30min	Real and virtual
[10]	Clinical data	NO	15 patients	--	30min	Real data
[11]	Freestyle Libre system	NO	13 patients	15min	13,30,40,60 min	Real data
[13]	FP7 EU project “DIAdvisor”	NO	20 patients	5min	30min	Virtual
[14]	(CGMS Gold, Medtronic, Northridge, CA	NO	17 patients	5min	75min	real
[15]	CGM devices	NO	15 patients	5min 1min	15, 30, and 45min	Real

From Table 2.9 and Table 2.11 it is evident that the small datasets, the accuracy is usually low. But when we increase the dataset the complexity increased which is not a desired attribute for real-time diagnosis devices. Similarly, from Table 2.9 and Table 2.11, it shows that when we reduce the features the accuracy reduces but when we increase the number of features the accuracy increases but it produces more complexity. We require a high prediction horizon (PH) but in all the previous work when we increase the prediction horizon time e.g. 60 given in Table 2.1 and Table 2.3. The accuracy decreased terribly. Different techniques have been used to get better results such as automatic neuron optimization [11] and generating larger dataset using AIDA diabetes simulator [7] but still, there are many challenges need be addressed to get an autonomous blood glucose level prediction and insulin delivery for a diabetic type 1 patient.

2.7 Neural Networks

A Neural Network Model (NNM) is a group of neurons simulated on a computer. These are the mathematical models for processing information. NNMs are nonlinear models which adapt their behavior based on inputs (external/internal). Because of the non-linearity and adaptive behavior, NNM is best suited for prediction of glucose level in a particular PH [14].

There are two main types of neural networks

- Feed-forward NN
- Feed-back NN

2.7.1 Feed-forward networks

Feed-forward Artificial Neural Networks (ANN) moves in a forward direction from input towards output, it is also called a bottom-up approach. The data is given at the input which process to the hidden layer and to the output layer as Shown in Figure 2.7. Feed-forward ANNs (Figure 2.7) allow signals to travel one way only; from input to output. They are not considered good for time series problem [90].

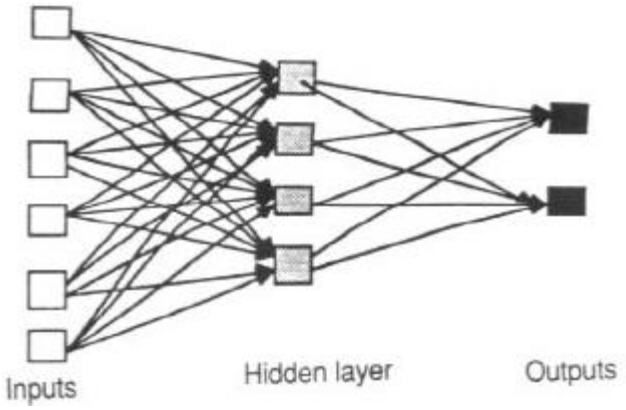

Figure 2.7: Feed-forward neural network [90]

2.6.1 Feedback networks

In feedback neural networks in the input is given at the output. It is also called out-star/fan-out. The data is given at the output with is then processed in the hidden layer and move towards the inputs. It has a very useful utility in recurrent neural networks, when the network is moving in both direction to get the best solution. Learning laws are Hebbian law and Delta law [90].

2.6.2 Network layers

Artificial neural network mainly consists of three layers, first layer is input layer, which is connected to a second layer also called a hidden layer and finally an output later [90].

- Input layer: The raw data that is input to the system
- Hidden layer: Function of this layer is based on the hidden neurons and the weight coming to his layer.
- Output layer: The result of the layer depends on the hidden layer and the weights

This is the simplest type of a neural network which is constructed only using three layers. The weight between the layers and the neuron determines the output of a neural network [90].

2.6.3 Perceptron

Perceptron refers to the basic unit of human nervous system. According to the Rosenbaltt;s perceptron model is a combination of weight, rate of change, error and inputs [90].

2.6.4 The Learning Process

Learning of a network is meant to memorize certain pattern in a data by updating the weights of a network. There are many different law for learning.

- Hebbian Law
- Delta Law
- Error correlation Law
- Reinforcement learning

2.7.6 Transfer Function

The behavior of an Artificial Neural Networks mainly depends on two things, firstly the weight and secondly the transfer function which is also called an input-output function. A transfer function falls under any of the following three categories.

- **linear (or ramp)**
- **threshold**
- **sigmoid**

2.7.1.1 Linear function

Linear function is also called a ramp because it graphs is a straight line moving in a z direction. The direction of the line is controlled by the weight.

2.7.1.2 Threshold

Threshold is also called a binary function. In this case the units, the output is set at one of two levels, depending on whether the total input is greater than or less than some threshold value.

2.7.1.3 Sigmoid

For sigmoid units, the output varies continuously but not linearly as the input changes. Sigmoid units bear a greater resemblance to real neurons than do linear or threshold units, but all three must be considered rough approximations [90]. In our research work we are using sigmoid function as a transfer function.

2.6.8 The Back-Propagation Algorithm

For achieving minimum error Back-Propagation (BP) Algorithms are very useful. To reduce the error between actual output and desired output, we must back propagate the error and update the weights of the network in such a way to achieve minimum possible error. The neural network compute the derivate of the error for each weight inputs. It calculate the amount of error for each weight value [90].

2.8Neural Networks in Practice

Artificial neural network has been broadly applied to real world problem in different industries. It has a very acceptable success rate for medical applications as well. As it very successful in many industries and processes, ANN is very well suited for forecasting and prediction in the following areas. E.g.

- Sales forecasting for different companies
- Control processes
- Customer management
- Validating data
- Cost management
- Medical diagnostics

2.9 Neural networks in diabetic treatment

Neural network have wide range of application in the field of health informatics. In last decade it has been widely used for the treatment of diabetes. Neural network has proved its efficiency in the management of diabetic treatment. For example, in diagnosing diabetes, selecting proper features, proper amount of insulin suggestion and for Artificial Pancreases (AP). It is

a great tool for physician. Neural networks are becoming more common for treatment and management of diabetes both type 1 and type 2 [1-15].

2.8.1 Insulin pumps and neural networks

For a diabetic patient, the control of insulin suggestion is of high importance. Neural Networks has played a crucial role in model predictive controller (MPC) to control the quantity of insulin required for a particular patient. Here we want to stress the difference between the insulin therapy and the insulin dosage. The insulin therapy consists of the number of injections, the time of injection, the type(s) of insulin and the insulin dosage. The first is often only a directive and patients can adjust the actual insulin dosage depending on the situation (current glucose level, anticipated level of exercise, anticipated food intake, etc.). This is what is meant by determining the insulin dosage. It can be easily controlled by NNMPC [61] [62] [65].

Table 2.12: Random Literature review

#	Objective	Method	Dataset used	Accuracy/Results
[66]	Diabetes Diagnosis	Novel 5 layers Fuzzy Diabetes Ontology	Pima Indian Diabetes Dataset	91.2 for slightly old, 90.3 for slightly young, 86 for more or less young, 82 for very young, 77.3 for very very young
[67]	Diabetes Diagnosis	Expectation Maximization (EM) algorithm, h-means+ clustering and genetic Algo (GA)	Pima Indian Diabetes Dataset	Found that 35% of the population have Diabetes
[68]	Insulin quantity injection control	Recurrent Neural network	Only 1 patient	NA
[69]	Glucose quantity regulation	RBF Neural Network and NARX non-linear function estimation	Self-made dataset	NA
[70]	Insulin quantity injection control	Neural Network with 10 hidden layers	Raw data set with 25000 samples	NA

[71]	Glucose and insulin injection control	Neural Network	Clinical data	NA
[72]	Short term Glucose value prediction for children	Feed Forward Neural Network, Recurrent Neural Network	Insulin, glucose and food intake data from 4 children	NA
[73]	Glucose level control and insulin injection in blood	Developed their own algorithm	4 blood profiles of a patient with DM type 2	NA
[74]	Glucose level control in ICU patient	Particle Swarm Optimization PSO and Model Predictive Control MPC	Hospital data	100% performance as compared to Yale protocol
[75]	Glucose level and Insulin Delivery control	Model predictive control MPC	UVa/Padova TIDMS data	NA
[76]	Diabetes Diagnosis	Fuzzy, Neural Networks and Case based approach	NA	NA
[77]	Glucose level control	Systematic Literature Review SLR methodology used	Hospital data collection	NA
[78]	Diabetes Diagnosis	Artificial neural networks ANN	456 samples dataset	NA
[79]	Diabetes Diagnosis	Adaptive Neuro Fuzzy inference system, Neural networks, PCA and neural network	Pima Indian woman dataset with age 21 years	73 % for NN, 71% for ANFIS 89% for PCA +ANFIS

				90% for PCA + NN
[80]	Glucose level control in T1DM patient	Model predictive controller design	UVa/Padova TIDMS data	NA
[81]	Anomaly detection in blood Glucose	Hidden Markov Model HMM	2 Datasets used	95%
[82]	Glucose level monitoring and Insulin Infusion rate estimation	ANN and non -linear model predictive control NMPC	UVa simulator dataset	NA
[83]	Recommend insulin rate and Diet prescription	Multiple ML approaches like Expectation Maximization EM and C4.0 Decision Tree	Parc Tauli University hospital Spain. 90 patients	100 % patient support
[84]	Diabetes Diagnosis	Decision Trees, Artificial Neural Networks, Bayesian Classifier	NA	NA
[85]	Diabetes prediction	Decision Trees, CART, C 4.0 Tree etc	George John UCL ML repository	NA
[86]	Glucose monitoring and short term Glucose	Neural Networks	NA	NA

	level Prediction			
[87]	GLM and Insulin infusion rate	Fuzzy logic control	NA	NA
[88]	Glucose level prediction	Model predictive control MPC	UVa simulator data	NA
[89]	Glucose level Prediction	Auto Regressive Model	NA	NA

Table 2.12 is the initial literature review conducted. It has no restriction on time and journals. It was a general review on blood glucose-insulin regulation and glucose level prediction. All the techniques and methods used are mentioned in the above tables.

2.10 Time Series and Glucose level prediction

Throughout life, a diabetic patient has to measure his blood glucose. Since those measurements have a temporal order, we approach the task of predicting the future blood glucose levels as a time series forecasting problem. In time series prediction, the task is to estimate the future value of a target function based on the current and past data samples and can be generalized as shown in Equation 2.2.

$$z\,(t+PH\,) = f(zt, zt-1, zt-2, \ldots, zt-n+1)$$

Equation 2.2

For an observed time series Z with n points, where t is most recent observation, t – n is the oldest one and PH is the prediction horizon, i.e. the number of steps ahead of the actual point, a future value at t + PH can be estimated with a function f. This function is a model that can be used to get an estimated value to $zt+PH$. Several studies have been conducted to create methods to forecast the sugar level with the objective of warning the subject in advance [4] [28][29].

2.11 Summary

After getting through all the techniques and data sets used for glucose-insulin regulation and prior glucose level prediction. There are too many gaps which can be covered e.g. generating a new data set which included complete set of features e.g. exercise, disease of the patients, stress and other activities. Secondly, accuracy of the existing data sets can be increased by applying different machine learning techniques. As Neural Network is widely used for forecasting problems, I have considered it for increasing accuracy by manipulating it in different ways. Finally and more importantly, increasing prediction horizon from 60minutes to 120 minutes with better accuracy.

CHAPTER 3

METHODOLOGY

3.1 Introduction:

Research methodology is the systematic, theoretical analysis of the procedures applied to a field of study. Methodology involves procedures of describing, explaining and predicting phenomena so as to solve a problem; it is the 'how'; the process, or techniques of conducting research.

(Kothari, 2004)

In this chapter, we discussed the proposed optimized method for blood glucose level prediction for each patients. We first used feed-feedforward neural network and then we used non-linear autoregressive neural networks. Both methods involved the following steps

Step-1: Normalization of data

The first step is normalizing the data using the following Equation 3.1.

$$z_i = \frac{x_i - \min(x)}{\max(x) - \min(x)}$$

Equation 3.1: Data normalization

Step-2: Initialization of variables

Hidden and input neurons are assigned 10. Where minimum RMSE is assigned 10^-3mg/dl.

Step-3: Training

For training the Levenberg-Marquardt algorithm has been used, as it is faster than the back-propagation algorithm. The training parameters are: Combination coefficient = 0.1, Gradient weight error = 10^-7, Goal = 10^-5 and Training epochs = 100. ANN inputs are the current measurements G(t) and InNd-1 previous BGLs.

Step-4: Testing

The data has been split into 70% training and 30% testing, the latter has been performed using 'dividend' function ANN.

Step-5: Calculation RMSE

The performance of the proposed model has been measured using RMSE shown in Equation 3.2. As depicted in Table 15 and Table 16, the Mean Square Error (MSE) for case 001 are 0.6060, 1.127, ml/dl for 15 and 30, minutes respectively. Similarly, for case 002 the RMSEs are 0.7911 and 1.6756 ml/dl for 15 and 30 minutes respectively.

$$\mathrm{RMSE} = \sqrt{\frac{1}{n}\sum_{i=1}^{n}(X_i - X?_i)^2}$$

Equation 3.2: Root mean square error

Step-6: Assigning optimized neurons

The model terminates on two conditions, Firstly on minimum error which is 10^-3 and secondly on completed the max iterations. The output is the optimized neurons.

The following sections provide details description of the methodology with the help of flowcharts (Figure 3.1) and diagrams (Figure 3.2).

3.2 Optimized Artificial Neural Network (OANN)

Two objectives are considered for the model of OANN, i.e. 1) ANN optimal structure has been defined automatically and the number of neurons is optimized in each layer and 2) in order to predict perfect glucose in the blood, the proposed ANN is adopted. It is proposed, in order to acquire all previously defined objectives, that there must be a continuous prediction of glucose level in blood for Diabetes of Type 1 using ANN. The core concept for this particular ANN is to analyze previous measures of Input Nodes (InNd) in order to make the prediction for the next node. Furthermore, predicted measures are used usually with the previous node InNd-1 so that forecast about the next value can be acquired and so on. Here, the approach consists of InNd sliding window length and an increment step of sliding as well. As a benefit from activation of non-linearity in hidden and input layer, the prediction of the next values is generally non-linear, incremental and adaptive. The flowchart in Figure 3.1 represents the summarized algorithm for determining optimal ANN structure. In the flowchart, RMSE indicates Root Mean Square Error, InNd indicates the neurons present in the input layer, min_RMSE represents minimal RMSE which is most desired to attempt, Optimal_InNd indicates optimal neurons' number present in the input layer, Max_InNd represents maximum limit of neurons which is allowed in the input layer, similarly,

Max_HidNd represents maximum bound of neurons which is allowed in the hidden layer, HidNd represents the neurons number present in hidden layer and Optimal_HidNd represents that how many optimal neurons are present in hidden layer. An algorithm which is explained in Figure 3.1 helps in determining the Optimal_HidNd and Optimal_InNd. The algorithm, at first, fix the hidden neurons' number (HidNd), then the number of inputs i.e. InNd is increased and with each increment in InNd, RMSE is computed. Later, min_RMSE and RMSE are compared. There are two cases which can make this algorithm stop or quit i.e. if RMSE == Max_HidNd. It is noted that this procedure guarantees the accuracy of the training phase used in the proposed ANN with the minimum of error (RMSE 0), hence, enhancing the accuracy of the test-phase [68].

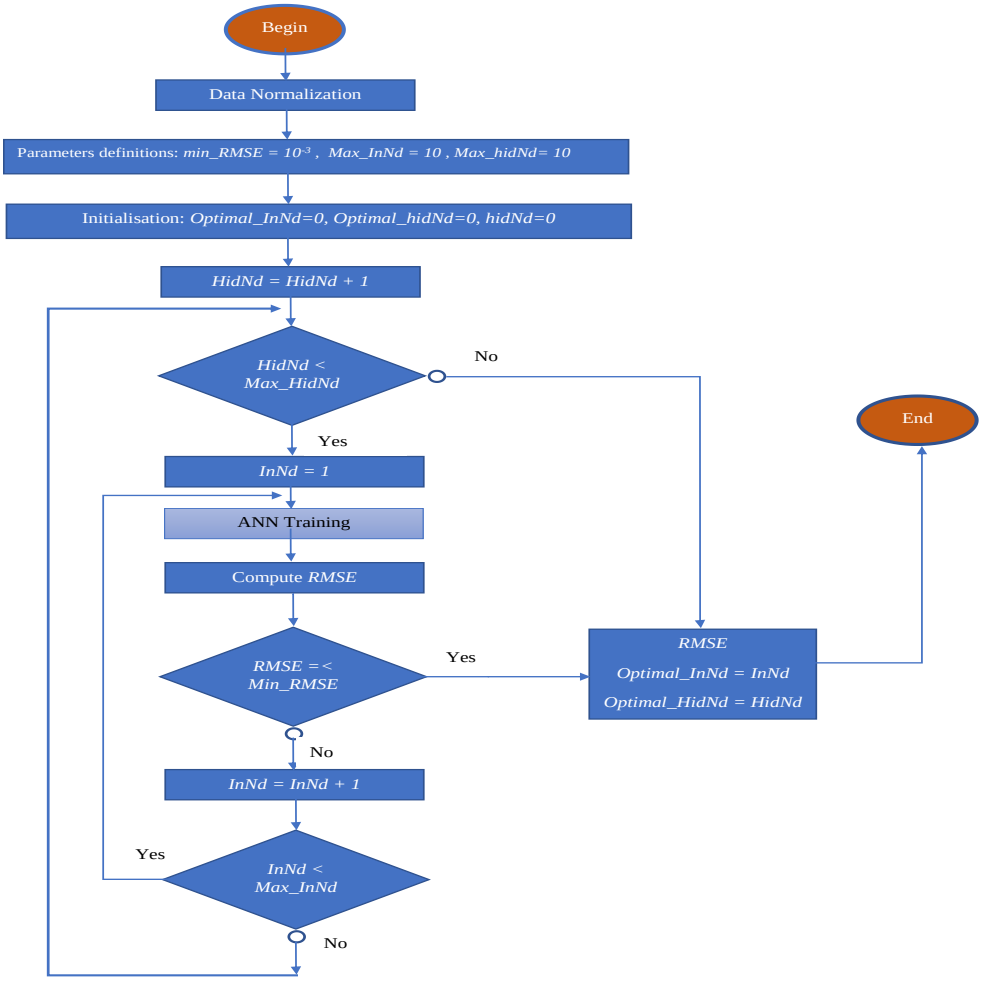

Figure 3.1: Feedforward NN optimization model

3.3 Model prediction for OANN

Prediction model An ANN has three layers, i.e. input, hidden and an output layer. The second layer is responsible for weight assignment, we use the tangent sigmoid transfer function, whereas the third layer has one node for activating the linear function. Every layer has a bias which is generated from its preceding later. The training epochs are dependent on neurons in the input layer (InNd) and in the hidden layer (HidNd). It is achieved through the aforementioned algorithm for OANN to achieve min_RMSE and convergence. The training algorithm of Levenberg- Marquardt is used to randomly initialize and update weights and biases for speedy convergence. Optimal weights are assigned through the back propagation of the error between actual and forecasted [3]. The training parameters are: Combination coefficient = 0.1, Gradient weight error = 10^-7, Goal = 10^-5 and Training epochs = 100. ANN inputs are the current measurements G(t) and InNd-1 previous BGLs. The output layer contains a single neuron which has the projected blood glucose G (t + PH), where PH is predefined, and it can be 15, 30 and 45 mins. For training the Levenberg-Marquardt algorithm [17] [18] [34] [37] has been used, as it is faster than the back-propagation algorithm, The data has been split into 70% training and 30% testing, the latter has been performed using 'dividend' function [37] [18] ANN is shown in Figure 3.2. E. Evaluating Performance The performance of the predictor has been measured using RMSE, where the objective is to obtain a close to zero RMSE relative to the magnitude of projected values. As depicted in Figure 3.1, the Mean Square Error (MSE) for case 001 are 0.99, 3.7, 5.0, 7.3 ml/dl for 15, 30, 45 and 60 minutes respectively. Hence, for case 002 the RMSEs are 1.4, 3.5, and 5, 9.7ml/dl for 15, 30, 45 and 60 minutes respectively.

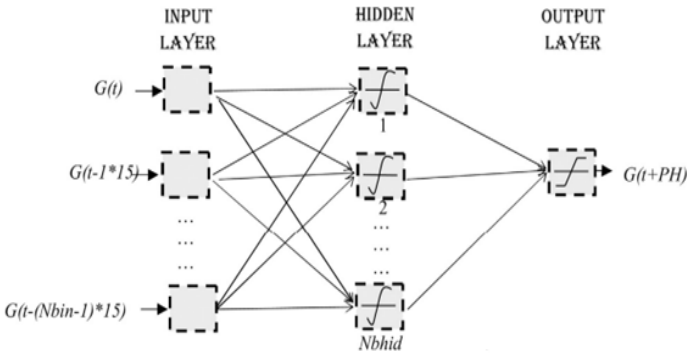

Figure 3.2: Window Model NN

3.4 Optimized nonlinear autoregressive Neural Network (ONARNN)

Nonlinear autoregressive (NAR) neural networks are powerful computational models for modeling and forecasting nonlinear time series [28][29] [30][31]. In this [32] paper, prediction models are developed using NAR and BP neural networks. The NAR neural network is used to predict the dynamic change of wheel diameter and therefore to predict the wheel wear high-speed trains. In this [33] study, the wind speed prediction model is created. Using the one-minute time series, the prediction of the next wind speed is performed with the NAR neural network model. Similarly, NAR networks were used for prediction of water level. In [34] NAR predicts a clearness index that is used to forecast global solar radiations. The NAR model is based on the feedforward multilayer perceptron model with two inputs and one output [35].

We propose a model which creates optimal feedback delay (Optimal_feedD) and optimal hidden neuron (Optimal_Nhid) to give an optimal solution to the problem. As evident from **Figure 3.3.** First, we normalize the data. We initialize the variable, min_RMSE to 10^-3 and Max_feedD and Max_Nhid to 10. The RMSE indicates root mean square error. The algorithm increment feedback delay and optimal neuron. Training is performed for each iteration, RMSE is calculated and optimal feedback delay and optimal neuron are assigned for each subject. The algorithm terminates on two conditions. First, if minimum RMSE is achieved and second, if maximum iteration is completed. If maximum iterations are completed then the minimum RMSE iteration is assigned as the optimal solution [17] [22].

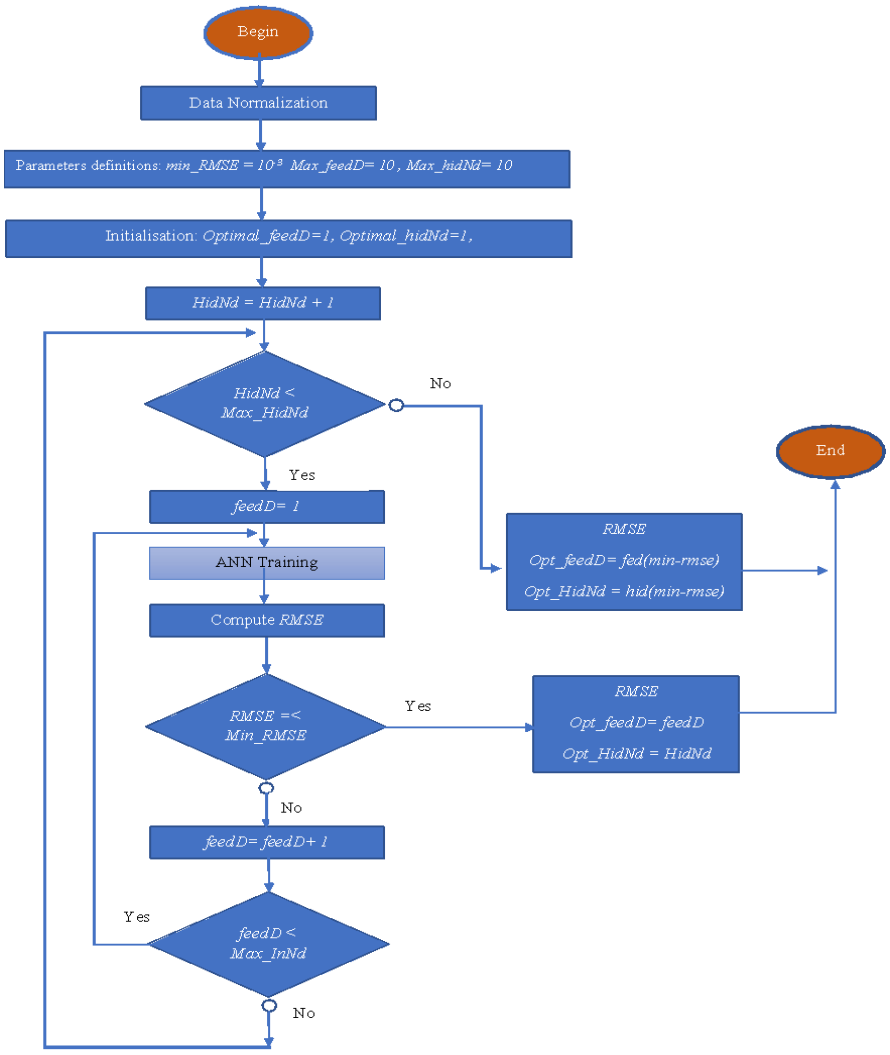

Figure 3.3: Proposed model (Optimized NAR Neural Network)

3.5 Prediction Model for NAR

The purpose of training an ANN is to learn that how an input variable is related to the output BGL for making predictions. The ANN architecture which is developed in this research has been shown in **Figure 3.4**. Nonlinear autoregressive networks can make predictions about time series with the help of feedback input. Input for ANN is CGM data (G(t), G(t-1), ..., G(t-d), where d represents the times tapped delays occur in the input for making future predictions. The NARANN has been designed in such a way that it contains only one hidden layer consisting one ANN output and optimal neurons in hidden layer. In this ANN model, previous inputs and outputs are considered for making future predictions about output value (G*(t+ 1), G*(t+ 2), ...). The relationship between input and output has been represented below in

Equation 4 i.e. Y(*) with the setup of delays. During the training phase, the NARANN works in the form of an open-loop. Once the training with the T1DM patients' data is done, NARANN started to work in form of closed-loop in the phase of testing i.e. prediction phase. The predictions of BGL is being made by ANN with the help of input datasets. Predict series **y(t)** given **d** past values of **y(t)** [28] -[36] .

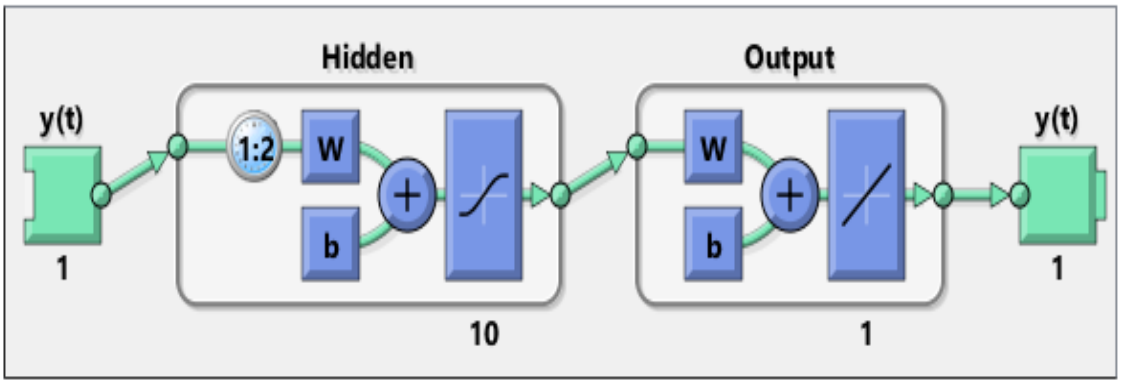

Figure 3.4: Nonlinear autoregressive neural network

$$Y(t) = Y(t-1)\ldots, Y(t-d)$$

Equation 3.3: Prediction using past values

3.6 Evaluating Performance

The performance of the proposed model has been measured using RMSE shown in Equation 3.4.

$$\text{RMSE} = \sqrt{\frac{1}{n}\sum_{i=1}^{n}(X_i - X?_i)^2}$$

Equation 3.4: Root mean square error

3.7 Window Model

Window model takes the previous value and predict the next value. It works like sliding window, taking the current and previous value in consideration for prediction the next value. As shown in the Figure 3.5.

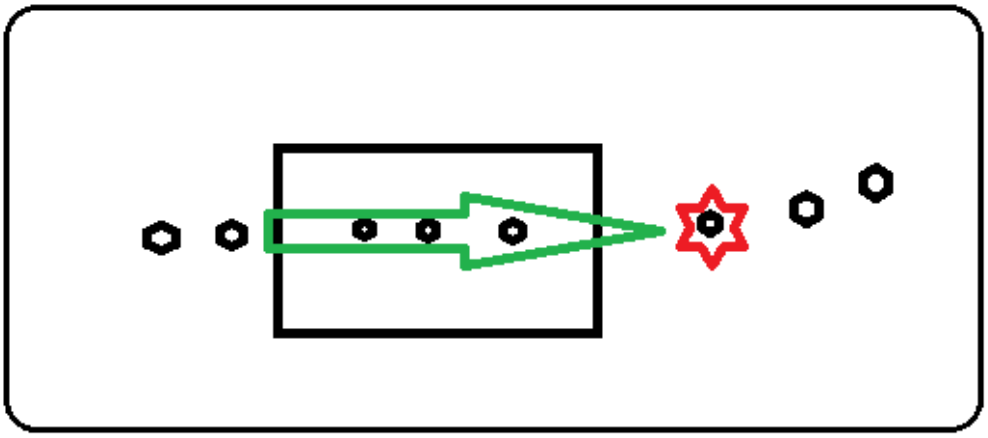

Figure 3.5: Sliding window model

3.8 Dataset Used

We have made use of AIDA which is a free online diabetes simulator in order to generate data in correspondence with BGL information that is present built-in.

Short-term predictions are up to one hour, for those, OANNs have been trained using BGL data of AIDA. The current time step moves incrementally forward across the prediction period, particularly in time-steps of 15 minutes. That is how a trained OANN can, for every time-step can make BGL predictions, in the prediction period. This can be illustrated as a moving window which has the current time-step at its center. The current time-step is preceded by the input vector values, given that the targeted BGL is defined at a defined future interval. Two patients' studies data for 24 hours is extracted from the system. The data of continuous BGL is given in the following two figures (i.e. Figure 3.6 and Figure 3.7) for both the cases [21] [22]

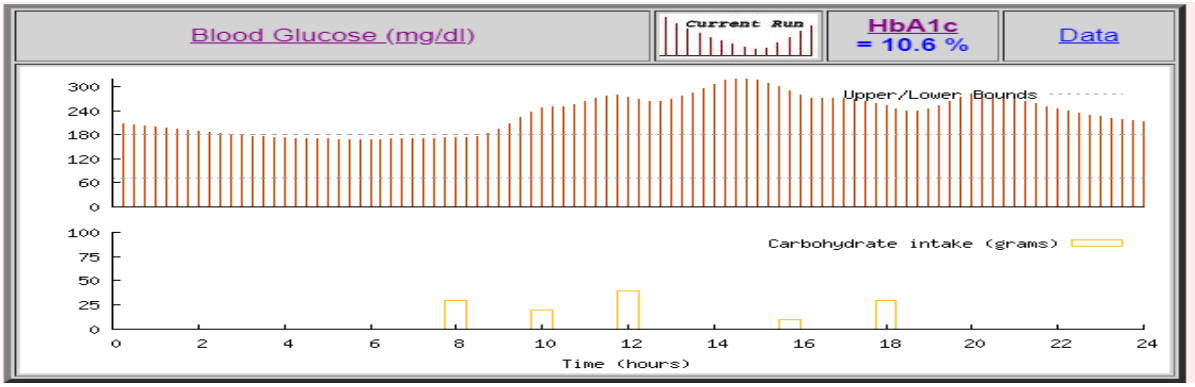

Figure 3.6: Case 001

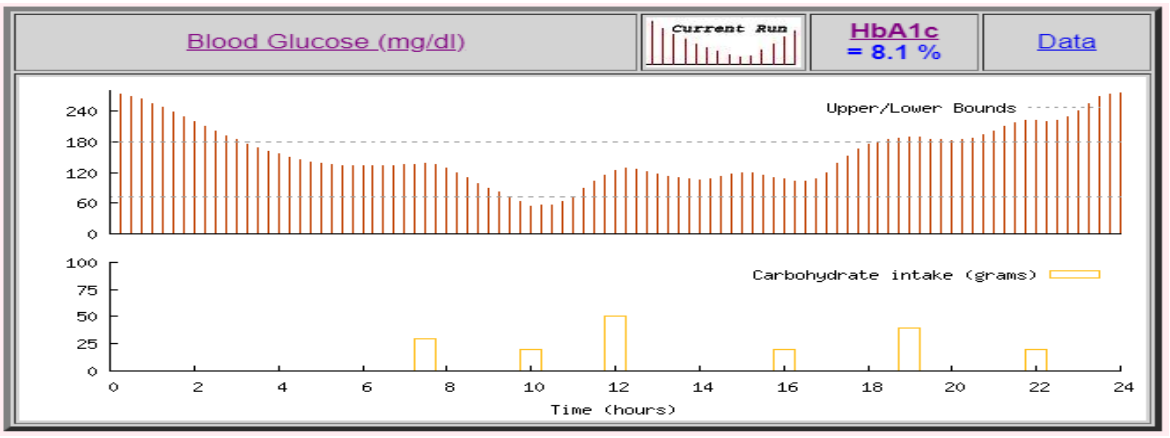

Figure 3.7: Case 002

3.9 Justification of using AIDA Data set

We have adopted and utilized the online simulator of AIDA to generate patient's data because a) It is extremely difficult to obtain real patients' data because of issues that are private and ethical, b) It is very expensive and time-consuming to conduct experiments on human subjects, c) The simulator, in fact, is able to generate a large dataset, and d) Simulations provide us with a greater flexibility. Moreover, an independent assessment is conducted founded on feedbacks from internal evaluators and healthcare personnel by British Diabetic Association (BDA). When it received a considerably accurate rating from the healthcare personnel, the BDA has decided to list the simulator in their healthcare brochure [21] [22].

3.10 Summary

We applied different type of Neural Networks. But from literature it can be seen that Nonlinear Autoregressive Neural Networks is widely used for time series problems in forecasting future values. Therefore, we have used NAR NN for forecasting future value of a particular patient blood glucose level. It act as a sliding window model, which takes the previous values as inputs and predict the next value.

CHAPTER 4

RESULTS AND ANALYSIS

4.1 Introduction:

In this chapter, we are discussing the results we get from simulating different techniques on different data sets. In this chapter we have selected 10 subject from AIDA online diabetic simulator and used OANN and NAR NN on both of them, we compared both results and with previous techniques as well. Finally we selected two UCI machine learning repository datasets (Abalone and servo) to validate our technique.

4.2 Optimized Feedforward Neural Network (OANN)

In order to prove the robustness and effectiveness of our proposed system, the controller performance for two patients with a wide range of medical particulars and patterns of meal ingestion have been simulated as shown in Figure 4.1 and Figure 4.2. Minimum variables are selected which is only CGM. Case 1 is of a patient who has normal weight, pre-pregnancy, less hyper and less insulin dosage. On the other hand, in Case 2 the patient has the same weight, nocturnal hyper and 4 insulin doses per day. It is revealed that the control system is able to keep the BGL between 70 and 140mg/ld. after two hours of meal ingestion, which can be deemed consistent with the standards of the American Diabetic Association [16]. The conditions of termination for training are 100 epochs, a μ of 1e20, or a gradient of 1e−7.

Table 4.1: RMSE FOR CASE 001

Optimal input neurons	Optimal hidden neurons	PH(minutes)	RMSE (ml/ld.)
5	6	15min	0.9984
7	1	30min	3.7681

9	6	45min	5.0338
10	10	60min	7.371

Table 4.2: RMSE FOR CASE 002

Optimal input neurons	Optimal hidden neurons	PH(minutes)	RMSE (ml/ld.)
3	2	15min	1.4370
9	15	30min	3.517
7	6	45min	5.093

The above TABLE 4.1 and TABLE 4.2 shows RMSE for different PH (15, 30, 45 and 60minutes). For case 001 it is 0.99,3.7,5,7.3ml/dl for 15, 30, 45 and 60minutes prediction horizon respectively. Similarly, for case 002 it is 1.43, 3.5, 5, and 9.7 ml/dl for 15, 30, 45 and 60 minutes PH respectively. The above results illustrates that when we increase the prediction horizon, the RMSE error increases.

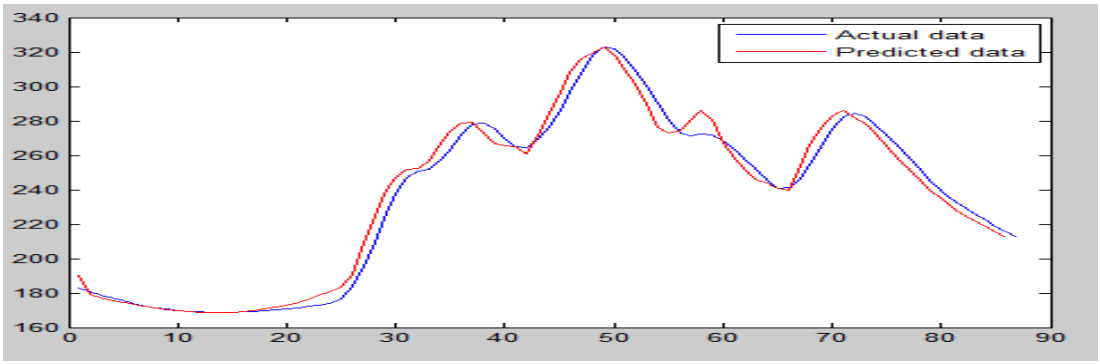

Figure 4.1: Case 001 PH= 30min graph

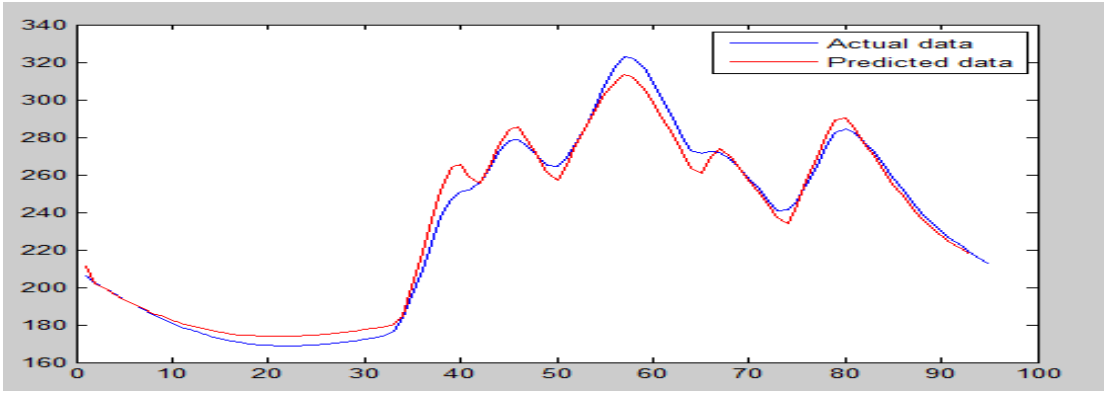

Figure 4.2: Case 001 PH= 45min graph

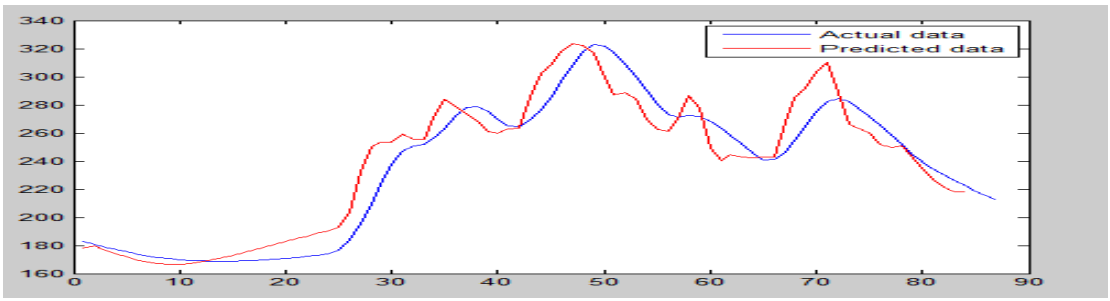

Figure 4.3: Case 001 PH= 60min graph

Figure 4.1-4.3 show the graphs of actual and predicted blood glucose concentration for different PH (15, 30, 45 and 60 minutes) for Case 001. It is evident from the results and the graphs that the more we increase the PH the more the accuracy is deteriorated [19] [20].

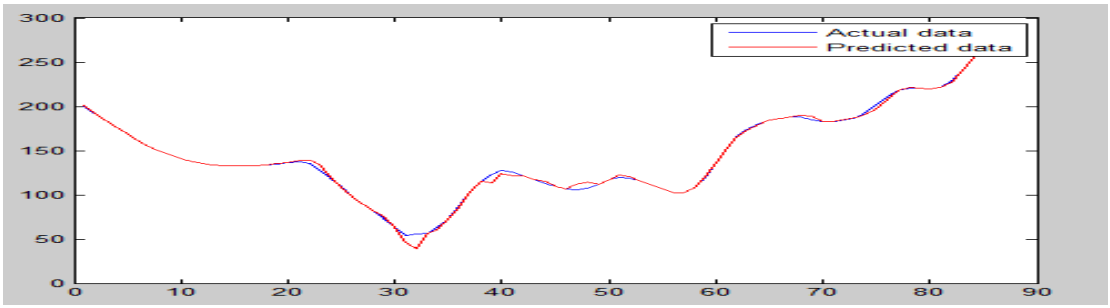

Figure 4.4: Case 002 PH= 15min graph

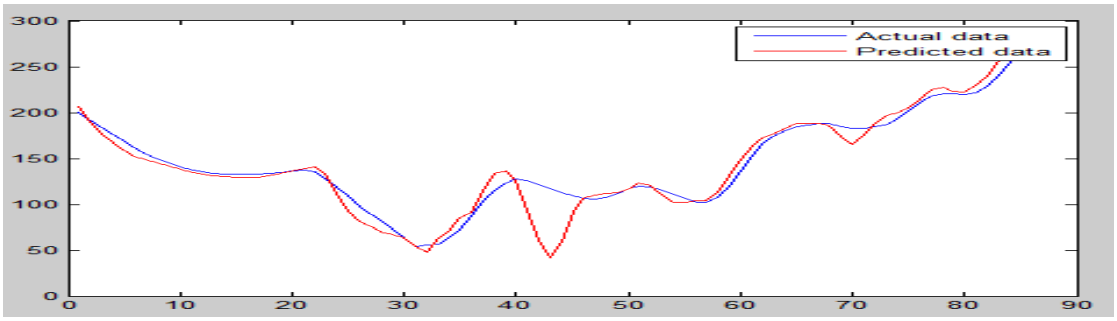

Figure 4.5: Case 002 PH= 30min graph

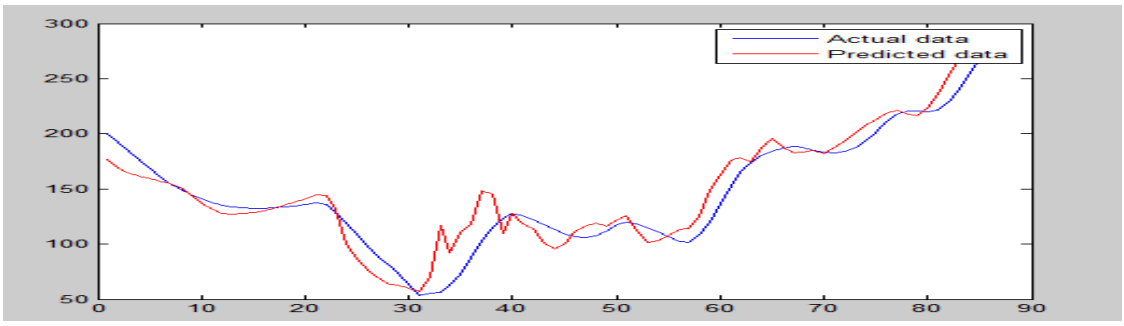

Figure 4.6: Case 002 PH= 45min graph

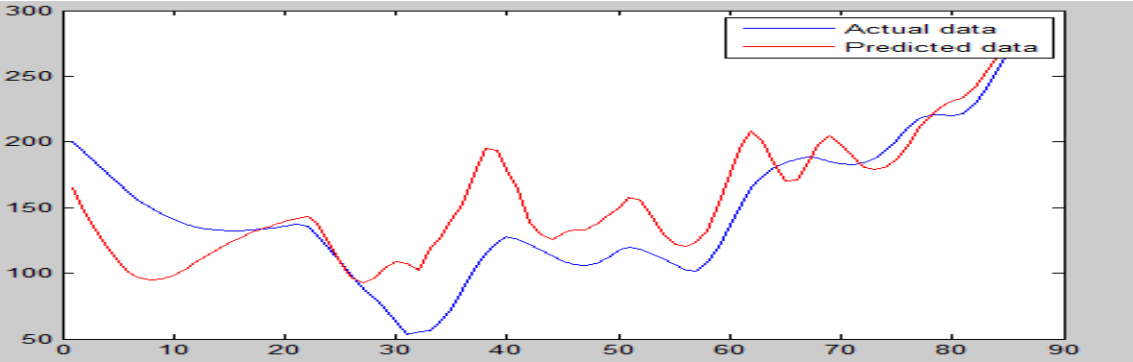

Figure 4.7: Case 002 PH= 60min graph

Figure 4.4-4.7 show the graphs of actual and predicted blood glucose concentration for different PH (15, 30, 45 and 60 minutes) for Case002. It is evident from the results and the graphs that the more we increase the PH the more the accuracy is deteriorated [19] [20].

4.2.1 Comparison of OANN with previous models

TABLE 4.3 illustrates the comparison of previous works and the proposed work. It is evident from the results that the proposed system has better performance than all other methods. However, the RMSE of Elman Network has less RMSE but on the contrary, it requires more inputs than the proposed model. The proposed system reduces the burden of more inputs for the patients than other models do. The proposed model only uses Blood glucose concentration to predict the future value and is a time series problem.

For case 001 it is 0.99,3.7,5,7.3ml/dl for 15, 30, 45 and 60minutes prediction horizon respectively. Similarly, for case 002 it is 1.43, 3.5, 5, and 9.7 ml/dl for 15, 30, 45 and 60 minutes PH respectively. Firstly, it has reduced the burden of collecting too many features, secondly, it is an individualized and adaptive model. Moreover, whilst previous studies merely focus to accurately predict BGL, our research targets to enhance T1D patients' life quality by making use of CGM data and by restraining human involvement.

Table 4.3: COMPARISON WITH PREVIOUS WORK

Referen-ce	Method	Inputs	Dataset	Prediction horizon (min)	RMSE (ml/dl)
[3]	ERN	4	AIDA case 002	15,30,45,60	2.3-3
[2]	ANN	1	13 patients	15,30,45,60	7.76
[4]	NN-PID	23	AIDA simulator	90	5.9
[5]	SVR	4	AIDA simulator	--	19% error
[8]	NN-LPA	3	UVa/Padova Simulator	15,30,45	9.7
[9]	AR	--	28 patients	30	--
[10]	ESN	--	8 patients	15,45,60	16.32
[11]	ANN	--	Hospital data	15	6.43
[12]	ELM	11	15 patients	30mins	9.3
Propose d model	OANN	1	AIDA Simulator	15, 30, 45, 60	4.5

4.3Validation with more subjects

In order to prove the robustness and effectiveness of our proposed system, the controller performance for ten patients (Table 4.4) with a wide range of medical particulars and patterns of meal ingestion have been simulated. Minimum variables are selected which is only CGM. The conditions of termination for training are 100 epochs, a μ of 1e20, or a gradient of 1e−7. Shows RMSE for PH (15 minutes). The average root mean square error for all the 10 cases is 1.26ml/dl.

Table 4.4: For 10 subjects

Case	Optimal input neurons	Optimal hidden neurons	PH(minutes)	RMSE (ml/ld.)
001	5	6	15min	0.9984
002	3	2	15min	1.4370
003	6	8	15min	0.87
004	5	3	15min	2.79
005	8	1	15min	0.707
006	6	1	15min	0.81
007	4	2	15min	1.68
008	3	3	15min	1.452
009	5	1	15min	1.00
010	7	6	15min	0.954

4.3.1 Comparison for 10 subjects with PH=15min

Table 4.5 illustrates the comparison of previous works and the proposed work. It is evident from the results that the proposed system has better performance than all other methods. The proposed system reduces the burden of more inputs for the patients than other models do. The proposed model only uses Blood glucose concentration to predict the future value and is a time series problem.

Table 4.5: Comparison

Reference	Method	Inputs	Dataset	Prediction horizon (min)	RMSE (ml/dl)
[3]	ERN	4	AIDA case 002	15	2.3-3

[2]	ANN	1	13 patients	15	6.43
[8]	NN-LPA	3	UVa/Padova Simulator	15	9.7
[10]	ESN	--	8 patients	15	12
[11]	ANN	--	Hospital data	15	6.43
Used model	ANN	1	AIDA Simulator	15	1.25

4.4 Nonlinear Autoregressive Neural Network (NAR NN)

In this section, two neural network techniques are compared. Firstly, optimal feedforward neural network .Which acts as a window model for these time series data, it optimally selects the input and hidden neuron. Secondly, the proposed optimal nonlinear autoregressive neural network.

Table 4.6: RMSE FOR CASE 001

Optimal Feedback Delay	Optimal Hidden Neurons	NAR NN with optimal inputs (RMSE ml/dl)	
		Y(T)=15min	Y(t+1)=30min
3	10	0.6060	1.127

Table 4.7: RMSE FOR CASE 002

Optimal Feedback Delay	Optimal Hidden Neurons	NAR NN with optimal inputs (RMSE m/dl)	
		Y(T)=15min	Y(t+1)=30min
9	4	0.791	1.675

Table 4.6 and Table 4.7 show RMSE for optimal autoregressive neural networks for PH (15 and 30 minutes). For case 001 it is 0.60 and 1.12 ml/dl for 15 and 30 prediction horizon respectively. Similarly, for case 002 it is 0.7911 and 1.6756 ml/dl for 15 and 30 minutes PH respectively.

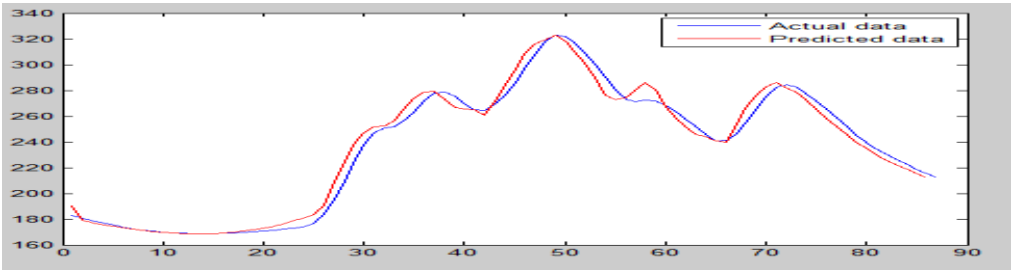

Figure 4.8: Case 001 PH= 30 min graph-feedforward

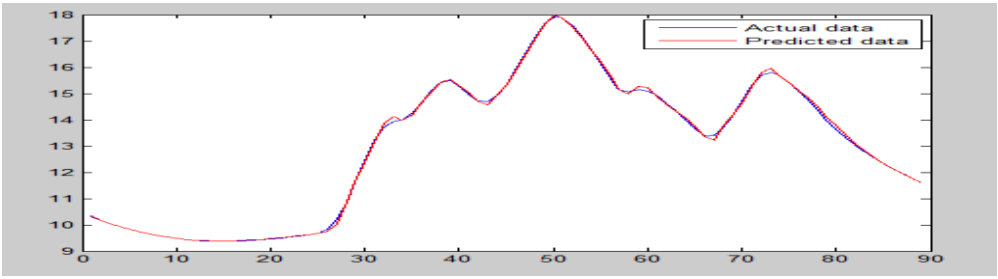

Figure 4.9: Case 001 PH= 30 min graph-autoregressive

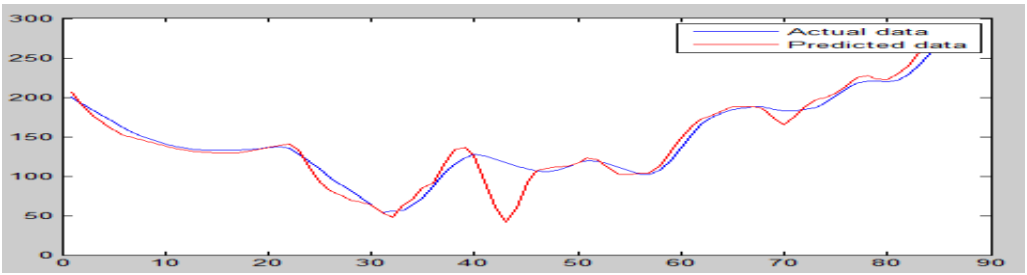

Figure 4.10: Case 002 PH= 30 min graph-feedforward

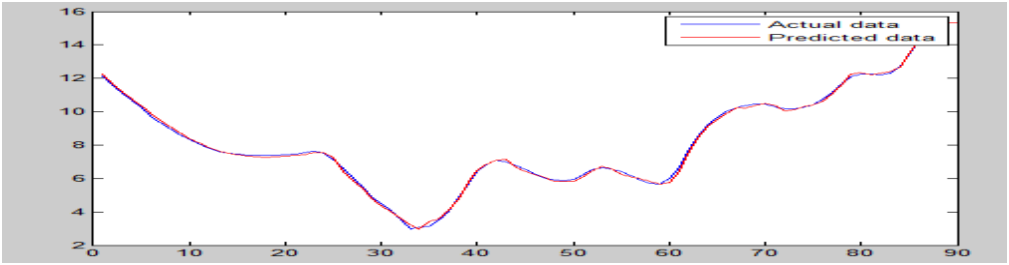

Figure 4.11: Case 002 PH= 30min graph autoregressive

Figure 4.8 and Figure 4.9 show the graphs of actual and predicted blood glucose concentration for different PH (30 minutes) of optimal feedforward neural network and optimal nonlinear autoregressive neural network. Similarly, for case 002 shown in Figure 4.10 and Figure 4.11

.It is evident from the results and the graphs that the optimal nonlinear autoregressive neural network is showing more accurate results compared to feedforward neural network. As it shows in

4.4.1 Comparison of OANN with NARNN

Table 4.8 for optimal feedforward neural network, RMSE is 0.9984 and 3.78 ml/dl which is improved using the optimal autoregressive neural network to 0.60 and 1.12 ml/dl for 15 min and 30 min prediction horizon respectively for patient 1.

Similarly, for patient 2 for optimal feedforward neural network, RMSE is 1.43 and 3.51ml/dl which is improved using the optimal autoregressive neural network to 0.7911 and 1.6756 ml/dl for 15min and 30min predication horizon respectively. To validate the model, we used two UCI machine learning repository datasets (Abalone and Servo), results are given in Table 4.9 and Table 4.10.

Table 4.8: Comparison of Feedforward and Nonlinear Autogressive Models

Data Set	Source	Feedforward NN (RMSE) ml/dl	NAR NN with optimal inputs (RMSE ml/dl)	
			Y(t)=15min	Y(t+1)=30min
Patient1	AIDA	15min=0.9984 30min=3.78	0.6060	1.127
Patient2	AIDA	15min=1.43 30min=3.51	0.7911	1.6756
Abalone	UCI	Y(t)=3.36	2.417713	2.56211
Servo	UCI	Y(t)=1.81	0.781796	1.493887

4.5 Validation of technique using UCI ML Datasets

We validate our proposed model using UCI machine learning datasets (Abalone and Servo) and it shows improved results on that as well. From Table 4.9 it can be seen that for Y (t) Abalone has 3.36 value and for Servo it is 1.81. The values improved for NARNN which are 2.41 and .781 for both Abalone and Servo respectively shown in Table 4.9 and Table 4.10.

Table 4.9: RMSE for Abalone Dataset

Optimal Feedback Delay	Optimal Hidden Neurons	NAR NN with optimal inputs (RMSE ml/dl)	
		Y(T)=15min	Y(t+1)=30min
4	2	2.417713	2.56211

Table 4.10: RMSE for Servo Dataset

Optimal Feedback Delay	Optimal Hidden neuron	NAR NN with optimal inputs (RMSE ml/dl)	
		Y(T)=15min	Y(t+1)=30min
8	5	0.781796	1.493887

4.6 Summary

In this chapter, we compared optimal feedforward neural network with optimal nonlinear autoregressive neural networks for blood glucose prediction 15-30 minutes earlier for diabetic type 1 patients. For optimal feedforward neural network, RMSE is 0.9984 and 3.78 ml/dl which is improved using the optimal autoregressive neural network to 0.60 and 1.12 ml/dl for 15 min and 30 min prediction horizon respectively for patient 1. Furthermore, this study targets to make life easier for T1D patients by minimizing human input to the system. We further validate our proposed model using UCI machine learning datasets (Abalone and Servo) and it has shown improved results as well. The proposed optimal autoregressive neural network model performs better than feedforward window model for time series data.

CHAPTER 5

CONCLUSION AND FUTURE WORK

5.1 Introduction

After discussion of related work, proposed methodology, and results of the proposed methodology in detail, we are able to conclude our research work. In this chapter, overall research done in this thesis is concluded and future work is discussed.

In this research work, we studied glucose-insulin regulation to find research gaps. We find out that predicting blood glucose level in advance is necessary to overcome the lag time between insulin delivery and insulin absorption. We studied previous literature and followed the latest work to increase the accuracy of blood glucose level prediction in 15-60minutes prediction horizon. We compiled our data set from AIDA diabetic simulator.

5.2 Applications of this research work

Diabetic is one of the rapidly increasing diseases worldwide. Early prediction of blood glucose level can be helpful in the management of blood glucose level e.g.

- Diabetic Type 1: No insulin produces
- Diabetic Type2: Some quantity of insulin produces
- In pregnancy for Women.

5.3 CONCLUSION

Diabetes Mellitus is one of the most common diseases, which deteriorates the conditions of those suffering from it. Early detection of Blood Glucose Level not only helps in better management of Diabetes Mellitus and but also decreases the cost of treatment. In the recent past, numerous researches have been carried out to monitor blood glucose level which

suggests the quantity of insulin i.e. artificial pancreas etc. This study emphasizes on the pros of the methods used in past and how they lack in determining other aspects for achieving a completely autonomous, adaptive and individualized model.

Furthermore, we summarize the recent researches for blood glucose prediction using different forms of neural networks, the different data set used, and data set availability. Future work and challenges have been filtered out by finding the research gap for further research work which can be done by improving accuracy, increasing the prediction horizon and provide a better model and improve results.

In this research, we use Continuous Glucose Monitoring (CGM) data to predict future blood glucose level using the previous data points. We propose optimal nonlinear autoregressive neural networks. We compared optimal feedforward neural network with optimal nonlinear autoregressive neural networks for blood glucose prediction 15-30 minutes earlier for diabetic type 1 patients. For optimal feedforward neural network, RMSE is 0.9984 and 3.78 ml/dl which is improved using the optimal autoregressive neural network to 0.60 and 1.12 ml/dl for 15 min and 30 min prediction horizon respectively for patient 1. Furthermore, this study targets to make life easier for T1D patients by minimizing human input to the system. We further validate our proposed model using UCI machine learning datasets (Abalone and Servo) and it has shown improved results as well. The proposed optimal autoregressive neural network model performs better than feedforward window model for time series data. In the future, we intend to investigate a greater collection of AIDA scenarios and multivariate data and using the nonlinear autoregressive neural network with exogenous inputs.

5.4 FUTURE WORK

For future work, we propose a novel individualized adaptive optimized framework for efficient and high accuracy glucose prediction model. A non-linear autoregressive model with exogenous inputs (NARX) can be used instead of NN sliding window model. Moreover, more patients and a greater number of features can be added to improve accuracy. The most important challenge is that the prediction horizon must be improved in such a way that the level of accuracy must not be compromised. Moreover, dynamic adaptation, detection of exercise and meal inclusion with respect to the physiological changes and patient behavior should also be taken under consideration.

Furthermore, we are in coordination with few hospitals who agreed to provide facilities to generate a real data set. The CGM devices/services will be provided by Agha Medical University and the procedure will be conducted in Lady Reading Hospital (LRH) Peshawar.

Moreover, using the above NARX and the real data set we can extend the work to develop a complete model predictive controller (MPC) which can be trained using the real data set, which will be able to regulate blood glucose-insulin with better accuracy and efficiency. The NARX will act as system Identification (SI) module and the MPC will be then tuned to an external plant model.

Moreover, recording more variables e.g. exercise, diseases, diet and stress etc. can further improve the results. With adding more records we can increase the prediction horizon from 60minutes to 120 minutes which will further decrease the lag time between insulin delivery and insulin absorption.

REFERENCES

[1] F. Allam, Z. Nossai, H. Gomma, I. Ibrahim and M. Abdelsalam, "A Recurrent Neural Network Approach for Predicting Glucose Concentration in Type-1 Diabetic Patients", *International Conference on Engineering Applications of Neural Networks*, vol. 363, pp. 254-259, 2011.

[2] A. Ahmad, A. Mustapha, E. Zahadi, N. Masah and N. Yahaya, "Comparison between Neural Networks against Decision Tree in Improving Prediction Accuracy for Diabetes Mellitus", *Digital Information Processing and Communications*, pp. 537-545, 2011.

[3] B. Malik, A. Naqash and G. Bhat, "Backpropagation artificial neural network for determination of glucose concentration from near-infrared spectra", *2016 International Conference on Advances in Computing, Communications and Informatics (ICACCI)*, 2016.

[4] N. Li, J. Tuo and Y. Wang, "Chaotic time series analysis approach for prediction blood glucose concentration based on echo state networks", *2018 Chinese Control And Decision Conference (CCDC)*, 2018.

[5] T. Hamdi, J. Ben Ali, N. Fnaiech, V. Di Costanzo, F. Fnaiech, E. Moreau and J. Ginoux, "Artificial neural network for blood glucose level prediction", *2017 International Conference on Smart, Monitored and Controlled Cities (SM2C)*, 2017.

[6] S. Bamgbose, X. Li and L. Qian, "Closed loop control of blood glucose level with neural network predictor for diabetic patients", *2017 IEEE 19th International Conference on e-Health Networking, Applications and Services (Healthcom)*, 2017.

[7] G. Robertson, E. Lehmann, W. Sandham and D. Hamilton, "Blood Glucose Prediction Using Artificial Neural Networks Trained with the AIDA Diabetes Simulator: A Proof-of-Concept Pilot Study", *Journal of Electrical and Computer Engineering*, vol. 2011, pp. 1-11, 2011.

[8] C. Zecchin, A. Facchinetti, G. Sparacino, G. De Nicolao and C. Cobelli, "Neural Network Incorporating Meal Information Improves Accuracy of Short-Time Prediction of Glucose Concentration", *IEEE Transactions on Biomedical Engineering*, vol. 59, no. 6, pp. 1550-1560, 2012.

[9] C. Zecchin, A. Facchinetti, G. Sparacino, G. De Nicolao and C. Cobelli, "A new neural network approach for short-term glucose prediction using continuous glucose monitoring time-series and meal information", *2011 Annual International Conference of the IEEE Engineering in Medicine and Biology Society*, 2011.

[10] E. Georga, V. Protopappas, D. Polyzos and D. Fotiadis, "Online prediction of glucose concentration in type 1 diabetes using extreme learning machines", *2015 37th Annual International Conference of the IEEE Engineering in Medicine and Biology Society (EMBC)*, 2015.

[11] J. Ben Ali, T. Hamdi, N. Fnaiech, V. Di Costanzo, F. Fnaiech and J. Ginoux, "Continuous blood glucose level prediction of Type 1 Diabetes based on Artificial Neural Network", *Biocybernetics and Biomedical Engineering*, vol. 38, no. 4, pp. 828-840, 2018.

[12] P. Ong and Z. Zainuddin, "Calibrating wavelet neural networks by distance orientation similarity fuzzy C-means for approximation problems", *Applied Soft Computing*, vol. 42, pp. 156-166, 2016.

[13] C. Zecchin, A. Facchinetti, G. Sparacino and C. Cobelli, "Jump neural network for online short-time prediction of blood glucose from continuous monitoring sensors and meal information", *Computer Methods and Programs in Biomedicine*, vol. 113, no. 1, pp. 144-152, 2014.

[14] S. Pappada, B. Cameron, P. Rosman, R. Bourey, T. Papadimos, W. Olorunto and M. Borst, "Neural Network-Based Real-Time Prediction of Glucose in Patients with Insulin-Dependent Diabetes", *Diabetes Technology & Therapeutics*, vol. 13, no. 2, pp. 135-141, 2011.

[15] C. Pérez-Gandía, A. Facchinetti, G. Sparacino, C. Cobelli, E. Gómez, M. Rigla, A. de Leiva and M. Hernando, "Artificial Neural Network Algorithm for Online Glucose Prediction from Continuous Glucose Monitoring", *Diabetes Technology & Therapeutics*, vol. 12, no. 1, pp. 81-88, 2010.

[16] from Continuous Glucose Monitoring", *Diabetes Technology & Therapeutics*, vol. 12, no. 1, pp. 81-88, 2010.

[17] T. Hamdi, J. Ben Ali, N. Fnaiech, V. Di Costanzo, F. Fnaiech, E. Moreau and J. Ginoux, "Artificial neural network for blood glucose level prediction", *2017 International Conference on Smart, Monitored and Controlled Cities (SM2C)*, 2017.

[18] G. Sparacino, F. Zanderigo, S. Corazza, A. Maran, A. Facchinetti and C. Cobelli, "Glucose Concentration can be Predicted Ahead in Time From Continuous Glucose Monitoring Sensor Time-Series", *IEEE Transactions on Biomedical Engineering*, vol. 54, no. 5, pp. 931-937, 2007.

[19] T. Hamdi, J. Ben Ali, N. Fnaiech, V. Di Costanzo, F. Fnaiech, E. Moreau and J. Ginoux, "Artificial neural network for blood glucose level prediction", *2017 International Conference on Smart, Monitored and Controlled Cities (SM2C)*, 2017

[20] K. Zarkogianni, K. Mitsis, E. Litsa, M. Arredondo, G. Fico, A. Fioravanti and K. Nikita, "Comparative assessment of glucose prediction models for patients with type 1 diabetes mellitus applying sensors for glucose and physical activity monitoring", *Medical & Biological Engineering & Computing*, vol. 53, no. 12, pp. 1333-1343, 2015.

[21] S. Pappada, B. Cameron and P. Rosman, "Development of a Neural Network for Prediction of Glucose Concentration in Type 1 Diabetes Patients", *Journal of Diabetes Science and Technology*, vol. 2, no. 5, pp. 792-801, 2008.

[22] M. Reymann, E. Dorschky, B. Groh, C. Martindale, P. Blank and B. Eskofier, "Blood glucose level prediction based on support vector regression using mobile platforms", *2016 38th Annual International Conference of the IEEE Engineering in Medicine and Biology Society (EMBC)*, 2016.

[23] Chakrabarty, S. Zavitsanou, F. Doyle and E. Dassau, "Event-Triggered Model Predictive Control for Embedded Artificial Pancreas Systems", *IEEE Transactions on Biomedical Engineering*, vol. 65, no. 3, pp. 575-586, 2018.

[24] S. Asadi and V. Nekoukar, "Adaptive fuzzy integral sliding mode control of blood glucose level in patients with type 1 diabetes: In silico studies", *Mathematical Biosciences*, vol. 305, pp. 122-132, 2018.

[25] E. Georga, V. Protopappas, D. Ardigo, M. Marina, I. Zavaroni, D. Polyzos and D. Fotiadis, "Multivariate Prediction of Subcutaneous Glucose Concentration in Type 1 Diabetes Patients Based on Support Vector Regression", *IEEE Journal of Biomedical and Health Informatics*, vol. 17, no. 1, pp. 71-81, 2013.

[26] C. Druet, V. Baltakse, D. Chevenne, S. Dorgeret, I. Zaccaria, Y. Wang and C. Levy-Marchal, "Independent Effect of Visceral Adipose Tissue on Metabolic Syndrome in Obese Adolescents", *Hormone Research*, vol. 70, no. 1, pp. 22-28, 2008.

[27] D. Rollins, N. Bhandari, J. Kleinedler, K. Kotz, A. Strohbehn, L. Boland, M. Murphy, D. Andre, N. Vyas, G. Welk and W. Franke, "Free-living inferential modeling of blood glucose level using only noninvasive inputs", *Journal of Process Control*, vol. 20, no. 1, pp. 95-107, 2010.

[28] Tealab, H. Hefny and A. Badr, "Forecasting of nonlinear time series using ANN", *Future Computing and Informatics Journal*, vol. 2, no. 1, pp. 39-47, 2017.

[29] K. Benmouiza and A. Cheknane, "Forecasting hourly global solar radiation using hybrid k-means and nonlinear autoregressive neural network models", *Energy Conversion and Management*, vol. 75, pp. 561-569, 2013

[30] W. Pawlus, H. Karimi and K. Robbersmyr, "Data-based modeling of vehicle collisions by nonlinear autoregressive model and feedforward neural network", *Information Sciences*, vol. 235, pp. 65-79, 2013

[31] Z. Du, M. Qin, F. Zhang and R. Liu, "Multistep-ahead forecasting of chlorophyll a using a wavelet nonlinear autoregressive network", *Knowledge-Based Systems*, vol. 160, pp. 61-70, 2018.

[32] S. Bahremand, H. Ko, R. Balouchzadeh, H. Felix Lee, S. Park and G. Kwon, "Neural network-based model predictive control for type 1 diabetic rats on artificial pancreas system", *Medical & Biological Engineering & Computing*, 2018.

[33] N. Fan, S. Wang, C. Liu and X. Liu, "Wheel Wear Prediction of High-Speed Train Using NAR and BP Neural Networks", *2017 IEEE International Conference on Internet of Things*

(iThings) and IEEE Green Computing and Communications (GreenCom) and IEEE Cyber, Physical and Social Computing (CPSCom) and IEEE Smart Data (SmartData), 2017.

[34] S. Karasu, A. Altan, Z. Sarac and R. Hacioglu, "Prediction of wind speed with non-linear autoregressive (NAR) neural networks", *2017 25th Signal Processing and Communications Applications Conference (SIU)*, 2017.

[35] Hamzic, Z. Avdagic and S. Omanovic, "A sequential approach for short-term water level prediction using nonlinear autoregressive neural networks", *2016 XI International Symposium on Telecommunications (BIHTEL)*, 2016.

[36] K. Gairaa, F. Chellali, S. Benkaciali, Y. Messlem and K. Abdallah, "Daily global solar radiation forecasting over a desert area using NAR neural networks comparison with conventional methods", *2015 International Conference on Renewable Energy Research and Applications (ICRERA)*, 2015.

[37] Ahmad, A. Mustapha, E. Zahadi, N. Masah and N. Yahaya, "Comparison between Neural Networks against Decision Tree in Improving Prediction Accuracy for Dia**b**etes Mellitus", *Digital Information Processing and Communications*, pp. 537-545, 2011.

[38] B. Malik, A. Naqash and G. Bhat, "Backpropagation artificial neural network for determination of glucose concentration from near-infrared spectra", *2016 International Conference on Advances in Computing, Communications and Informatics (ICACCI)*, 2016.

[39] E. Lehmann, "Research Use of the AIDA www.2aida.org Diabetes Software Simulation Program: A Review—Part 1. Decision Support Testing and Neural Network Training", *Diabetes Technology & Therapeutics*, vol. 5, no. 3, pp. 425-438, 2003.

[40] E. Lehmann, "Research Use of the AIDA www.2aida.org Diabetes Software Simulation Program: A Review—Part 2. Generating Simulated Blood Glucose Data for Prototype Validation", *Diabetes Technology & Therapeutics*, vol. 5, no. 4, pp. 641-651, 2003.

[41] D. Association, "Standards of medical care in diabetes - 2017," Diabetes Care, vol. 40, no. 1, pp. S1–S135, 2018.

[42] S. Schaller, J. Lippert, L. Schaupp, T. Pieber, A. Schuppert and T. Eissing, "Robust PBPK/PD-Based Model Predictive Control of Blood Glucose", IEEE Transactions on Biomedical Engineering, vol. 63, no. 7, pp. 1492-1504, 2016.

[43] R. Visentin, C. Man and C. Cobelli, "One-Day Bayesian Cloning of Type 1 Diabetes Subjects: Toward a Single-Day UVA/Padova Type 1 Diabetes Simulator", IEEE Transactions on Biomedical Engineering, vol. 63, no. 11, pp. 2416-2424, 2016.

[44] M. Messori, G. Incremona, C. Cobelli and L. Magni, "Individualized model predictive control for the artificial pancreas: In silico evaluation of closed-loop glucose control", IEEE Control Systems, vol. 38, no. 1, pp. 86-104, 2018.

[45] C. Zhao and C. Yu, "Rapid Model Identification for Online Subcutaneous Glucose Concentration Prediction for New Subjects With Type I Diabetes", IEEE Transactions on Biomedical Engineering, vol. 62, no. 5, pp. 1333-1344, 2015.

[46] Chakrabarty, S. Zavitsanou, F. Doyle and E. Dassau, "Event-Triggered Model Predictive Control for Embedded Artificial Pancreas Systems", IEEE Transactions on Biomedical Engineering, vol. 65, no. 3, pp. 575-586, 2018.

[47] Toffanin, R. Visentin, M. Messori, F. Palma, L. Magni and C. Cobelli, "Toward a Run-to-Run Adaptive Artificial Pancreas: In Silico Results", IEEE Transactions on Biomedical Engineering, vol. 65, no. 3, pp. 479-488, 2018.

[48] Y. Ruan, M. Wilinska, H. Thabit and R. Hovorka, "Modeling Day-to-Day Variability of Glucose–Insulin Regulation Over 12-Week Home Use of Closed-Loop Insulin Delivery", IEEE Transactions on Biomedical Engineering, vol. 64, no. 6, pp. 1412-1419, 2017.

[49] T. MohammadRidha, M. Ait-Ahmed, L. Chaillous, M. Krempf, I. Guilhem, J. Poirier and C. Moog, "Model Free iPID Control for Glycemia Regulation of Type-1 Diabetes", IEEE Transactions on Biomedical Engineering, vol. 65, no. 1, pp. 199-206, 2018.

[50] N. Magdelaine, L. Chaillous, I. Guilhem, J. Poirier, M. Krempf, C. Moog and E. Le Carpentier, "A Long-Term Model of the Glucose–Insulin Dynamics of Type 1 Diabetes", IEEE Transactions on Biomedical Engineering, vol. 62, no. 6, pp. 1546-1552, 2015.

[51] S. El-Sappagh, J. Alonso, F. Ali, A. Ali, J. Jang and K. Kwak, "An Ontology-Based Interpretable Fuzzy Decision Support System for Diabetes Diagnosis", IEEE Access, vol. 6, pp. 37371-37394, 2018.

[52] D. Boiroux, V. Bátora, M. Hagdrup, S. Wendt, N. Poulsen, H. Madsen and J. Jørgensen, "Adaptive model predictive control for a dual-hormone artificial pancreas", Journal of Process Control, vol. 68, pp. 105-117, 2018.

[53] Patra and P. Rout, "Adaptive sliding mode Gaussian controller for artificial pancreas in TIDM patient", Journal of Process Control, vol. 59, pp. 13-27, 2017.

[54] F. Mansourypoor and S. Asadi, "Development of a Reinforcement Learning-based Evolutionary Fuzzy Rule-Based System for diabetes diagnosis", Computers in Biology and Medicine, vol. 91, pp. 337-352, 2017.

[55] S. Asadi and V. Nekoukar, "Adaptive fuzzy integral sliding mode control of blood glucose level in patients with type 1 diabetes: In silico studies", Mathematical Biosciences, vol. 305, pp. 122-132, 2018.

[56] M. Messori, C. Toffanin, S. Del Favero, G. De Nicolao, C. Cobelli and L. Magni, "Model individualization for artificial pancreas", Computer Methods and Programs in Biomedicine, 2016.

[57] S. El-Sappagh, M. Elmogy and A. Riad, "A fuzzy-ontology-oriented case-based reasoning framework for semantic diabetes diagnosis", Artificial Intelligence in Medicine, vol. 65, no. 3, pp. 179-208, 2015.

[58] G. Incremona, M. Messori, C. Toffanin, C. Cobelli and L. Magni, "Model predictive control with integral action for artificial pancreas", Control Engineering Practice, vol. 77, pp. 86-94, 2018.

[59] C. Cervigón, J. Hidalgo, M. Botella and R. Villanueva, "A genetic algorithm approach to customizing a glucose model based on usual therapeutic parameters", Progress in Artificial Intelligence, vol. 6, no. 3, pp. 255-261, 2017.

[60] N. Balakrishnan and K. Nisi, "A deep analysis on optimization techniques for appropriate PID tuning to incline efficient artificial pancreas", Neural Computing and Applications, 2018.

[61] S. Bahremand, H. Ko, R. Balouchzadeh, H. Felix Lee, S. Park and G. Kwon, "Neural network-based model predictive control for type 1 diabetic rats on artificial pancreas system", Medical & Biological Engineering & Computing, 2018.

[62] J. Yadav, A. Rani and V. Singh, "Performance Analysis of Fuzzy-PID Controller for Blood Glucose Regulation in Type-1 Diabetic Patients", Journal of Medical Systems, vol. 40, no. 12, 2016.

[63] Beneyto and J. Vehi, "Postprandial fuzzy adaptive strategy for a hybrid proportional derivative controller for the artificial pancreas", Medical & Biological Engineering & Computing, vol. 56, no. 11, pp. 1973-1986, 2018.

[64] J. Ben Ali, T. Hamdi, N. Fnaiech, V. Di Costanzo, F. Fnaiech and J. Ginoux, "Continuous blood glucose level prediction of Type 1 Diabetes based on Artificial Neural Network", Biocybernetics and Biomedical Engineering, vol. 38, no. 4, pp. 828-840, 2018.

[65] Kitchenham, B. 2004. Procedures for Performing Systematic Reviews. Elsevier. (July 2004)

[66] [1]Chang-Shing Lee and Mei-Hui Wang, "A Fuzzy Expert System for Diabetes Decision Support Application", *IEEE Transactions on Systems, Man, and Cybernetics, Part B (Cybernetics)*, vol. 41, no. 1, pp. 139-153, 2011.

[67] [2]C. Velu and K. Kashwan, "Visual data mining techniques for classification of diabetic patients", *2013 3rd IEEE International Advance Computing Conference (IACC)*, 2013.

[68] [3]B. Leon, A. Alanis, E. Sanchez, F. Ornelas-Tellez and E. Ruiz-Velazquez, "Subcutaneous neural inverse optimal control for an Artificial Pancreas", *The 2013 International Joint Conference on Neural Networks (IJCNN)*, 2013.

[69] [4]Z. Trajanoski and P. Wach, "Neural predictive controller for insulin delivery using the subcutaneous route", *IEEE Transactions on Biomedical Engineering*, vol. 45, no. 9, pp. 1122-1134, 1998.

[70] [5]F. Andrianasy and M. Milgram, "Neural network-based insulin infusion control for an insulin-pump, using discontinuous blood glucose measurements", *Biological and Artificial Computation: From Neuroscience to Technology*, pp. 971-977, 1997.

[71] [6]M. Panella, F. Barcellona and A. Bersani, "Neural Network in Modeling Glucose-Insulin Behavior", *Biological and Artificial Intelligence Environments*, pp. 367-374.

[72] [7]S. Mougiakakou, A. Prountzou, D. Iliopoulou, K. Nikita, A. Vazeou and C. Bartsocas, "Neural Network based Glucose - Insulin Metabolism Models for Children with Type 1

Diabetes", *2006 International Conference of the IEEE Engineering in Medicine and Biology Society*, 2006.

[73] [8]T. Shimauchi, N. Kugai, N. Nagata and O. Takatani, "Microcomputer-aided insulin dose determination in intensified conventional insulin therapy", *IEEE Transactions on Biomedical Engineering*, vol. 35, no. 2, pp. 167-171, 1988.

[74] [9]Youqing Wang, Hongzhi Xie, Xu Jiang and Bo Liu, "Intelligent Closed-Loop Insulin Delivery Systems for ICU Patients", *IEEE Journal of Biomedical and Health Informatics*, vol. 18, no. 1, pp. 290-299, 2014.

[75] [10]S. Zavitsanou, A. Mantalaris, M. Georgiadis and E. Pistikopoulos, "<italic>In Silico</italic> Closed-Loop Control Validation Studies for Optimal Insulin Delivery in Type 1 Diabetes", *IEEE Transactions on Biomedical Engineering*, vol. 62, no. 10, pp. 2369-2378, 2015.

[76] [11]M. Thirugnanam, P. Kumar, S. Srivatsan and C. Nerlesh, "Improving the Prediction Rate of Diabetes Diagnosis Using Fuzzy, Neural Network, Case Based (FNC) Approach", *Procedia Engineering*, vol. 38, pp. 1709-1718, 2012.

[77] [12]H. Thabit, A. Lubina-Solomon, M. Stadler, L. Leelarathna, E. Walkinshaw, A. Pernet, J. Allen, A. Iqbal, P. Choudhary, K. Kumareswaran, M. Nodale, C. Nisbet, M. Wilinska, K. Barnard, D. Dunger, S. Heller, S. Amiel, M. Evans and R. Hovorka, "Home use of closed-loop insulin delivery for overnight glucose control in adults with type 1 diabetes: a 4-week, multicentre, randomised crossover study", *The Lancet Diabetes & Endocrinology*, vol. 2, no. 9, pp. 701-709, 2014.

[78] [13]O. Karan, C. Bayraktar, H. Gümüşkaya and B. Karlık, "Diagnosing diabetes using neural networks on small mobile devices", *Expert Systems with Applications*, vol. 39, no. 1, pp. 54-60, 2012.

[79] [14]R. Motka, V. Parmarl, B. Kumar and A. Verma, "Diabetes mellitus forecast using different data mining techniques", *2013 4th International Conference on Computer and Communication Technology (ICCCT)*, 2013.

[80] [15]K. van Heusden, E. Dassau, H. Zisser, D. Seborg and F. Doyle, "Control-Relevant Models for Glucose Control Using A Priori Patient Characteristics", *IEEE Transactions on Biomedical Engineering*, vol. 59, no. 7, pp. 1839-1849, 2012.

[81] [1]Y. Zhu, "Automatic detection of anomalies in blood glucose using a machine learning approach", *Journal of Communications and Networks*, vol. 13, no. 2, pp. 125-131, 2011.

[82] [2]K. Zarkogianni, A. Vazeou, S. Mougiakakou, A. Prountzou and K. Nikita, "An Insulin Infusion Advisory System Based on Autotuning Nonlinear Model-Predictive Control", *IEEE Transactions on Biomedical Engineering*, vol. 58, no. 9, pp. 2467-2477, 2011.

[83] [3]E. Caballero-Ruiz, G. García-Sáez, M. Rigla, M. Villaplana, B. Pons and M. Hernando, "A web-based clinical decision support system for gestational diabetes: Automatic diet prescription and detection of insulin needs", *International Journal of Medical Informatics*, vol. 102, pp. 35-49, 2017.

[84] [4]V. VijayanV and A. Ravikumar, "Study of Data Mining Algorithms for Prediction and Diagnosis of Diabetes Mellitus", *International Journal of Computer Applications*, vol. 95, no. 17, pp. 12-16, 2014.

[85] [5]S. Sankaranarayanan and T. Perumal, "A Predictive Approach for Diabetes Mellitus Disease through Data Mining Technologies", *2014 World Congress on Computing and Communication Technologies*, 2014.

[86] [6]C. Zecchin, A. Facchinetti, G. Sparacino, G. De Nicolao and C. Cobelli, "A new neural network approach for short-term glucose prediction using continuous glucose monitoring time-series and meal information", *2011 Annual International Conference of the IEEE Engineering in Medicine and Biology Society*, 2011.

[87] [7]P. Grant, "A new approach to diabetic control: Fuzzy logic and insulin pump technology", *Medical Engineering & Physics*, vol. 29, no. 7, pp. 824-827, 2007.

[88] [8]A. Abu-Rmileh and W. Garcia-Gabin, "A Gain-Scheduling Model Predictive Controller for Blood Glucose Control in Type 1 Diabetes", *IEEE Transactions on Biomedical Engineering*, vol. 57, no. 10, pp. 2478-2484, 2010.

[89] [9]G. Sparacino, F. Zanderigo, S. Corazza, A. Maran, A. Facchinetti and C. Cobelli, "Glucose Concentration can be Predicted Ahead in Time From Continuous Glucose Monitoring Sensor Time-Series", *IEEE Transactions on Biomedical Engineering*, vol. 54, no. 5, pp. 931-937, 2007.

[90] Neural Networks", *Doc.ic.ac.uk*, 2019. [Online]. Available: https://www.doc.ic.ac.uk/~nd/surprise_96/journal/vol4/cs11/report.html. [Accessed: 12- Jan- 2019].

APPENDIX A: Simulation

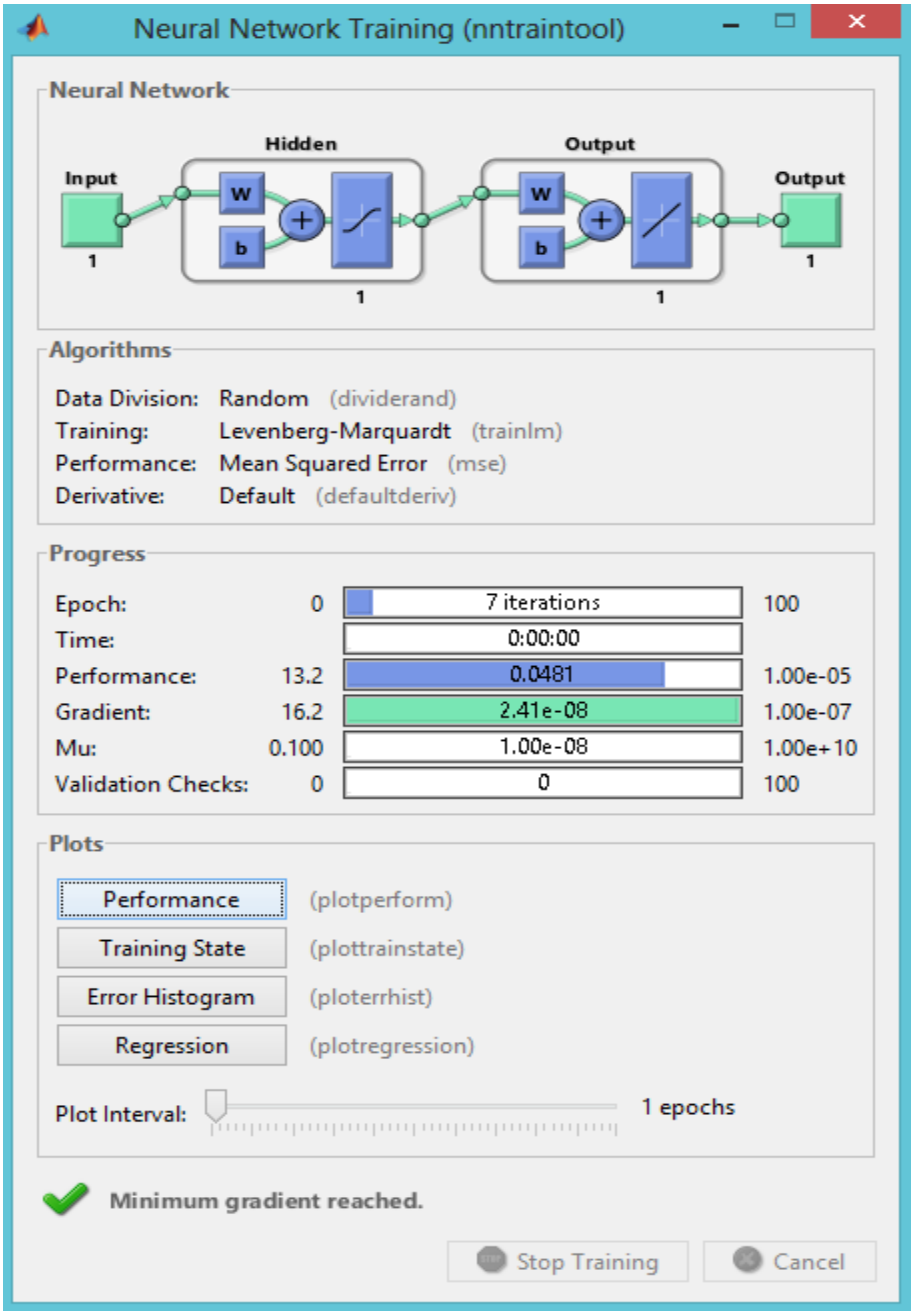

Figure A1: Training

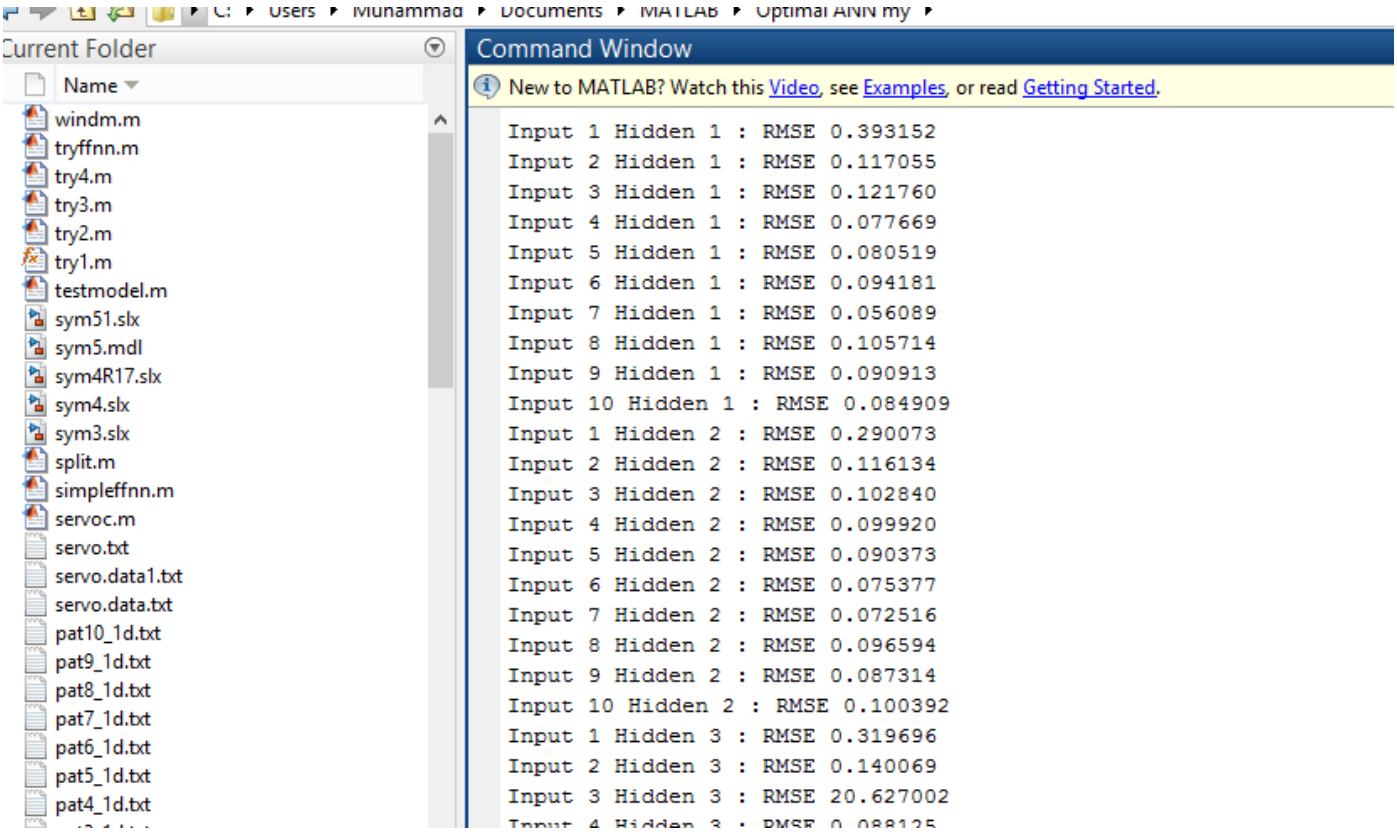

Figure A2: Window Model NN simulation-1

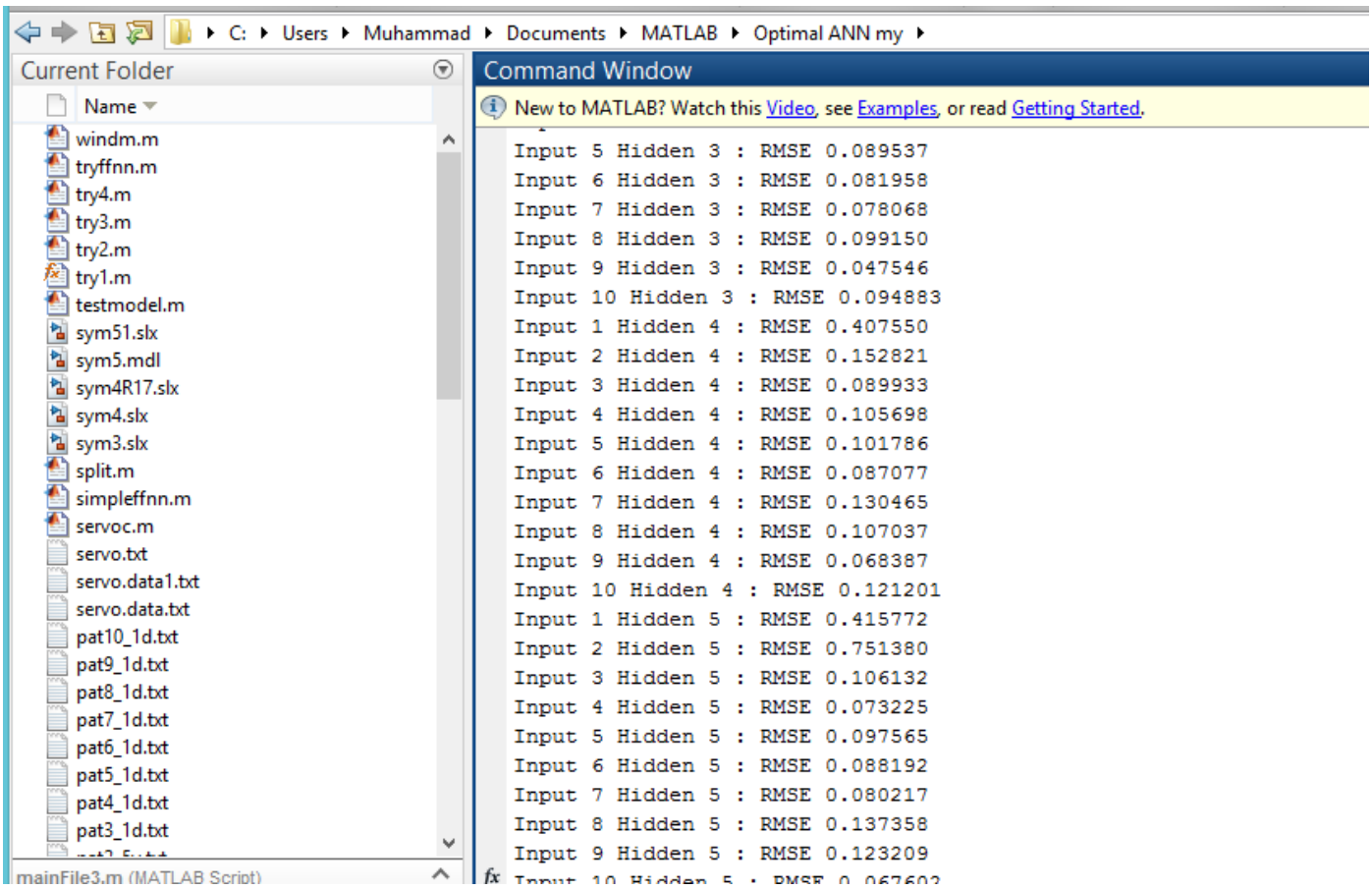

Figure A3: Window Model NN simulation-2