A novel and superior approach to diabetic management: utilization of a fuzzy-logic based system for precision insulin dosing in Type 2 diabetes patients

A project submitted

by

Proma Roy Orni

ID 13246001

Batch: Spring 2014

to

The Department of Pharmacy

in partial fulfillment of the requirements for the degree of

Bachelor of Pharmacy (Hons.)

Inspiring Excellence

BRAC University

Dhaka, Bangladesh

August, 2018

Dedicated to my parents

Certificate Statement

This is to certify that this project titled 'A novel and superior approach to diabetic management: utilization of a fuzzy-logic based system for precision insulin dosing in Type 2 diabetes patients' submitted for the partial fulfillment of the requirements for the degree of Bachelor of Pharmacy, BRAC University constitutes my own work under the supervision of Saif Shahriar Rahman Nirzhor, Senior Lecturer of Department of Pharmacy, BRAC University and that appropriate credit is given where I have used the language, ideas or writings of another.

Signed,

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Countersigned by the supervisor,

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Acknowledgement

First of all, I would like to express my appreciation and deepest gratitude to my supervisor, Saif Shahriar Rahman Nirzhor, Senior Lecturer of Department of Pharmacy, BRAC university, for his constant guidance and effort for the preparation of this project. He has helped me to explore this vast topic in an orderly manner and without his proper supervision, it would be impossible for me to complete this project. I am grateful to my supervisor for his continuous advice, comments, feedback and cooperation, at the need of time even after his office hours.

I would like to show my heartiest gratitude to Dr. Eva Rahman Kabir, Chairperson of Department of Pharmacy, BRAC University for her supportive supervision and monitoring during the project.

I am also thankful to Rubayat Islam Khan, Senior lecturer of Department of pharmacy, BRAC University for the motivation and inspiration for this project. I would like to specially thank Ahmed Masud Chowdhury who has given his expert suggestion for the development of the base of my project and were always available for help whenever required.

I would like to extend my appreciation and heartiest gratitude to my fellow mate, Tariqul Islam Tareq for his immense all round support during the entire period of the project work. Without his support, this entire project work would have been much harder.

Last but not the least, I would like to express my special gratitude to Almighty, my parents and my sister for their continuous support to help me stay focused and calm in the oddest of times and help me keep moving on times when there was no hope.

Abstract

Diabetes, a complex heterogeneous disease, characterized mainly by hyperglycemia due to defects in the pancreatic β-cells. The treatment necessities and individualization of care of a diabetes depend on the patient's pathophysiology of Diabetes Mellitus, which underpins their clinical presentation and classification of diabetes. The management of normal blood glucose level in diabetes patient often possess many challenges due to the complexity of the disease, uncertainties and vagueness of the symptoms involved. Treatment of Diabetes Mellitus includes proper education, evaluation of macro-vascular and micro-vascular complications, minimization of cardiovascular complications and most importantly normalization of blood glucose level to prevent long-term risk factors. Most often patient with diabetes mellitus fails to maintain their glycemic target after initial therapy with oral therapeutic agents. The therapeutic option for such patients include switching to insulin therapy. The conventional way of adjusting insulin dose often includes incorporating uncertainties in the physician's decision, which leads to vagueness in the prediction of insulin dose. This study aims on the management of normal blood glucose concentration for type 2 diabetes patient who are on insulin therapy, through the intervention of a fuzzy-logic based system that will provide a precise insulin dosage, preventing future health complications. The fuzzy logic controller system has sculpted an important place in the field of medical science, whose fuzzy-rule based output provides very precise and an accurate approach. In this study, two patient-related factors, which are average daily fat intake (grams) and duration of diabetes (years), for 18 patients are taken under consideration to utilize the data for the development of fuzzy rule base in MATLAB. The fuzzy logic system was then used to develop an output, which was later compared with the physician's prescribed dose for each patient. This system was found to generate output (customized insulin dose for individual patient) that was found to be more credible and reasonable when compared with the patient's past medical history. Moreover, the predicted insulin dose by the fuzzy-logic system used in this study recommends insulin dose for patients which suggests to eliminate incidence of hyperglycemic and hypoglycemic events in patients with type 2 diabetes. Thus, the use of fuzzy-logic system provides future hope for the customization of insulin dose for individual patient which will further improve the quality of life of type 2 diabetes patient.

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Chapter 1

Introduction

Diabetes Mellitus is a major and fast-growing public health concern with an estimation of about 422 million adults globally living with diabetes (World Health Organization, 2016). The global prevalence of diabetes has steadily risen over the past few decades, though the proper etiology of this disease is still unclear. Worldwide, the population of diabetes has risen from 108 million, which is about four times higher and are likely to increase by 50% for the next 19 years (Bergman, Phillips, & Cobelli, 1981; Whiting, Guariguata, Weil, & Shaw, 2011; World Health Organization, 2016). World Health Organization (WHO) estimates that the largest number of population living with diabetes falls under the South-East Asian and Western Pacific region, approximately 96 million and 131 million diabetes patients, respectively; which is almost half of the diabetes population in the World (World Health Organization, 2016). Diabetes is a chronic metabolic disorder that manifests when the pancreas cannot effectively produce enough insulin (Type 1) or the body fails to use insulin (Type 2) for controlling normal blood glucose level. It has been observed that Type 2 diabetes has demonstrated high prevalence globally where WHO's South-East Asian region is considered as the red zone for Type 2 diabetes mellitus showing almost 90% of the population having Type 2 diabetes (Al-Rubeaan, 2010; Dorji, 2017). The globally rising trend of obesity, physical inactivity, and the rich energy dense diet have further contributed to an unprecedented rise in the number of type 2 diabetes patients. According to the International Diabetes Federation, Bangladesh will soon be in the top 10 countries with the highest prevalence of diabetes (Al-Rubeaan, 2010). With the increased prevalence of diabetes and its complications, it brings about substantial economic burden to people and their families and is considered as one of the leading causes of premature death. When compared to people who do not have diabetes, patients with type 2 diabetes have an increased risk of 15% of all-cause mortality, which is twice than young people (Chatterjee, Khunti, & Davies, 2017).

Diabetes is a genetically and clinically heterogeneous group of disorders (M Harris, 1995) characterized by chronic elevated blood glucose (hyperglycemia) with the presence of carbohydrate, fat, and protein metabolic disturbance due to defect in insulin action, secretion, or both (Alberti & Zimmet, 1998).

Chronic elevated blood glucose levels lead to the burden of the long-list of health complications, thus significantly degrading the quality of life.

In a healthy person, blood glucose regulation is achieved through two main pathways. The pancreas is the key player of regulating blood glucose level by secreting blood glucose lowering hormones- insulin and glucagon, which keeps blood glucose level normal. The endocrine cells in the pancreas forms the islets of Langerhans that contains five different cell types; α-cells that produces glucagon which represents almost 15-20% of the total islet cells, insulin producing β-cells comprises of 65-80% of the total islets cells and the other types of cells makes up the rest (Röder, Wu, Liu, & Han, 2016). When the blood glucose level decreases due to exercise or physical activity, in between meals or during sleep, a hypoglycemic condition arises. A hypoglycemic event suppresses the secretion of insulin from β-cells and stimulates the production of glucagon from islets α-cells, bringing the blood glucose level to normal (Briant, Salehi, Vergari, Zhang, & Rorsman, 2016; Röder et al., 2016). The glucagon acts on the liver where it stimulates the breakdown of glycogen to glucose and also stimulates the production of new glucose molecules (gluconeogenesis) (Röder et al., 2016). Then again, increased blood glucose level, occurs after meal stimulates β-cells for the production of insulin, which promotes glycogen synthesis (glycogenesis) where glucose molecules are added to form chains of glucagon for storage, lipogenesis (metabolic formation of fat), and the formation of proteins from amino acids (Röder et al., 2016). Thus, hormones secreted from the islets of Langerhans cells of pancreas plays the key role in glucose homeostasis of the whole body. The dysfunction of the endocrine cells results into Type 1 and Type 2 diabetes mellitus (Briant et al., 2016).

The effects of diabetes mellitus includes long term progressive complications such as retinopathy (potential loss of vision), nephropathy (renal failure), peripheral neuropathy (foot ulcers), amputations, autoimmune dysfunctions, sexual dysfunctions and increase incidence of peripheral vascular, cerebrovascular and cardiovascular diseases (Alberti & Zimmet, 1998; M Harris, 1995). Thus, based on the majority of cases, diabetes can be classified into two broad categories: Type 1 and Type 2 diabetes.

Type 1, insulin-dependent diabetes mellitus indicates beta-cell destruction that lead the diabetes patient to depend on insulin in order to sustain life and prevent the development of ketoacidosis and other health complications such as coma. Usually, Type 1 diabetes is characterized by the presence of antibodies of-islets cells or insulin antibody (anti-GAD) which leads to the destruction of beta-cells (Alberti & Zimmet, 1998). It has multiple genetic predispositions and is related to environmental factors, which are not clearly defined. Classically, type 1 diabetes mellitus occurs in juveniles but can be symptomatic at any age (M Harris, 1995). These patients are more prone to autoimmune disorders such as vitiligo, autoimmune hepatitis, Graves' disease, myasthenia gravis, celiac sprue, hashimoto's thyroiditis and pernicious anemia (Silvio Inzucchi, MD; Richard Bergenstal, 2010). Although, Type 1 diabetes accounts for only 5-10% of the total diabetes population and almost 90-95% of the diabetes accounts for type 2 diabetes, non-insulin dependent diabetes mellitus (Alberti & Zimmet, 1998). Initially and throughout the patient's lifetime, they do not need injected form of insulin to survive. Type 2 diabetes can be frequently present with very little or no symptoms and the risk of developing type 2 diabetes increases with age, obesity, and reduced physical activity. Type 2 diabetes can stay undiagnosed for years (Harris, 1993) and possess high risk of developing macro-vascular and microvascular complications (Alberti & Zimmet, 1998; MI Harris, 1993). Type 2 diabetes is characterized by pancreatic β-cells failure, increased hyperinsulinemia and insulin resistance, with an estimation of up to 50% loss of β-cells at diagnosis (Chatterjee et al., 2017). β-cell loss occurs more quickly at a younger age of 10-17 years and this might be the reason for failure of use of medications in patients of a young age. These patients need the administration of insulin at a daily basis. The epidemiology of type 2 diabetes is mainly affected by environmental and genetic factors (Chatterjee et al., 2017). Genetic factors are more expressed when the individual is exposed to obesogenic environment with reduced physical activity, poor lifestyle with excessive consumption of fat and sugar (Chatterjee et al., 2017).

Diabetes is a very complicated disease, which requires self-management by incorporating physical activity into one's lifestyle, using medications safely for maximal effectiveness or taking correct dose of insulin and adhering to a food plan (Crawford, 2017). Type 2 diabetes mellitus can be managed with oral agents such as Thiazolidinedione, Sulfonylureas and Metformin but comes with many adverse effects and also have contradictions with certain health conditions such as sulfonylureas is contradictory with patients having cardiovascular problems (Crawford, 2017). Most of the oral agents for diabetes have some limitations for in-patients of type 2 diabetes. Insulin is the best choice of management of diabetes mellitus for its pronounced superiority over oral medications. When diabetes is not well managed, complications develop that not only threaten health but also endanger life, triggering diabetes ketoacidosis in both type 1 and 2, and hyperosmolar coma in type2 diabetes (World Health Organization, 2016). It has been seen that 25% of patients with diabetes suffers from increased depressive symptoms (Crawford, 2017).

Abnormally low blood glucose level can also appear when a meal is skipped or dosage of anti-diabetic medication taken too high. Therefore, considering all aspects of maintaining a healthy life, diabetes management needs to be patient-focused and responsive to individual's needs. Along with the maintenance of proper nutrition therapy, weight management and physical therapy, several pharmacological oral agents and insulin injection are required for controlling blood glucose level (Crawford, 2017). Diabetes patients on insulin regimen are usually self-monitoring their blood glucose level and the physicians prescribed dose of insulin is not always compatible with the other factors such as weight, height, age, physical activity, carbohydrate intake and BMI of the patient. This mismanagement of insulin often leads of hyperglycemia or hypoglycemia and thus resulting into adverse patient outcomes (Derr, Sivanandy, Bronich-Hall, & Rodriguez, 2007; McCall, 2014; Siddiqui et al., 2013). The Diabetic control and complications demonstrated that improved glycemic control significantly reduces the rate of microvascular, neuropathic and cardiovascular complications (Crawford, 2017). Therefore, in order to overcome such complications, the consideration of a superior insulin dosing system needs to be developed, providing patients with a more accurate dosing regimen of insulin. Such personalized therapy can be developed using a fuzzy-logic based system, which is a computer-based system that prescribes patient with an insulin dose while keeping under consideration of all the other factors that affects blood glucose level of the particular patient (Chowdhury et al., 2017). The fuzzy logic system has the tendency to take over vagueness and uncertainty in a set of data of any size (Lalka & Jain, 2015). This system is a powerful computational based system that learns through the incorporation of expert knowledge, provided as inputs and further using intra-factor and inter-factor relationships, it develops various membership functions (Chowdhury et al., 2017; Lalka & Jain, 2015). The fuzzy-logic system can be very useful to monitor biological system, which is quite difficult to model with simple and linear mathematics. Fuzzy-logic works by the use of 'adaptive controller' with adjustable inputs and outputs that can even be altered easily (Grant, 2007). By combining inputs of various factors affecting blood glucose level and adjusting the insulin dose according to that, running on fuzzy logic rules, we can hope for the better regulation of blood glucose level in patients with diabetes mellitus. Fuzzy-logic needs to be fed with information of the factors that affects the insulin dose of a patient, which are the patient's BMI, food intake (amount of carbohydrate, protein, and fat), weight, height, disease condition and others. This fuzzy-logic based system would provide an optimum dosage output for diabetes patient considering individual patient's requirement with their current diet, health condition, and lifestyle. This fuzzy logic computer system learns through continuous various inputs of data and it uses the inter-factor and intra-factors relationships to develop a very precise and accurate dose of insulin (Chowdhury et al., 2017).

In this study, we examined two independent variables – fat intake and duration of diabetes; and their respective effect on patient's insulin dose. These variables were selected as the inputs for our developed fuzzy system. A study conducted by Hoogt et al., (2017), showed that all macronutrients require insulin, with the addition of each 1g of fat in the diet, requires addition insulin dose. In his study, it was also found that duration of diabetes has a strong association with prandial hyperglycemia that further tend to develop the event of insulin resistance (van der Hoogt, van Dyk, Dolman, & Pieters, 2017). Carbohydrate intake alone cannot be count for the insulin dose, fat and protein intake, duration of diabetes all form an essential part for the calculation of correct insulin dose for the prevention of post-prandial hyperglycemia (Bell, Toschi, Steil, & Wolpert, 2016). Dietary fat greatly induces hyperglycemia, alters insulin requirement, and is an important factor for type 2 diabetes patients, deciding an insulin dose (Ahern, Gatcomb, Held, Petit, & Tamborlane, 1993; Derr et al., 2007; Wolpert, Atakov-Castillo, Smith, & Steil, 2013). In a study conducted by Ahern, it was found that a high-fat meal significantly increased the blood glucose level, sustaining post-prandial hyperglycemia (Ahern et al., 1993). Then again, there is significant positive relation with glycated hemoglobin and duration of diabetes. In normal people, who do not have diabetes mellitus, have small proportion of hemoglobin-A attached to a moiety of carbohydrate (glycated hemoglobin) compared to patient with diabetes mellitus (Verma, Paneri, Badi, & Raman, 2006). With growing duration of type 2 diabetes mellitus, impairment in the body's ability responding to insulin also decreases. Thus, depending on the duration of diabetes, patients need to adjustment their insulin dose accordingly for maintaining a normal blood glucose level (Derr et al., 2007; Verma et al., 2006). Poor glycemic control and other such age related complicacy, along with the duration of diabetes accelerated, causes further detritions of the human body (Verma et al., 2006). In order to live a healthy life, diabetes patient need to take just the right amount of insulin and respond to that insulin dose appropriately. Both hyperglycemia and hypoglycemia can impair insulin sensitivity in a type 2 diabetes (Whiting et al., 2011), resulting into insulin resistance and can even give rise to a different type to health complication (Verma et al., 2006).

This novel personalized self-dosing approach through the use of fuzzy-logic system will help overcome such events (the chances of hyperglycemic and hypoglycemic events), thus preventing further life-threatening complications.

Chapter 2

Experimental Materials and Methods

2.1 Patients Population

24 Type 2 diabetes in-patients from Bangladesh Institute of Research and Rehabilitation for Diabetes (BIRDEM) and PG hospital (renamed as Bangabandhu Sheikh Mujib Medical University), located at Shahbag Dhaka, Bangladesh, were randomly selected for the purpose of this study. They were currently undergoing insulin treatment and have Type 2 diabetes mellitus. In order to conduct the survey on patients, written permission from the Chairperson of both institutions from the Department of Endocrinology were obtained. This study included patients who had additional health problems besides diabetes. All patients participated in this study found to have health issues such as endocrine disorders and other clinically significant health problems, including renal diseases, cardiovascular, pulmonary, calcium homeostasis disorder, eating disorder and smoking. Out of 24 patients, 15 of them were male and 9 of them were female. As part of the survey, each patient's medical history and anthropometric information were recorded. The following information for individual patient was also recorded: gender, age, height, weight, daily food intake over a period of 7-days, average blood glucose level, duration of diabetes and prescribed insulin dose by the physician. Other medical information that is relevant to our studies such as physical activities, health complications, non-diabetic medications, lifestyle were also recorded.

Excluded were 6 subjects with known Type 2 diabetes due to different reasons. Two of the participants have missing data for average blood glucose level as they were on IV saline for the last few days. 2 subjects with less than a year duration of diabetes, 1 subject with 40+ years of diabetes and 1 subject with missing data for daily food intake, average blood glucose level and duration of diabetes were excluded from this study.

Each patient was well informed regarding the purpose of this study and thereby they strictly consented to its usage.

2.2 Baseline data

The input variables used in the fuzzy-logic based system were average fat intake (in grams) and duration of diabetes (in months) for each patient. The output data that was used in the system, contains several sets of insulin dose ranging from very low to very high, which assisted the fuzzy-logic system to provide a specific insulin dose for each patient. The physician's prescribed insulin dose is used while setting the fuzzy rule and will also be helpful for the comparison with the prescribed and predicted insulin dose.

Each sets of data for 7 days of individual patient was noted down for the purpose of this study.

2.2.1 Daily average fat intake and calculation:

The daily diet routine/food plan for each patient was noted down during the interview session. The food plan for breakfast, after breakfast, lunch, after lunch and dinner was separately noted down for all patients. The patient provided information regarding the amount of food content taken each time themselves. Fat content (in grams) in the food plan was later determined from the 'Nutritive Value of Food' chart, approved by the USDA (United Stated Department of Agriculture) (Gebhardt, 2002). Studies have showed that dietary fat consumption increases glucose concentration in blood and adjustment of prandial insulin doses are required. Results from a study shows that high fat meal (>40g of fat) when compared to low fat meal (<20g of fat), increases the blood glucose concentration by double (Bell et al., 2016). The range of values for the input in this study and the membership function for the fuzzy-logic system was fixed based on these findings and other literature (Ahern et al., 1993; Bell et al., 2016; van der Hoogt et al., 2017; Wolpert et al., 2013). The table 2.2.1.1 shows the data for the dietary fat intake for each patient at different interval and the average fat intake in gram

Table 2.2.1.1: Average dietary Fat intake at different intervals and average daily fat intake for each patient (in gm)

Patient Number	Average fat intake at breakfast (gm)	Average fat intake before lunch (gm)	Average fat intake at lunch (gm)	Average fat intake after lunch (gm)	Average fat intake at dinner (gm)	Average Daily Fat intake (gm)
1	2.1	0	8.86	10	12	32.96
2	1.38	10	9.68	10	0.38	31.44
3	1	18	9.3	10	2	40.3
4	3.5	0	1	12	2.5	19
5	1	5	8.8	5	2	21.8
6	2.88	8	9.3	12	9.18	41.36
7	0	6.7	3.5	2	7.3	19.5
8	7	6.6	0	0	8.3	21.9
9	3.9	8	7.7	12	9.2	40
10	9.4	10	9.3	8	9.8	46.5
11	3.38	4	8.86	8	7.3	31.54
12	8.5	8	8.68	8	7.68	40.86
13	3.5	18	10.18	11	8.8	50
14	0	0	8.3	0	2	10.3
15	7	0	8.3	0	2	17.3
16	1	0	8.8	6.9	2.4	19.1
17	8.4	12	5	3	8.3	36.7
18	9	5	9.13	11	8.3	42.43

2.2.2 Duration of diabetes

This data was collected from the patient's medical book approved by the hospital. There is a positive correlation between increased glycated hemoglobin (HbA1c) and duration of diabetes, which means that insulin resistance increases with increase in diabetes duration (Verma et al., 2006). In a study, low duration of diabetes patient (< 5years), when compared to patients with duration of diabetes greater than 5 years (one patient with 22years of diabetes), have fewer percentage of HbA1c of about 40% (Verma et al., 2006). In this study, maximum value for the duration of diabetes is 25 years. The set of ranges are fixed in accordance to knowledge from literature findings (Derr et al., 2007; McCall, 2014; Verma et al., 2006).

Table 2.2.2.1: Duration of diabetes (in years) for 18 patients.

Patient Number	Duration of diabetes (Years)
1	1
2	4
3	15
4	7
5	14
6	15
7	24
8	9
9	5
10	6
11	20
12	20
13	25
14	8
15	14
16	9
17	15
18	10

2.2.3 Prescribed Insulin dose

Prescribed insulin dose is one of the main data, we have used in our study to compare the physicians prescribed insulin dose unit with the predicted insulin dose unit that we have obtained from our study through the fuzzy-logic based system. The physicians have estimated the dose of insulin for each patient using their body weight and disease condition. The Table 2.2.3.1 below shows the prescribed insulin dose by the physician:

Table 2.2.3.1: Prescribed insulin dose by the physician.

Patient Number	Physician's Prescribed Insulin Dose (units)
1	32
2	26
3	34
4	17
5	34
6	34
7	25
8	22
9	39
10	30
11	29
12	20
13	31
14	32
15	34
16	30
17	42
18	22

2.3 Calculation for determining insulin dosage using computational tool

Fuzzy logic is a powerful tool, which incorporates experts' knowledge into the system. In this research, set of information are feed into the tool which designs an algorithm developed from expert knowledge for the dosage of insulin of individual patient depending on many physiological and other patient related factors. Here, the main factors on which the insulin dosage is dependent are average fat intake given in grams and duration of diabetes in years. Depending on these two variables, the fuzzy logic system will provide a superior insulin dosage.

Fuzzy logic is an advanced controlled system which imitates the thought of human and provides imprecise data into a more precise one (Sasi & Elmalki, 2013). For the development of such method, MATLAB is used where precise insulin dose was calculated using fuzzy logic interface. The process of fuzzy logic algorithm has four steps:

1) Fuzzification
2) Plotting the Decision Matrix
3) IF/THEN rule setting
4) Defuzzification

2.3.1 Fuzzification

Fuzzification is the process of transforming the input and an output characteristic with specific interval of variation for each factor and each type of membership function is associated with the fuzzy sets (Sasi & Elmalki, 2013).

Two variables are set for the input where each membership plots represents each factors. Input 1, in the study represents the membership function plot for AFI (Average Fat Intake) and Input 2 represents membership function plots for DD (Duration of diabetes). The fuzzy values are of different ranges: Low (L), Optimum (O) and High (H). The output comprises of 5 ranges of insulin dose starting from very low to very high (A-E).

The figure 2.3.1A below illustrates the process of fuzzification.

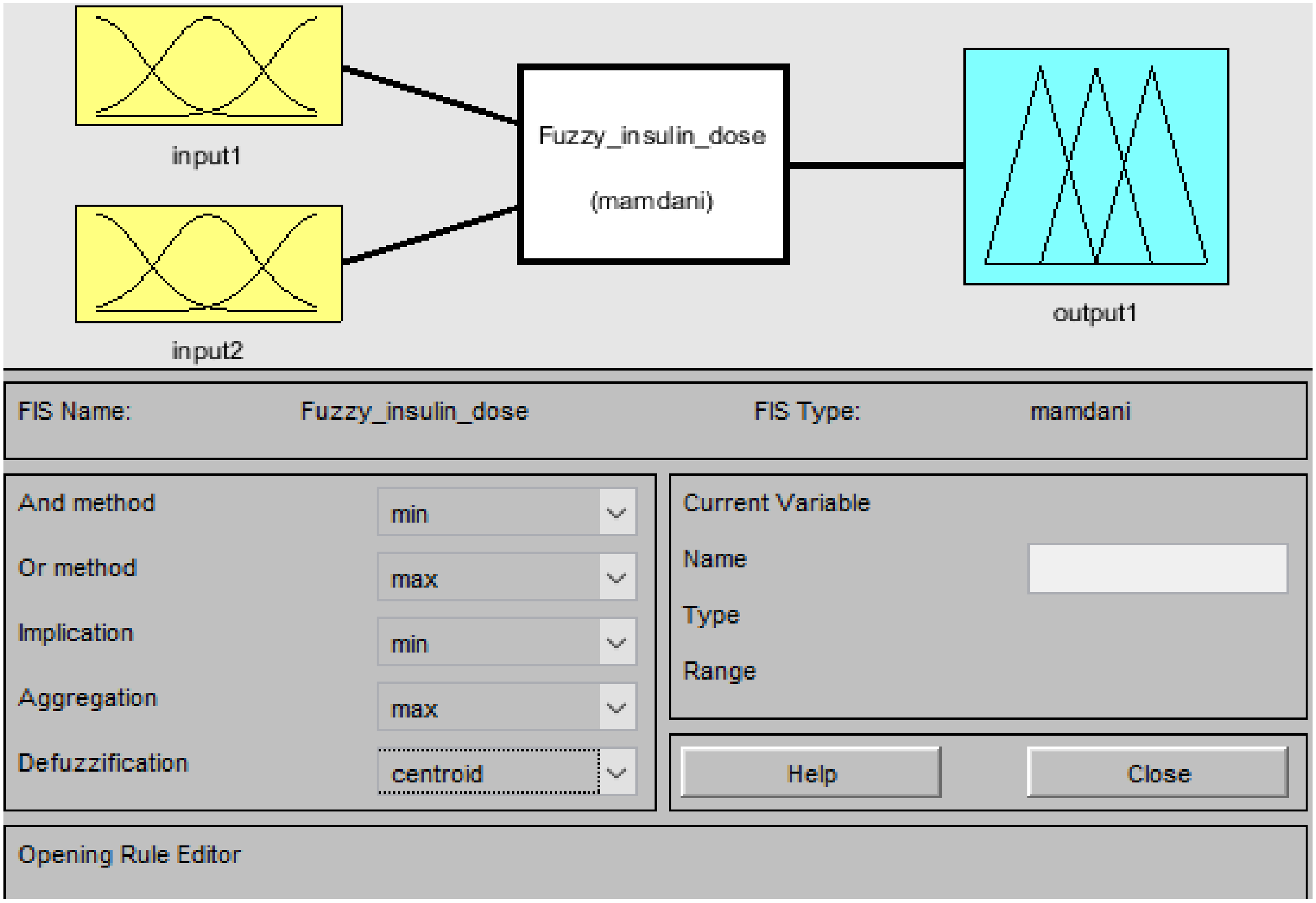

Figure 2.3.1A: The fuzzification Process

The total ranges of values for input (Average Fat Intake/gm and duration of diabetes/yrs.) and output (insulin dose/units) are shown in the table 2.3.1.1 below:

Table: 2.3.1.1: Input and Output range values.

Input		**Output**
AFI (gm)	**DD (duration of Diabetes/yrs.)**	**Insulin Dose**
10-50	30-100	15-45

The membership function for each factor/fuzzy set throws numerical value in the interval [0, 1], where the membership function of '0' means the factor/element does not belong to the fuzzy set while the membership function '1' fully belongs to the fuzzy set. In fuzzy logic, the membership function can never be greater than '1' and at this point, the membership value is known as 'Unity membership point'. Membership function for each fuzzy set (for the two factors) helps to represent linguistic term into a fuzzy graphical representation (Radha & Rajagopalan, 2007). In the membership function graph, the X-axis represents the universe of discourse and the Y-axis represents the degree of membership. In this study, we have used the Triangular function.

The fuzzy set variables (input) have been set up using the following ranges:

Input 1: Average Fat intake {low, medium, high}

Table 2.3.1.2: Fuzzy values, unity membership points and range of Average fat intake (AFI).

Average fat intake (AFI)		
Fuzzy values	**Unity Membership Points**	**Range**
Low (L)	20	10-30
Optimum (O)	30	20-40
High (H)	40	30-50

Membership function plot was made for each range (Low Medium High), where membership of unity for AFI_L (Average Fat Intake Low) set at 20, AFI_O (Average Fat Intake Optimum) at 30 and AFI_H (Average Fat Intake _High) at 40. Other values have a membership lower than 1. The total range for Input 1 has been set from 10-50.

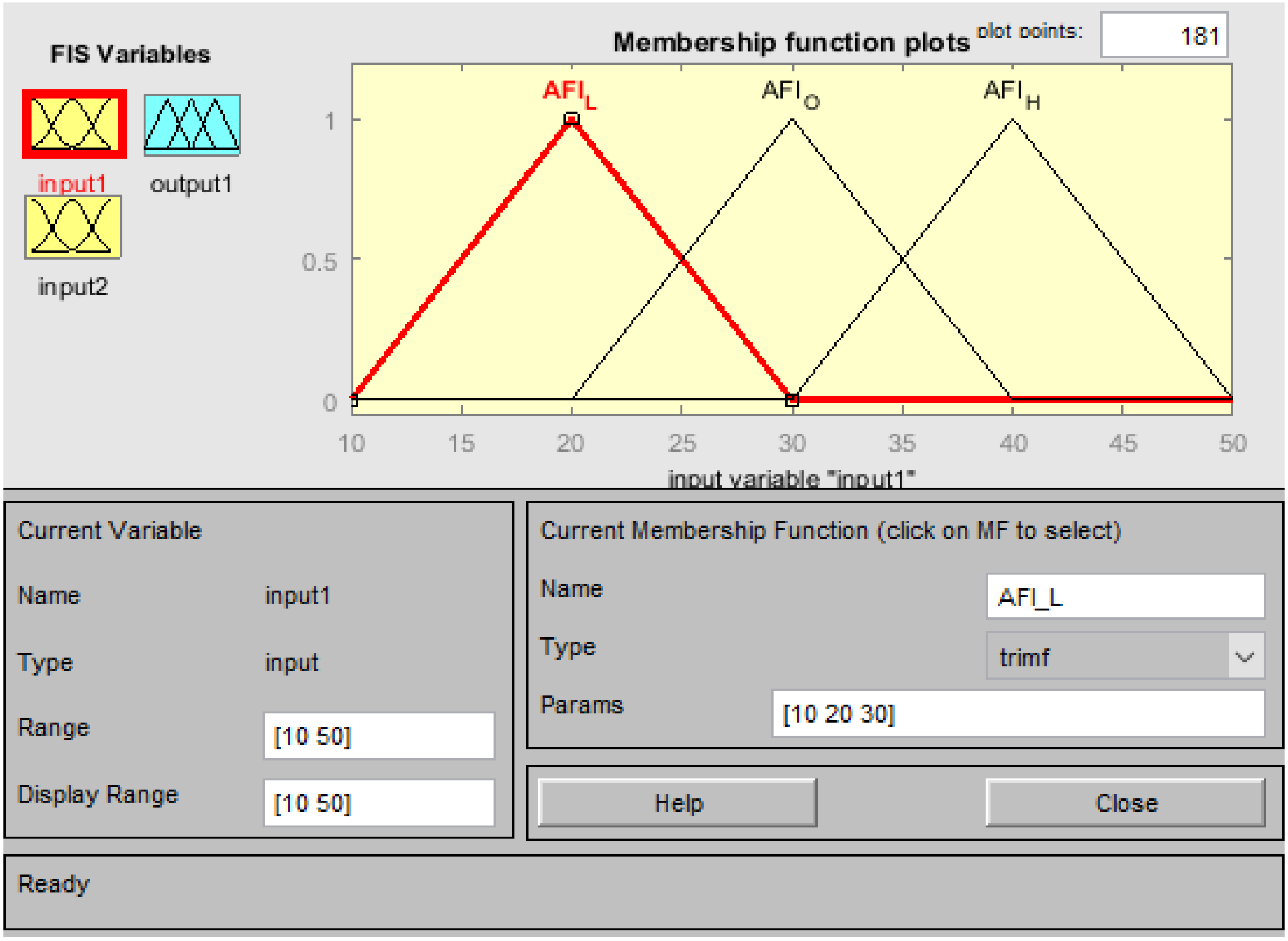

Figure 2.3.1B: Membership function for AFI_L

The membership function plots are all chosen to be triangular as stated previously. The Figure 2.3.1B specifically shows the membership function plot for AFI_L (Average fat Intake _L) where any value other than 20 within the range 10-30 have membership function less than 1.

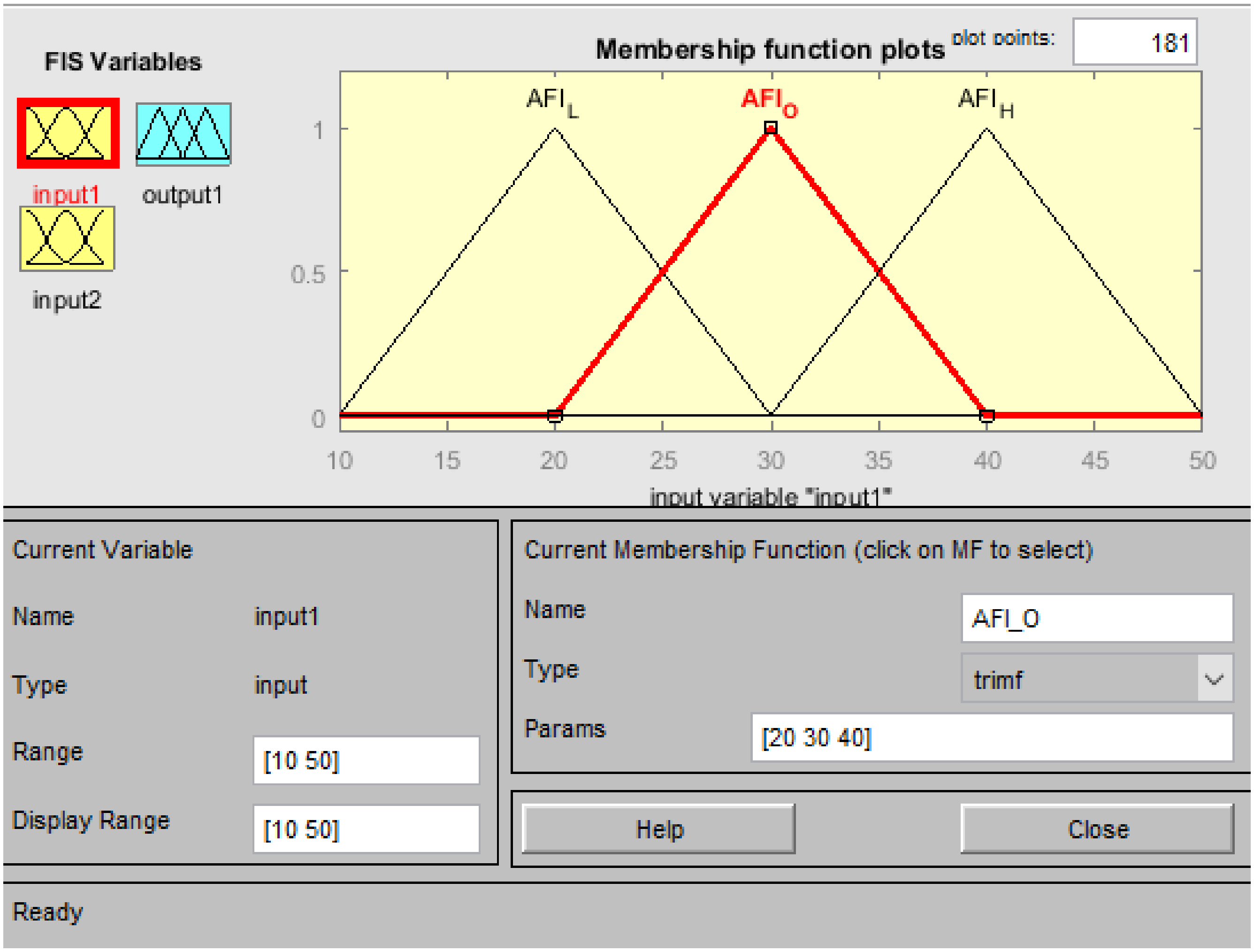

Figure 2.3.1C: Membership function for AFI_O

This Figure 2.3.1C illustrates the membership function plot for Average Fat Intake_Optimum (AFI_O) where values below and above 30 within the range 20-40 have membership value less than 1. The unity membership point of 1 for AFI_O is at 30.

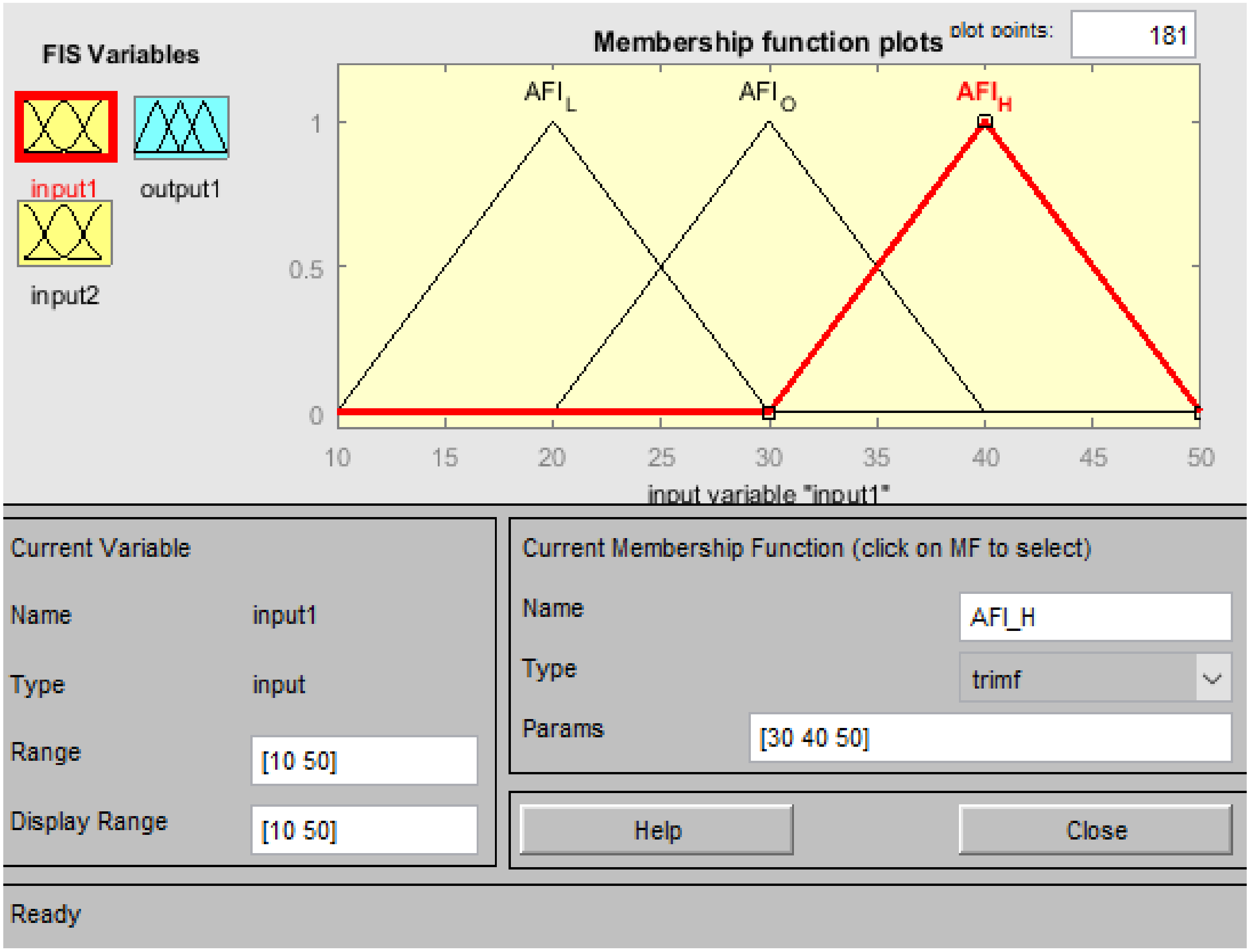

Figure 2.3.1D: Membership function for AF1_H.

Figure 2.3.1D: shows the Average Fat intake (AFI_H) where 40 is set to have membership value of 1 while the other values with the range 30-50 have membership value less than 1.

There are regions of overlapping membership in all the triangular function for AFI_L, AFI_O, AFI_H.

Input 2: Duration of diabetes {low, medium, high}

The range for the membership function plots for Input 2 is also triangular and is fuzzified with three Triangular membership function (Low, Optimum, High). The total range for duration of Diabetes has been set 1-25 and is shown in table 2.3.1.3.

Table 2.3.1.3: Fuzzy values, unity membership points and range for duration of diabetes (DD).

Duration of Diabetes (DD)		
Fuzzy values	Unity Membership Points	Range
Low (L)	4	1-7
Optimum (O)	10.5	5-16
High (H)	19	13-25

In table 2.3.1.3, DD of 4 signifies an absolute low duration of diabetes. Likewise, DD of 19 means a perfectly high duration of diabetes, which is the Unity membership point for the fuzzy value high (H). The Unity membership for Optimum (O) is 10.5, which is also the best optimum value for this range.

The membership functions for DD_L, DD_O and DD_H are all constructed in accordance with the unity membership function and their respective range. Table 2.3.1.3 are illustrated in figure 2.3.1E, 2.3.1F and 2.3.1G

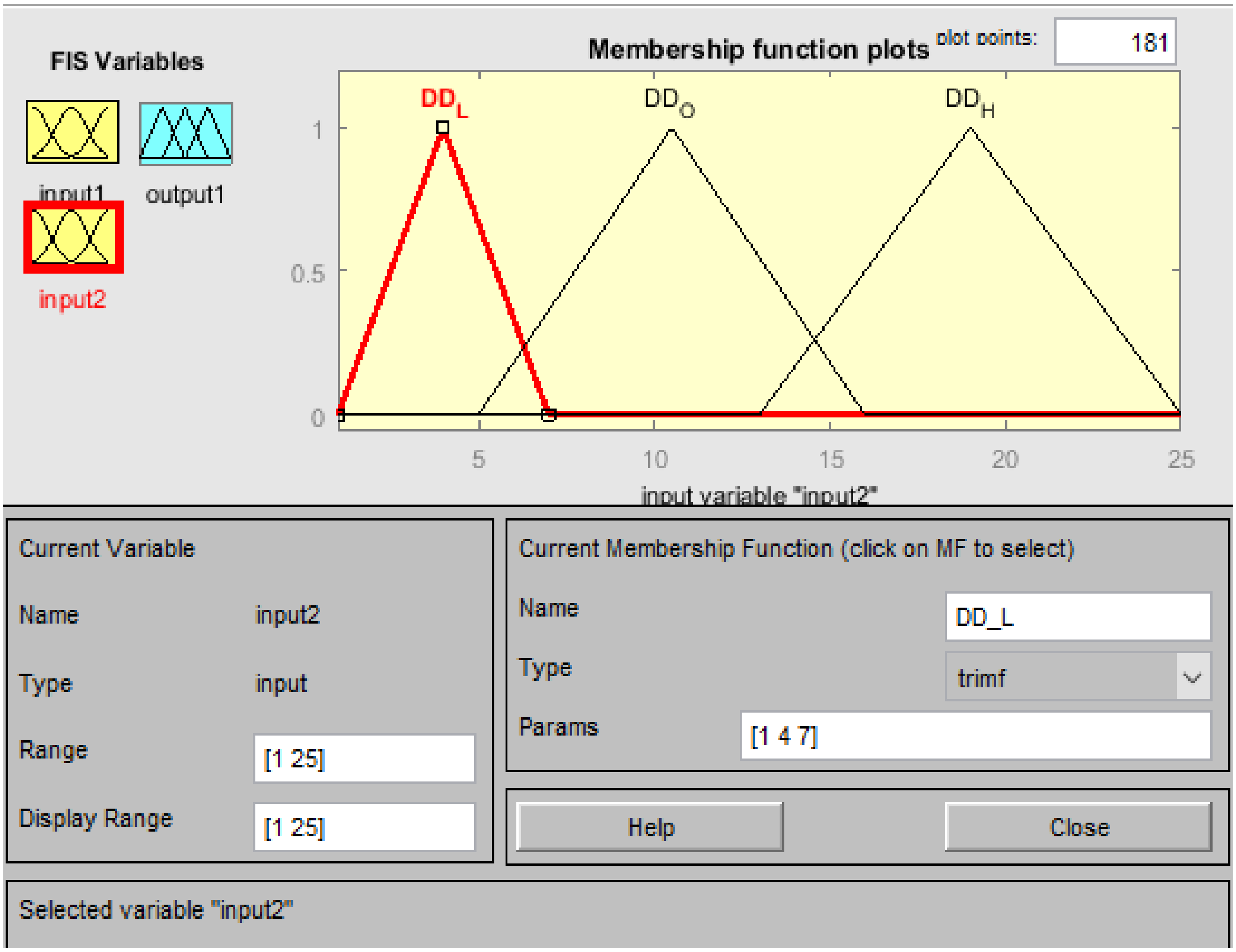

Figure 2.3.1E: Membership Function for DD-L.

The membership value for DD_L (Duration of Diabetes_Low) has been set within the range 1-7 where values other than 4 have membership less than 1.

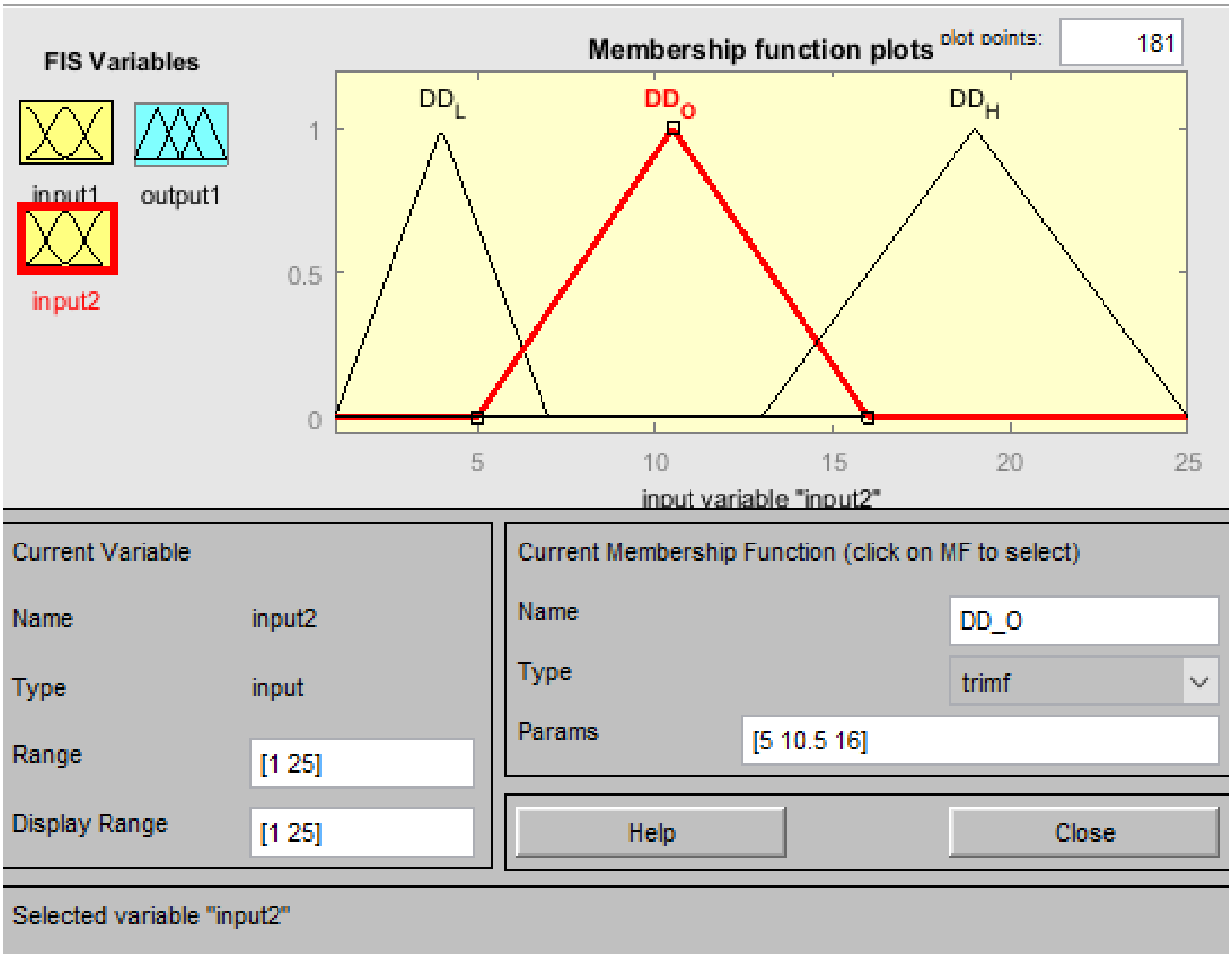

Figure 2.3.1F: Membership function for DD_O.

The membership value for DD_O (Duration of Diabetes_Low) below and above 10.5 is less than 1. There are regions of overlapping with the other function plots for DD_L and DD_H

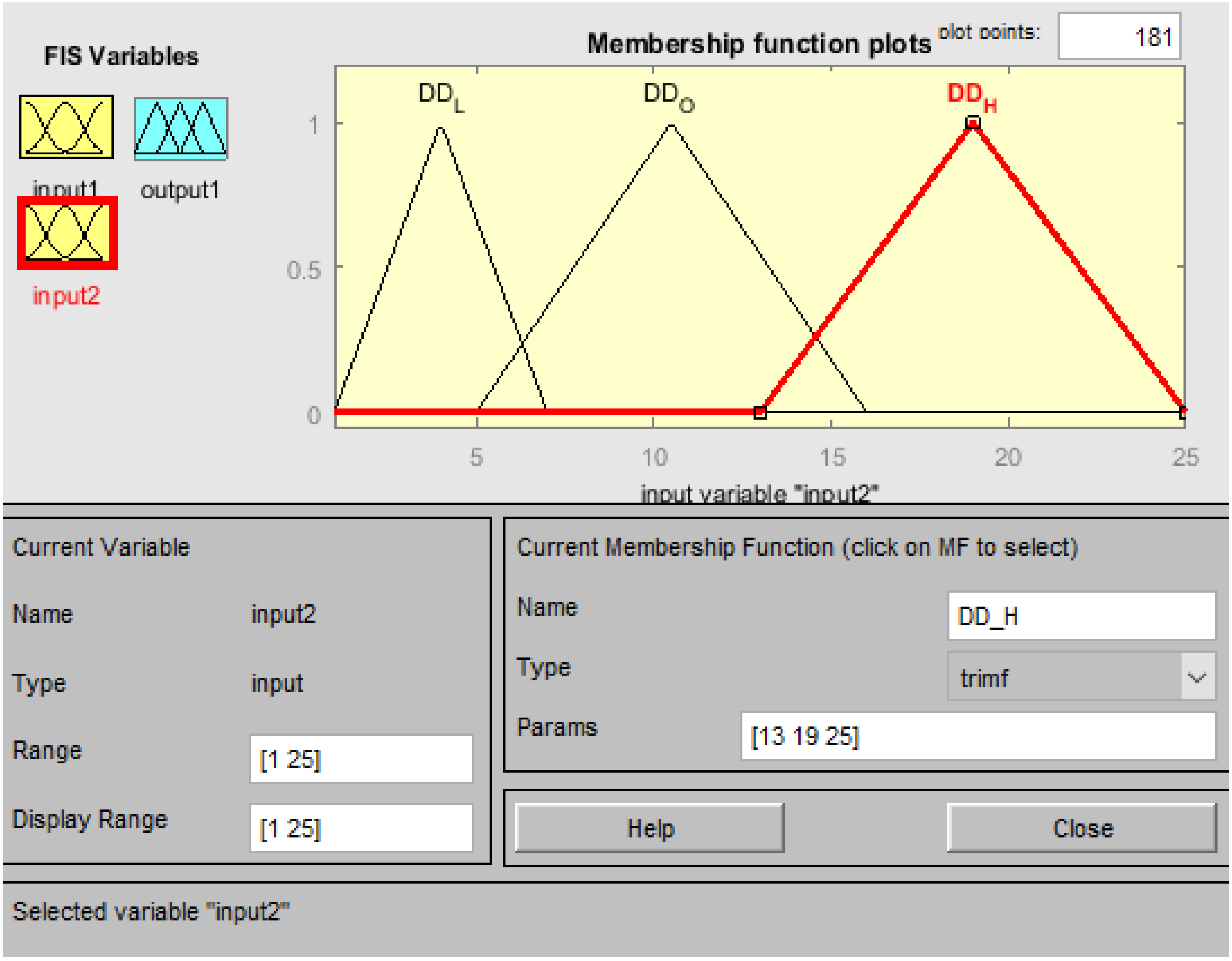

Figure: 2.3.1G: Membership function for DD_H.

For DD_H, values below and above 15 has been set with membership value less than 1.

All membership function for DD_L, DD_O and DD_H are triangular and have overlapping between them.

Output: Insulin Dose {A, B, C, D, E}

The last set of membership functions for the fuzzification is the output, which is the insulin dose. Five membership functions (A, B, C, D, E) are included with set of ranges for each function.

The total range lies within 15-45. There are regions of overlapping within all membership function plots and all are triangular. The fuzzy values, the Insulin Dose Range and their respective Unity membership points are given in the table 2.3.1.4 below:

Table 2.3.1.4: Fuzzy values, Unity membership points and range for Insulin dose.

Insulin Dose (ID)		
Fuzzy values	Unity Membership Points	Range
A	20	15-25
B	25	20-30
C	30	25-35
D	35	30-40
E	40	35-45

Figure 2.3.1H, 2.3.1I, 2.3.1J, 2.3.1K and 2.3.1L illustrates the Output for the A-E fuzzy membership functions. All membership functions are triangular and have overlapping between them.

Figure2.3.1H specifically illustrates the membership function plot for Range A with membership unity point at 20. Other values less than or greater than 20 have membership value less than 1

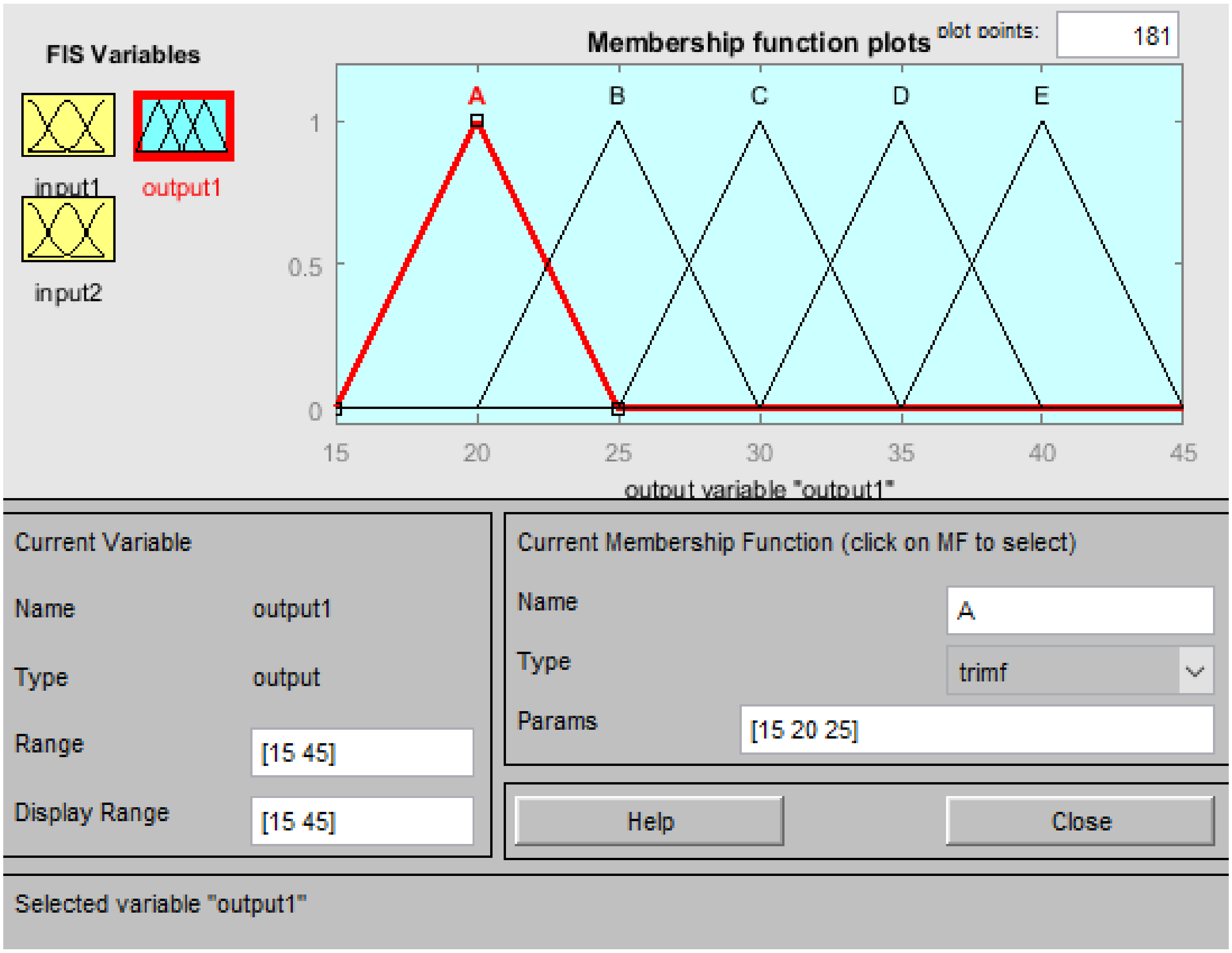

Figure 2.3.1H: Membership function for Insulin Dose_A.

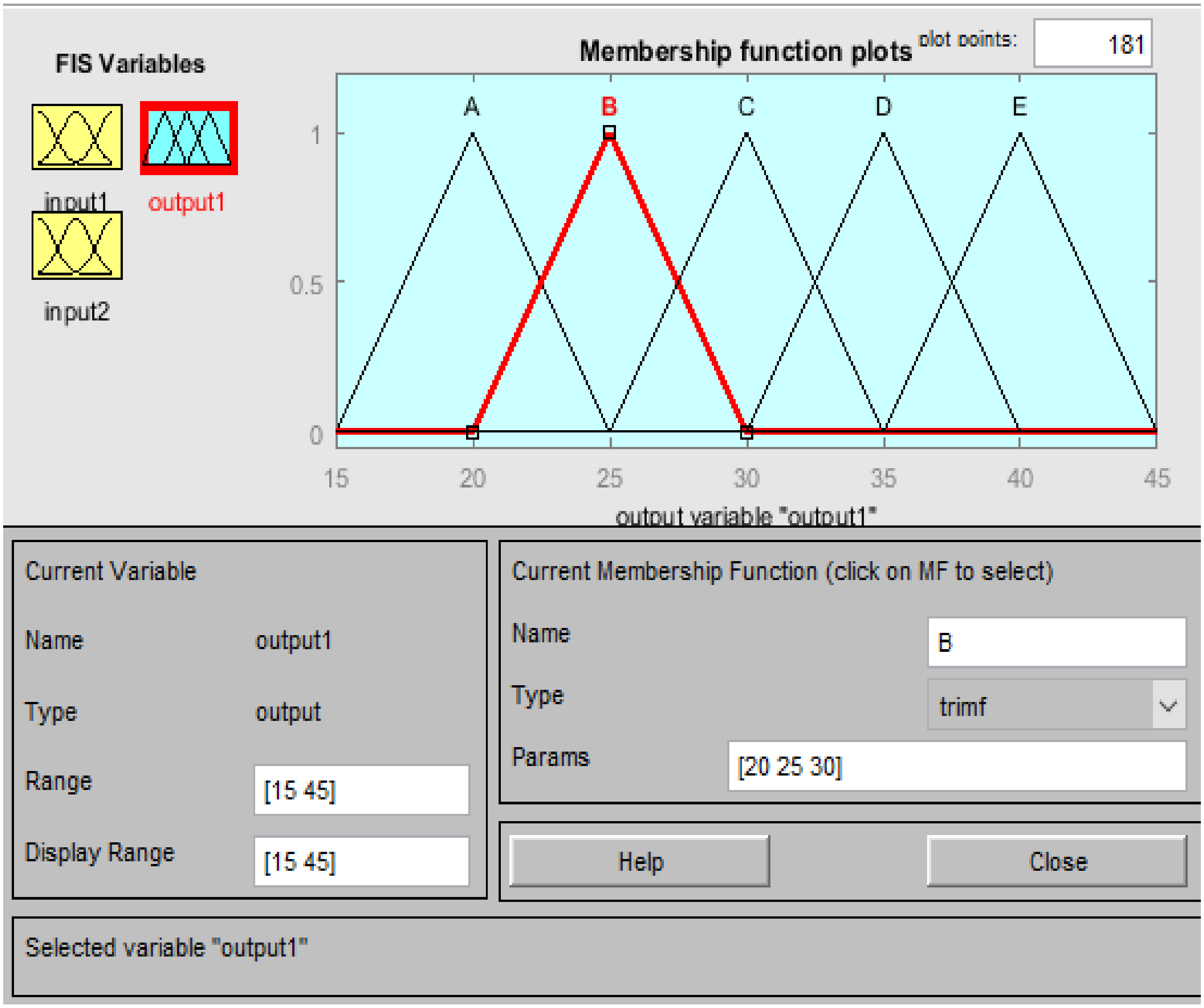

Figure: 2.3.1I: Membership function for Insulin Dose_B.

Figure 2.3.1I illustrates the membership function plot for Insulin Dose_B where values below and above 25 within the range 20-30 have membership value less than 1. The unity membership point of 1 for B is at 25.

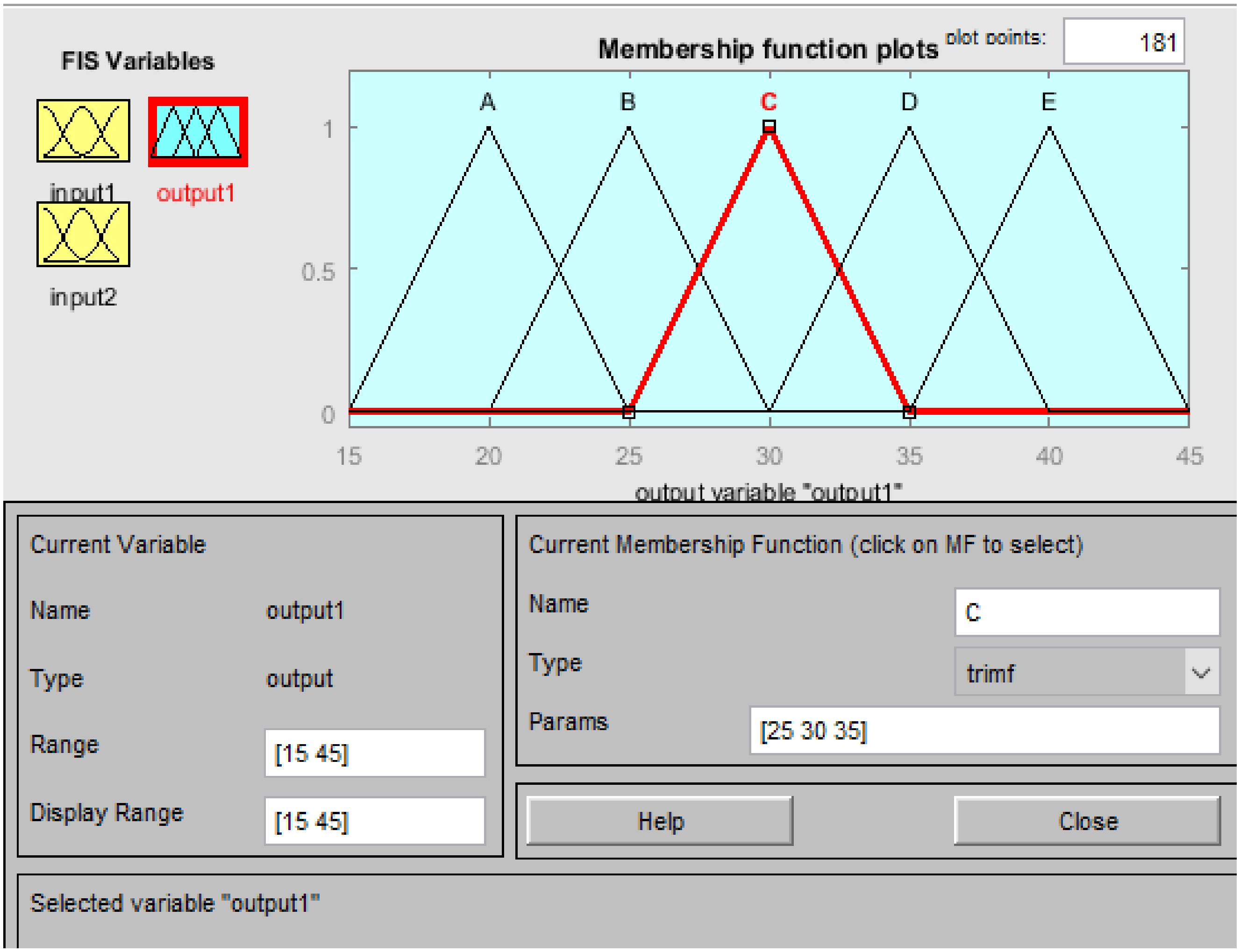

Figure: 2.3.1J: Membership function for Insulin Dose_C.

Figure 2.3.1J illustrates the membership function plot for Insulin Dose_C (C) where values below and above 30 within the range 25-35 have membership value less than 1. The unity membership point of 1 for O is at 30.

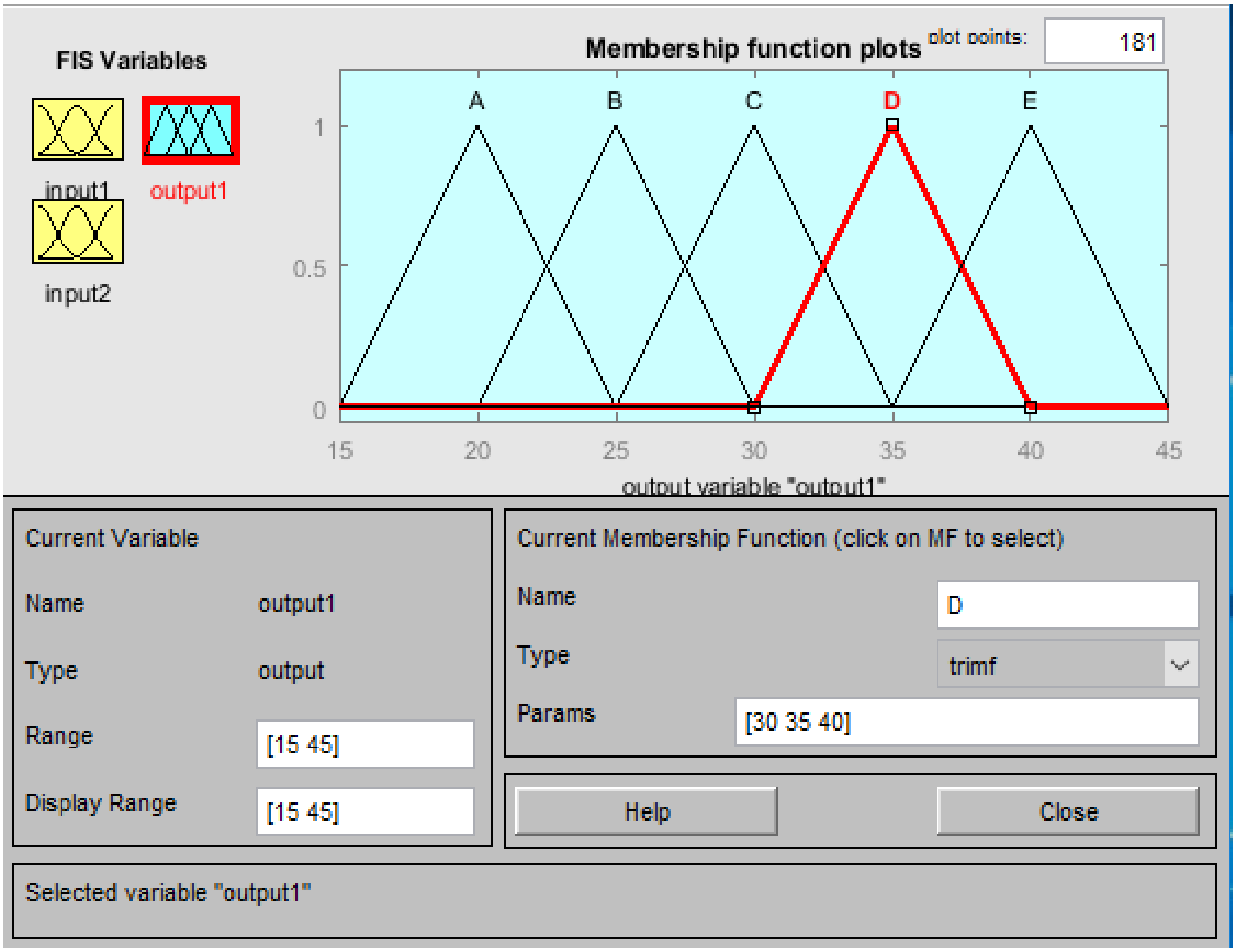

Figure 2.3.1K: Membership function for Insulin Dose_D.

Figure 2.3.1K illustrates the membership function plot for Insulin Dose_D where values below and above 35 within the range 30-40 have membership value less than 1. The unity membership point of 1 for D is at 35.

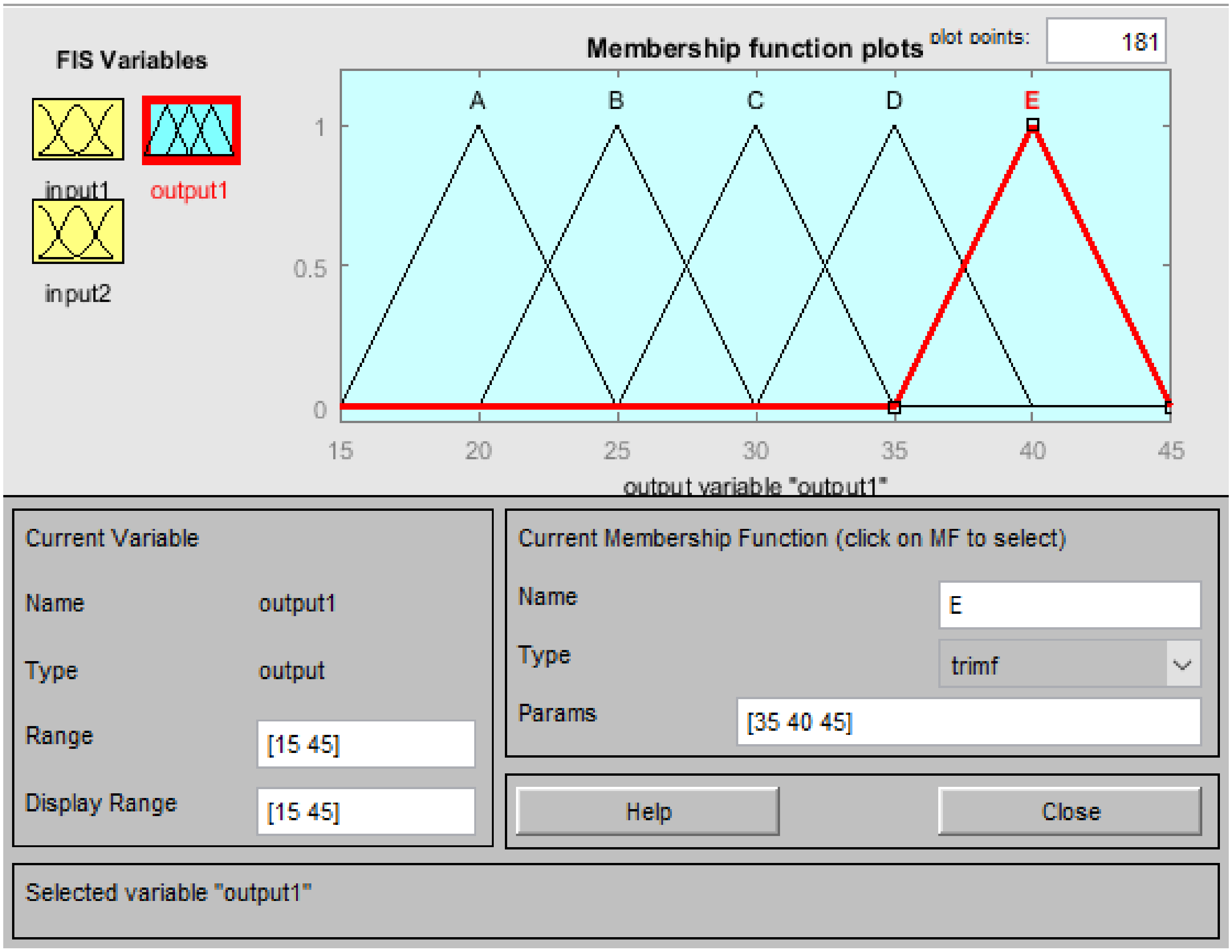

Figure 2.3.1L: Membership function for Insulin Dose_E.

Figure 2.3.1L illustrates the membership function plot for Insulin Dose_E where values below and above 40 within the range 35-45 have membership value less than 1. The unity membership point of 1 for E is at 40.

To summarize the fuzzification process, in this study, a two input and one output system has been used. Each input and output have different fuzzy values with different ranges, unity membership points and have varying overlapping regions, following a triangular shape.

2.3.2 Plotting decision matrix:

Once the membership functions were defined, the next step for fuzzy inferencing is to plot the decision matrix which will further enable us to set the if/then rule. The decision matrix is prepared from both expert knowledge and data collected from the survey. The best possible outcome ranges of insulin dose, considering the two factors are put on the decision matrix in the table 2.3.2.1 table below:

Table 2.3.2.1: Insulin Dose range

Insulin Dose	
Category	**Range**
A	15-25
B	20-30
C	25-35
D	30-40
E	35-45

The decision matrix is made with every possible combination of the set of categories for the two factors i.e. Average Fat Intake (AFI) and Duration of Diabetes (DD). Based on the knowledge from literature, expert knowledge and information from the data collected from the patient, a category from the Insulin Dose Ranges are set for each combinations of AFI and DD. The decision matrix is given below:

Table 2.3.2.2: Decision Matrix

AFI **DD**	**L**	**O**	**H**
L	A	C	C
O	B	D	D
H	C	D	E

The insulin dose can be easily recommended for a patient from the decision matrix in table 2.3.2.2. For example, if the AFI for the patient lies within the range of 10-30 which is Low (L) and the duration of diabetes is also Low (L), then the recommended insulin dosage should be A (range between 15-20 units). Here, fuzzy will provide a specific value for the patient rather than providing insulin dose within a range.

2.3.3 If/then rule setting:

Using the decision table, the fuzzy if/then rules are used for developing the system which will enable the fuzzy logic to provide an output of a more precise insulin dose for Type 2 diabetes patients. In this study, 9 rules have been developed, they are as follows:

1. *If* (AFI is L) *and* (DD is L) *then* (insulin Dose is A)
2. *If* (AFI is O) *and* (DD is L) *then* (insulin Dose is C)
3. *If* (AFI is H) *and* (DD is L) *then* (insulin Dose is C)
4. *If* (AFI is L) *and* (DD is O) *then* (insulin Dose is B)
5. *If* (AFI is O) *and* (DD is O) *then* (insulin Dose is D)
6. *If* (AFI is H) *and* (DD is O) *then* (insulin Dose is D)
7. *If* (AFI is L) *and* (DD is H) *then* (insulin Dose is C)
8. *If* (AFI is O) *and* (DD is H) *then* (insulin Dose is D)
9. *If* (AFI is H) *and* (DD is H) *then* (insulin Dose is E)

These nine set of rules are set in the fuzzy-login system and are illustrated in the figures 2.3.3A and 2.3.3B.

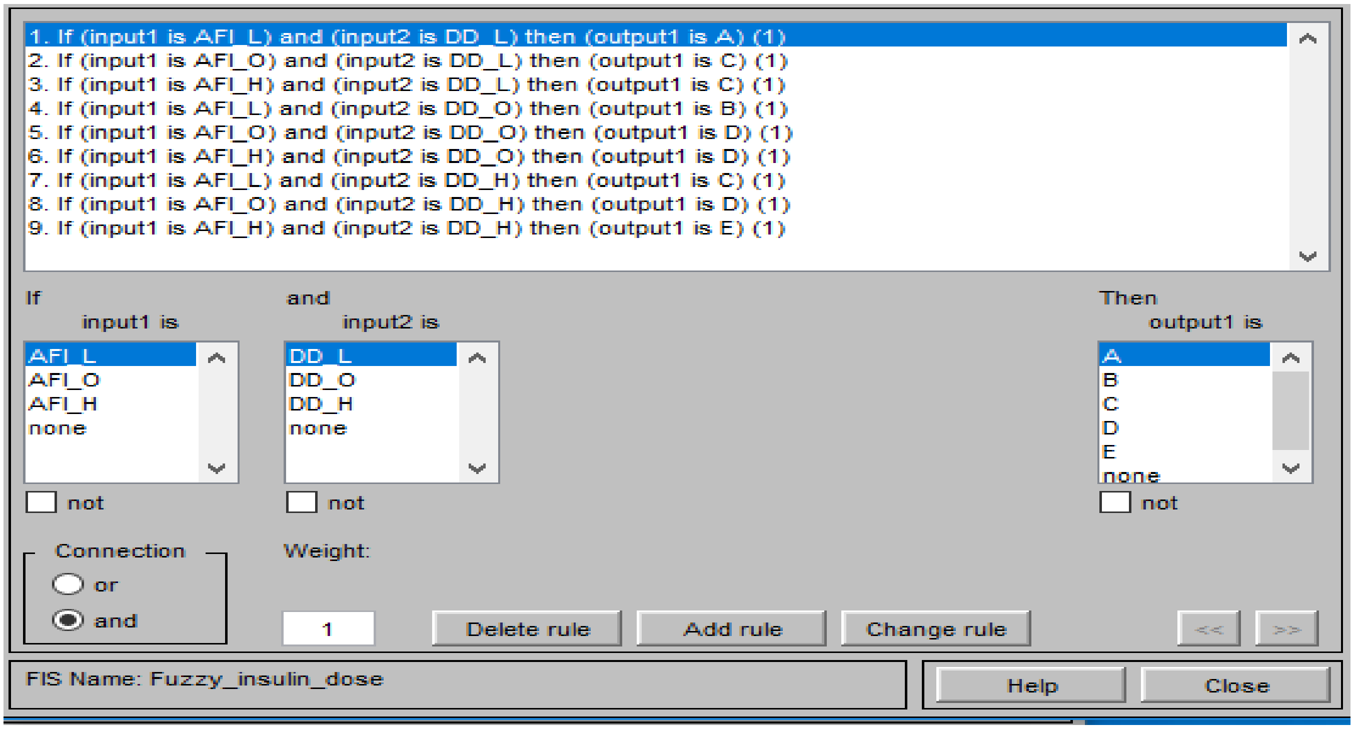

Figure 2.3.3A: If/then rule setting in the fuzzy-system.

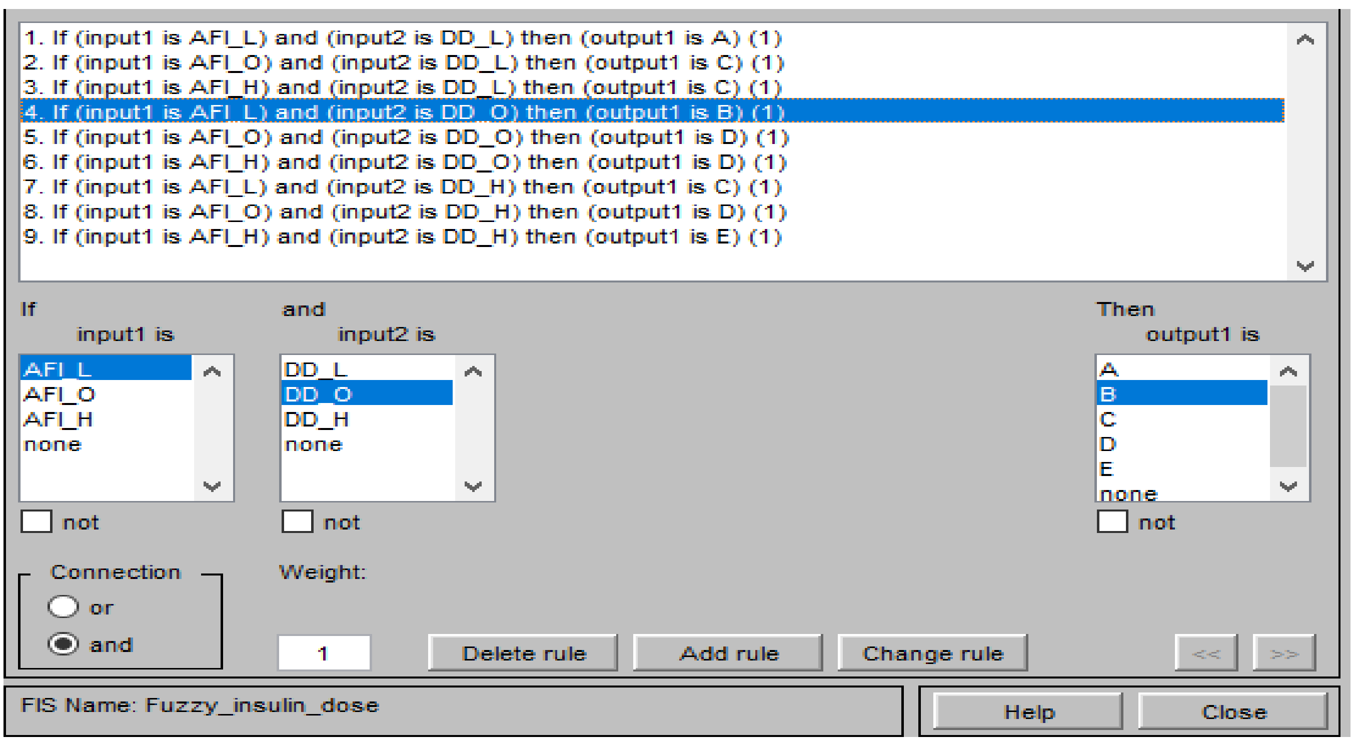

Figure 2.3.3B: If/then rule setting in the fuzzy system.

2.3.4 Defuzzification

Defuzzification is the process that converts the input aggregation results to a crisp value for the Output. This process transforms the fuzzy set of values into crisps values. The membership function and if/then rule have given values for the insulin dose in ranges, which is not precise. Thus, the last step in defuzzification gives an exact value for the insulin dose depending on the patient's average fat intake and duration of diabetes. Fuzzy methodology analyzes the personal physical data for each patient, converts the deduced data into knowledge and lastly presents the decision results into a precise value. In this study, 'centroid' is the default method used which provides the best preciseness.

The figures below show the defuzzified predicted value for the set of inputs given for patients that is viewed through the Rule Viewer feature of MATLAB fuzzy-logic toolbox and a precise predicted value for the insulin dose is provided by this software.

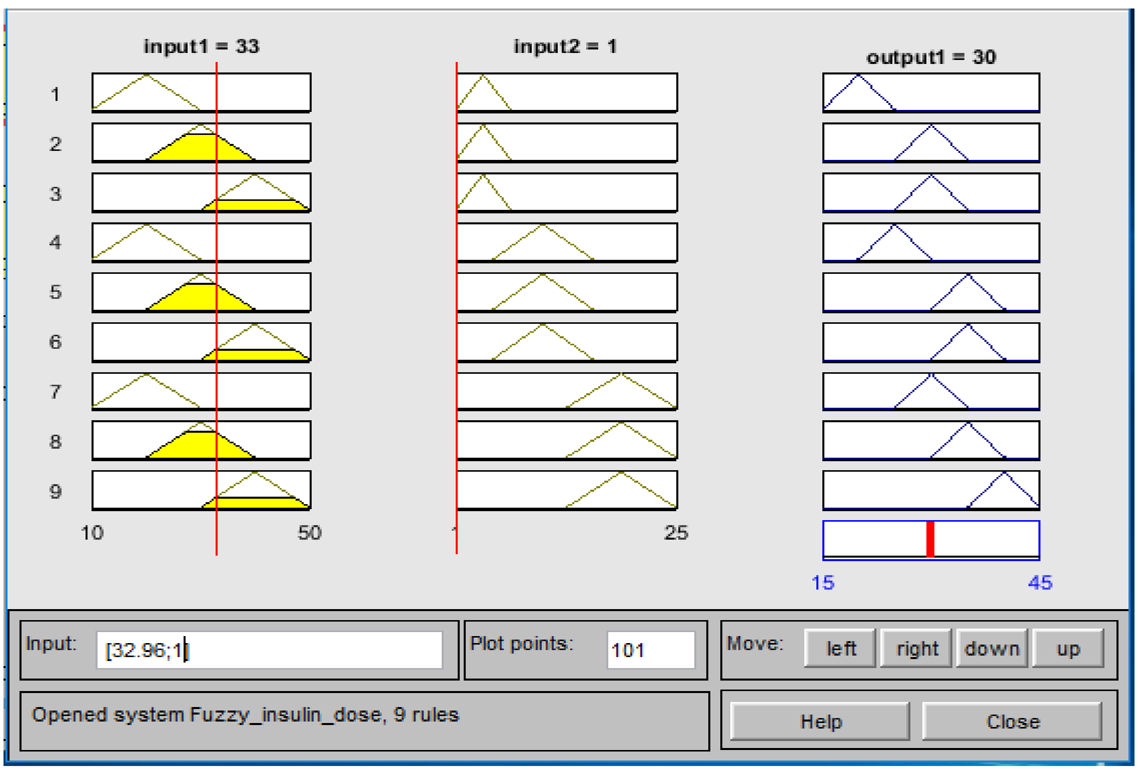

Figure 2.3.4A: Recommended insulin dosage for patient 1 by the Fuzzy-logic system.

Figure 2.3.4A shows input 1 which is the average fat intake (AFI) and input 2 (DD) which is duration of diabetes for patient number 1, where AFI= 32.96 grams and DD= 1 year. The Fuzzy logic system recommended the patient an insulin dosage of 30 units.

The figure 2.3.4B below represents the recommended insulin dosage by the fuzzy-login system after input value of AFI and DD for individual patient is provided in the system:

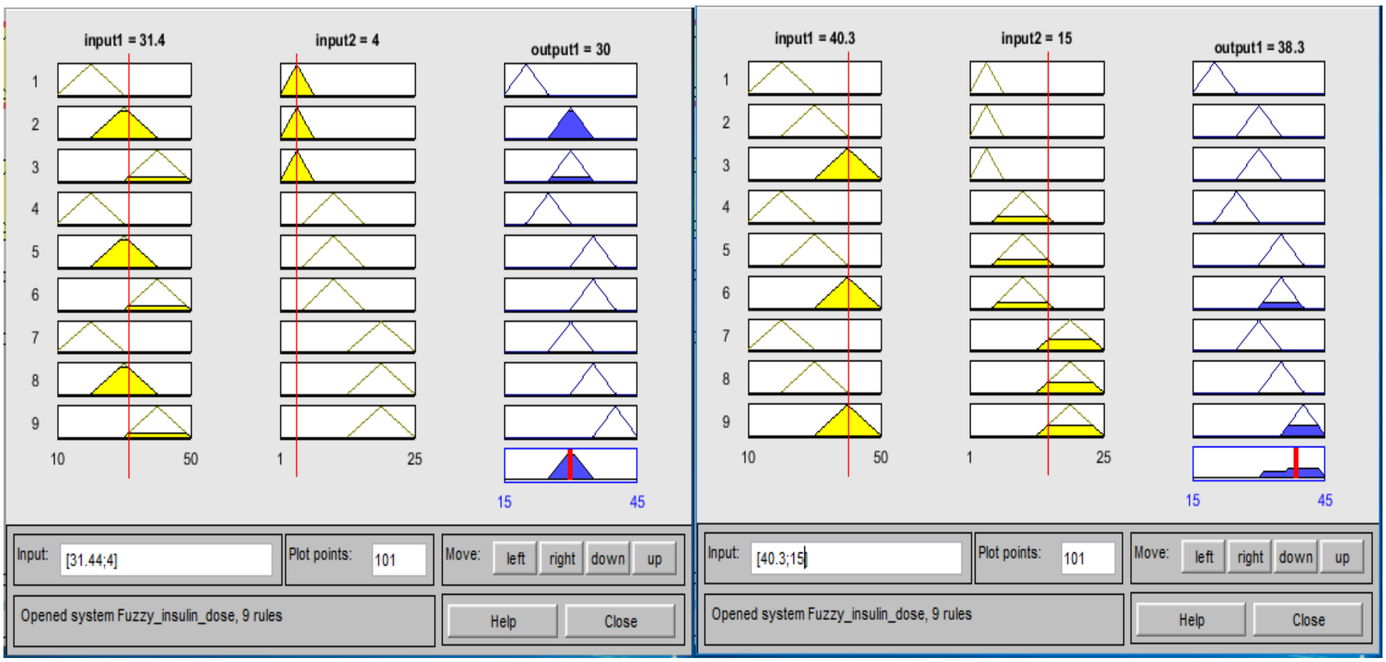

Figure 2.3.4B: Defuzzified output value for patient 2 and patient 3 from left to right with AFI=31.44; DD=4 and AFI=40.3; DD= 15 respectively.

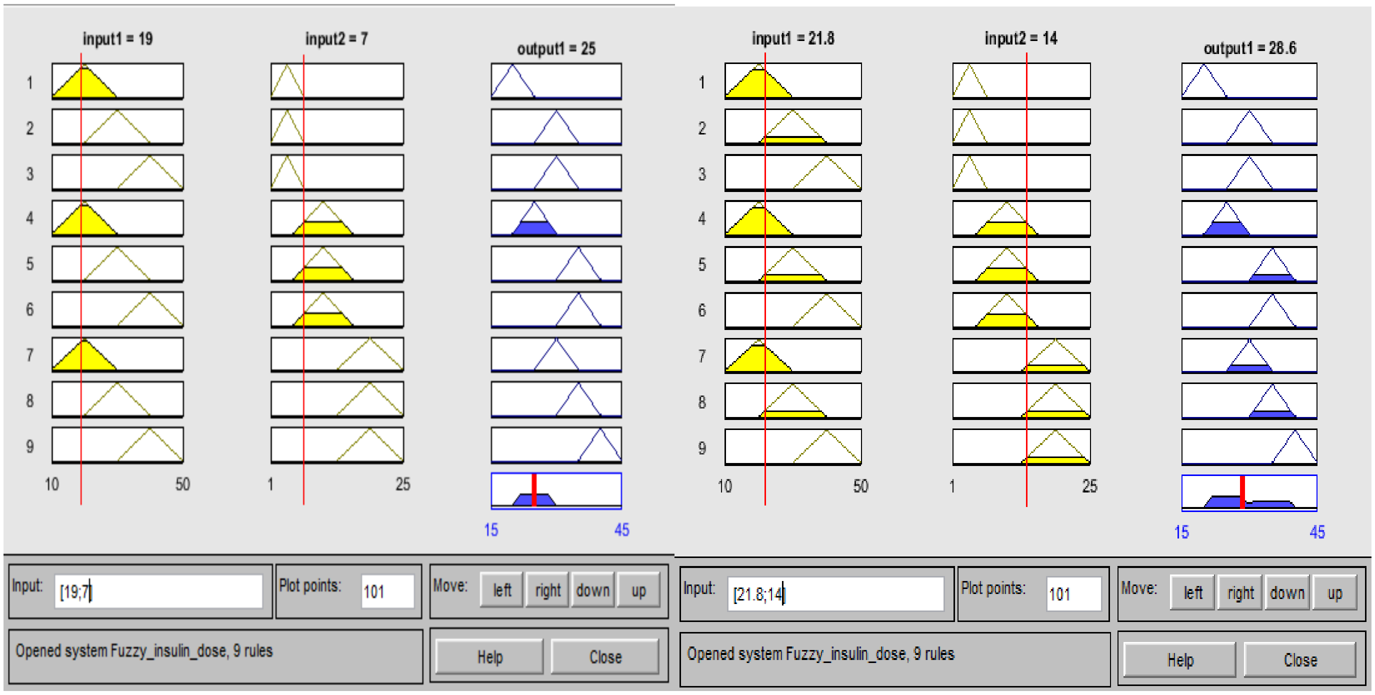

Figure 2.3.4C: Defuzzified output value for patient 4 and patient 5 from left to right with AFI=19; DD=7 and AFI=21.8 ; DD= 14 respectively.

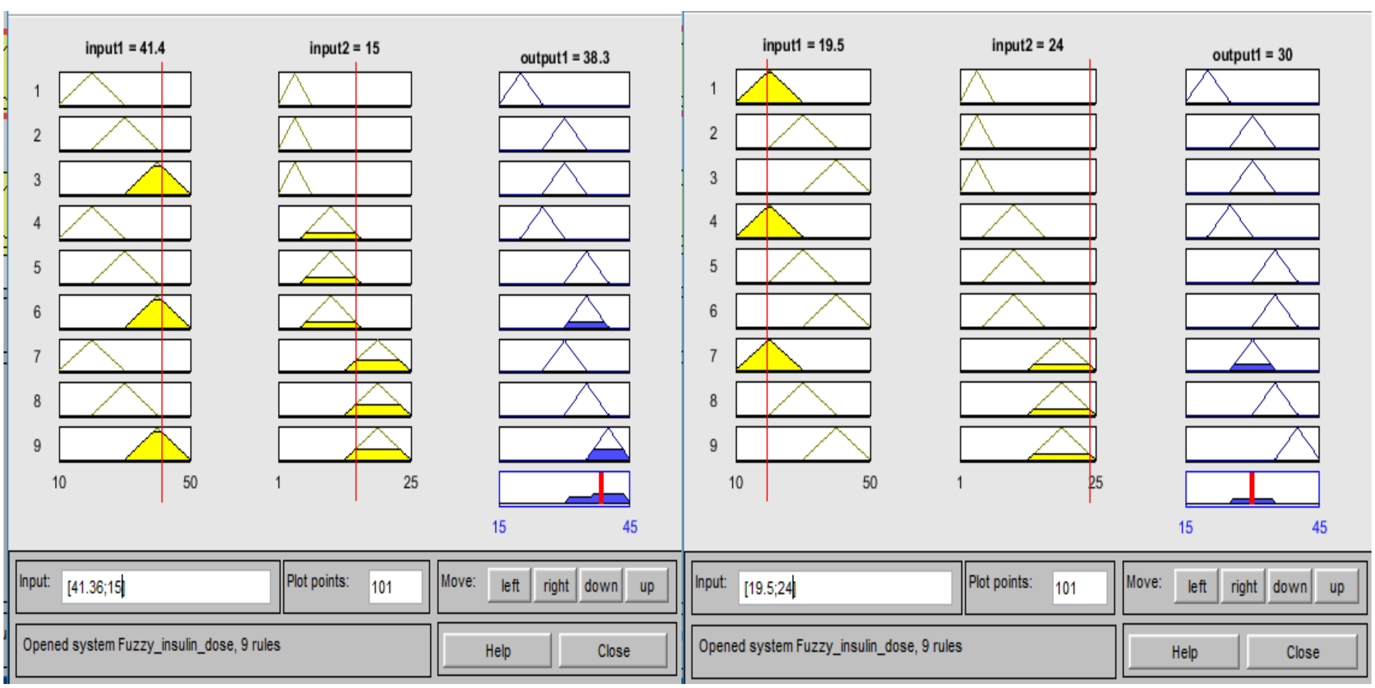

Figure 2.3.4D: Defuzzified output value for patient 6 and patient 7 from left to right with AFI=41.36; DD=15 and AFI= 19.5; DD= 24 respectively.

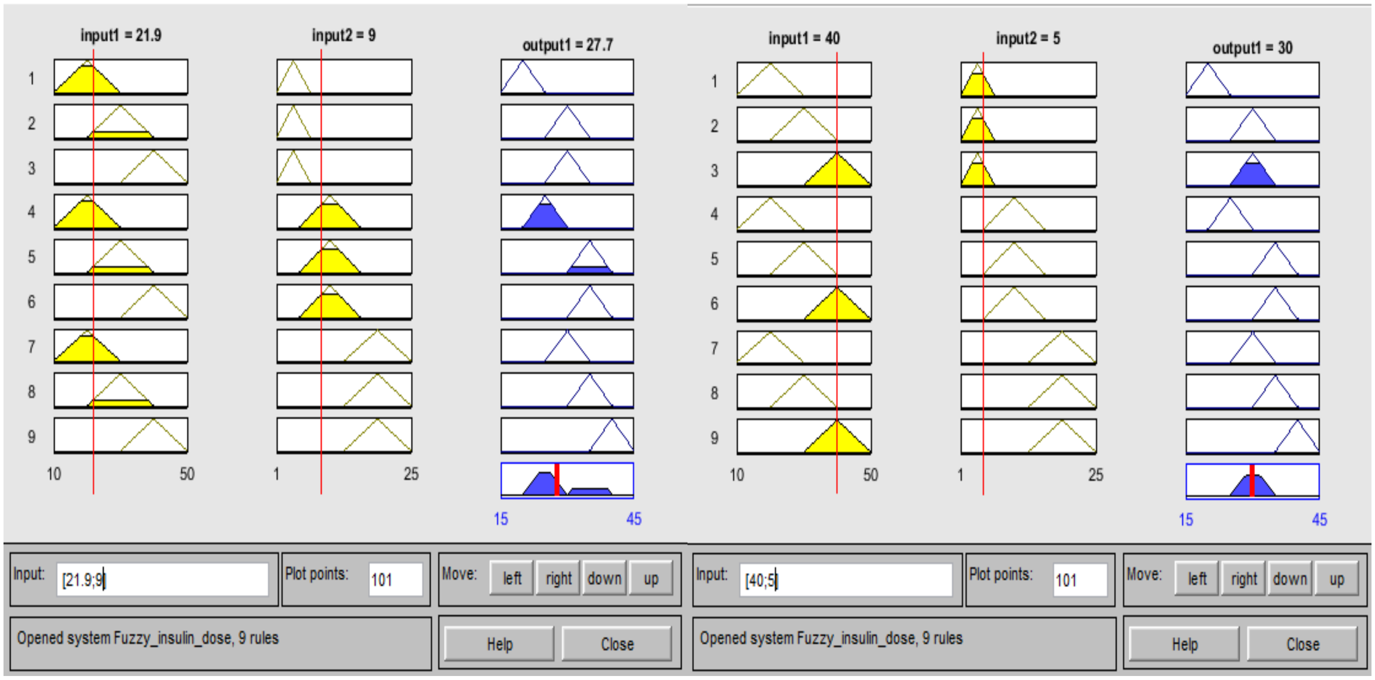

Figure 2.3.4E: Defuzzified output value for patient 8 and patient 9 from left to right with AFI=21.9; DD=9 and AFI=40; DD= 5 respectively.

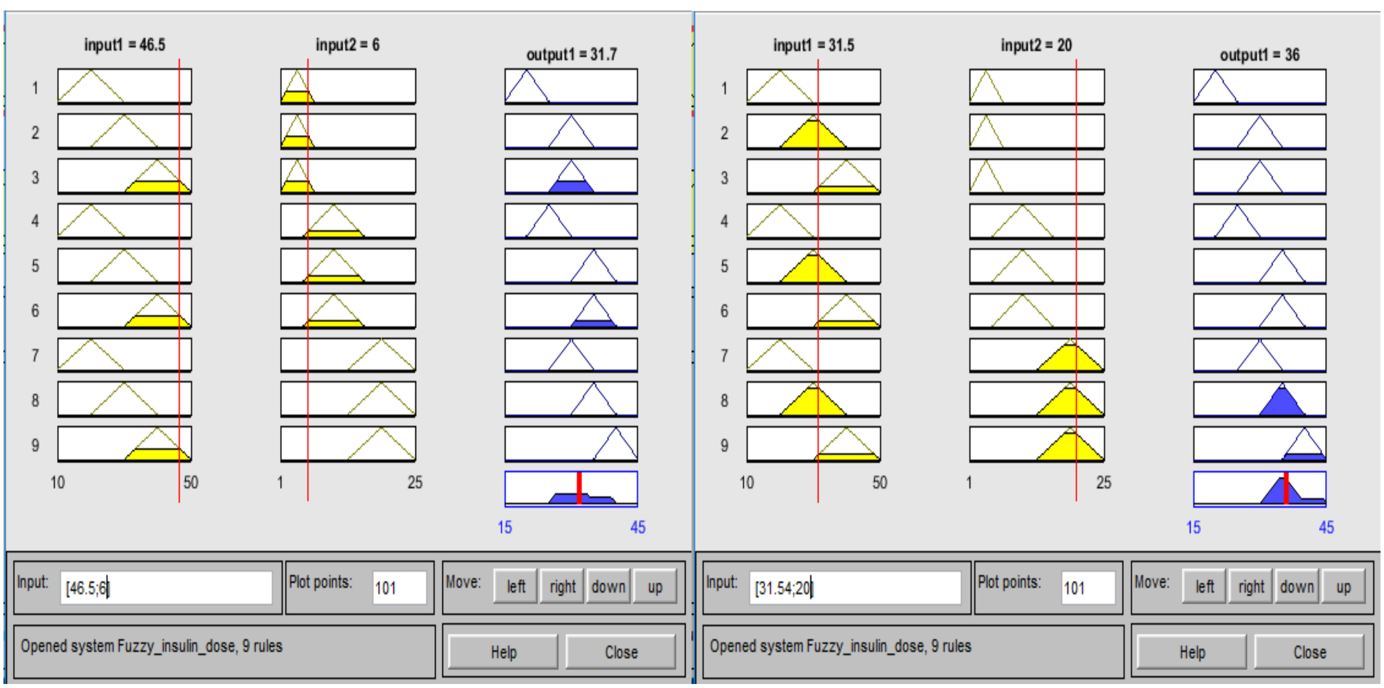

Figure 2.3.4F: Defuzzified output value for patient 10 and patient 11 from left to right with AFI=46.5; DD=6 and AFI=31.54; DD= 20 respectively.

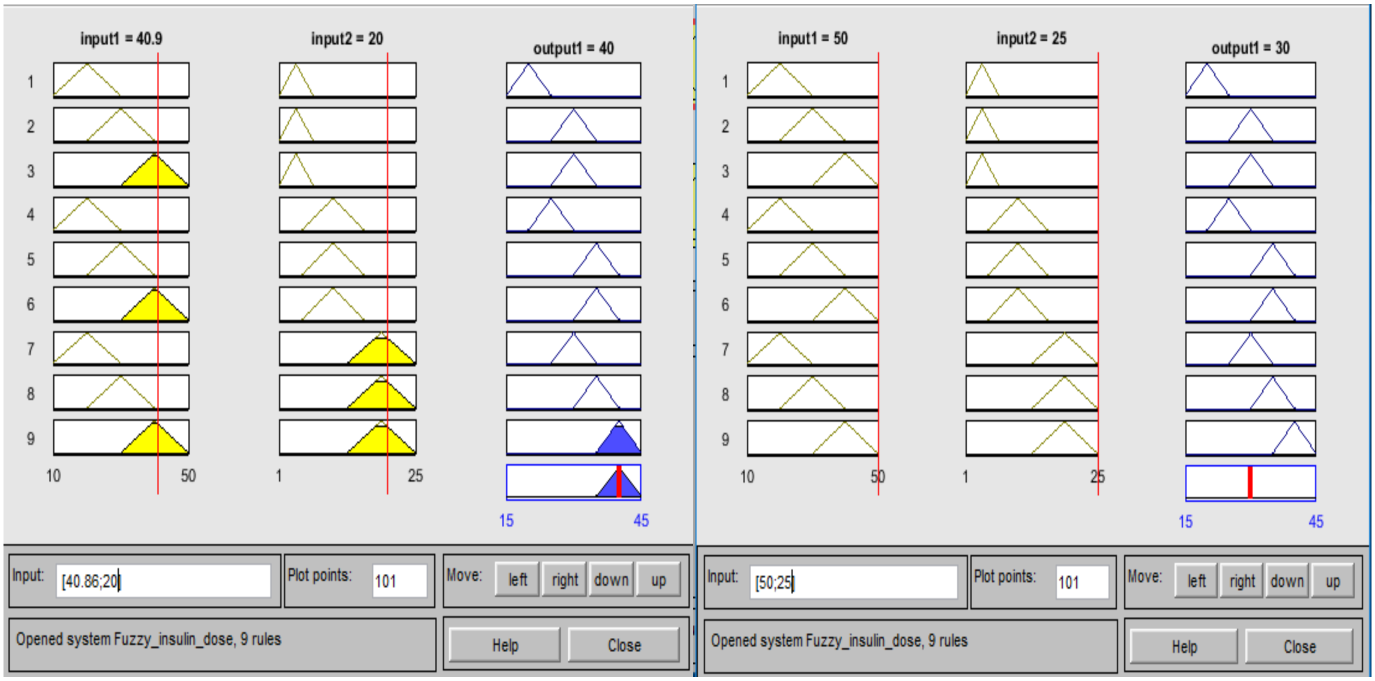

Figure 2.3.4G: Defuzzified output value for patient 12 and patient 13 from left to right with AFI=40.89; DD= 20 and AFI= 50; DD= 25 respectively.

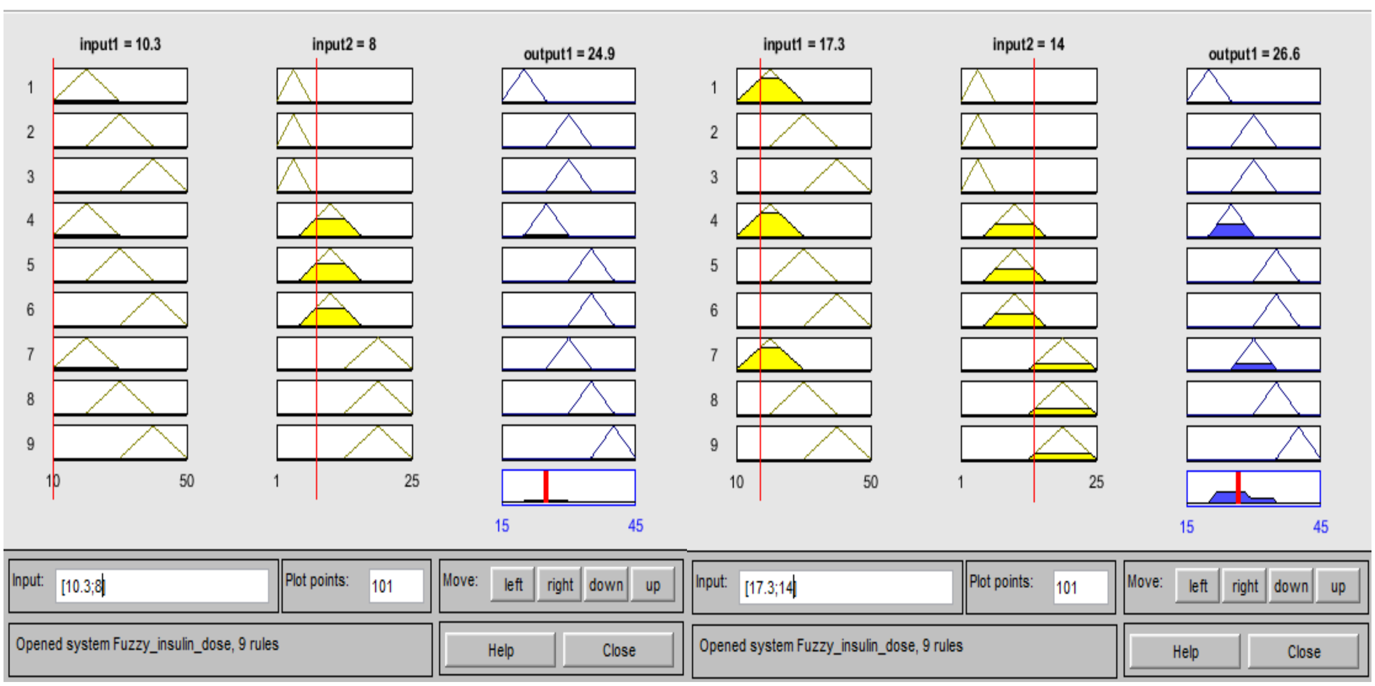

Figure 2.3.4H: Defuzzified output value for patient 14 and patient 15 from left to right with AFI=10.3; DD=8 and AFI=17.3; DD= 14 respectively.

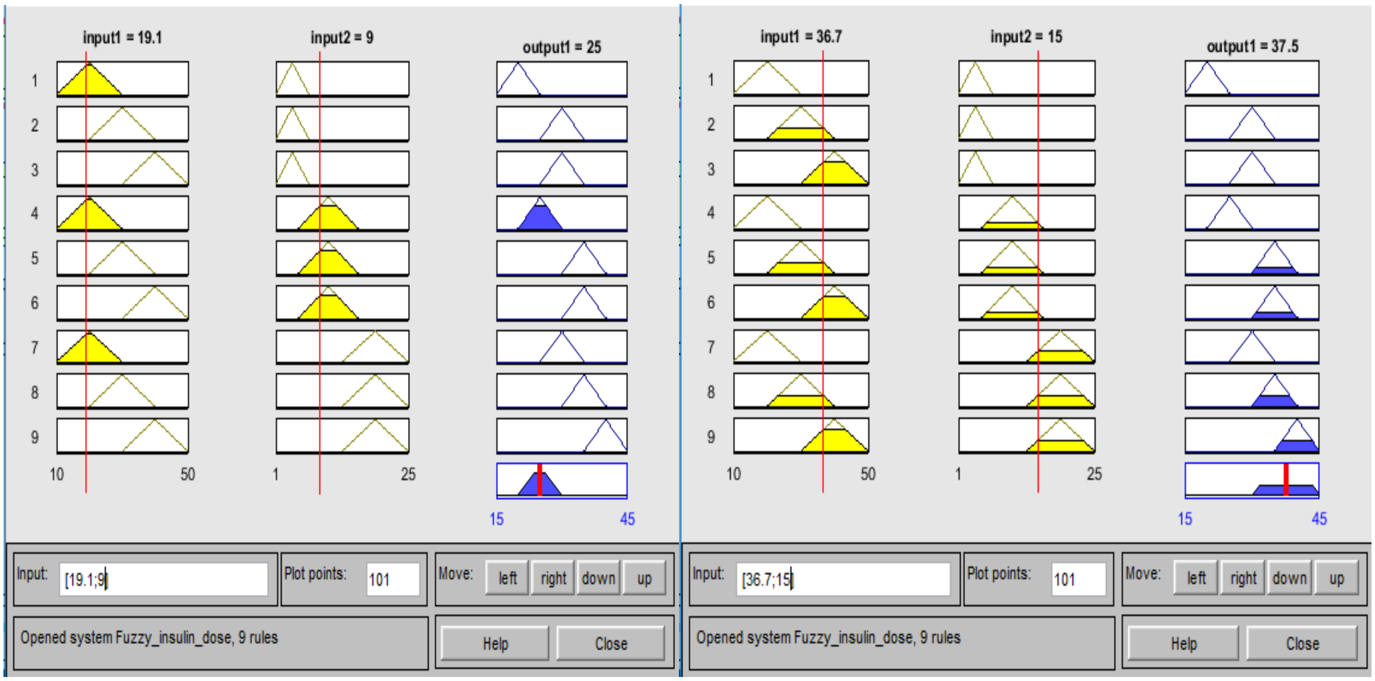

Figure2.3.4I: Defuzzified output value for patient 16 and patient 17 from left to right with AFI=19.1; DD=9 and AFI=36.7; DD= 15 respectively.

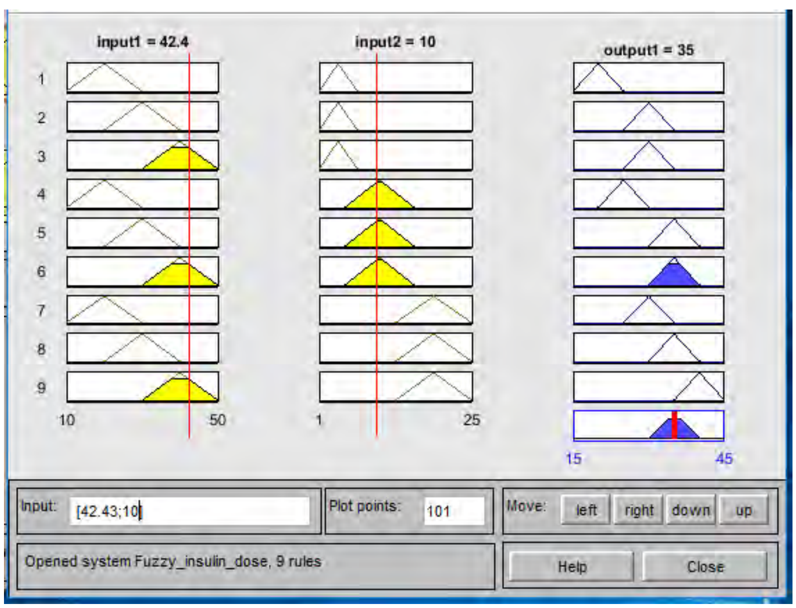

Figure 2.3.4J: Defuzzified output value for patient 18 with AFI= 42.43; DD=10.

2.4 Surface Diagram for the fuzzy interface

The surface diagram provides a graphical interface, which represents the output in a 3-dimensional surface for the given input/inputs. For this study, the two input variables are assigned to the two axes (X and Y), and the output variable is assigned to the Z-axis.

The surface diagram illustrates the relationship between Average fat intake (AFI), diabetes duration (DD) and insulin dose. Here in figure 2.4A, AFI is assigned to the X-axis, DD to the Y-axis and Insulin dose to the Z-axis.

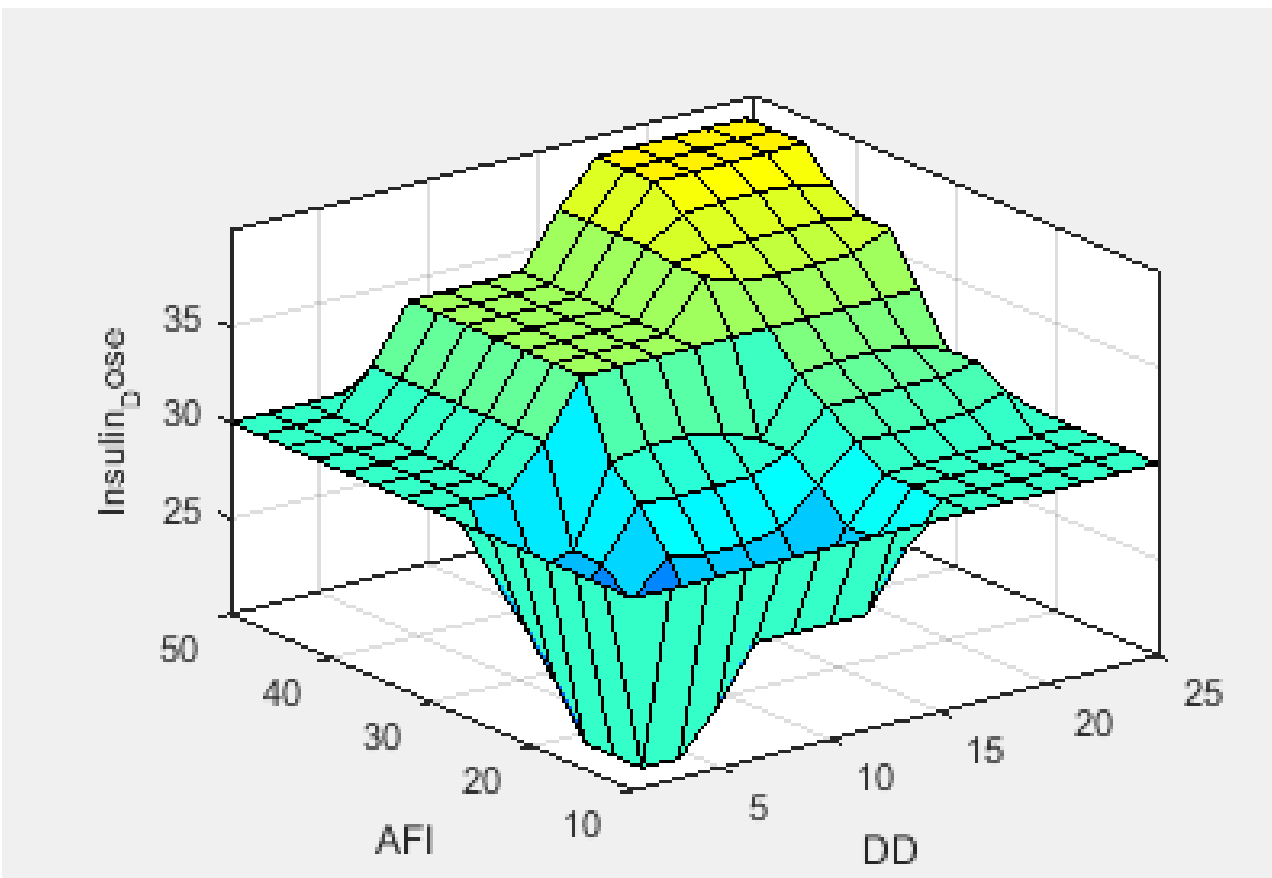

Figure 2.4A: Surface Diagram of Insulin dose against AFI (x-axis) and DD (y-axis).

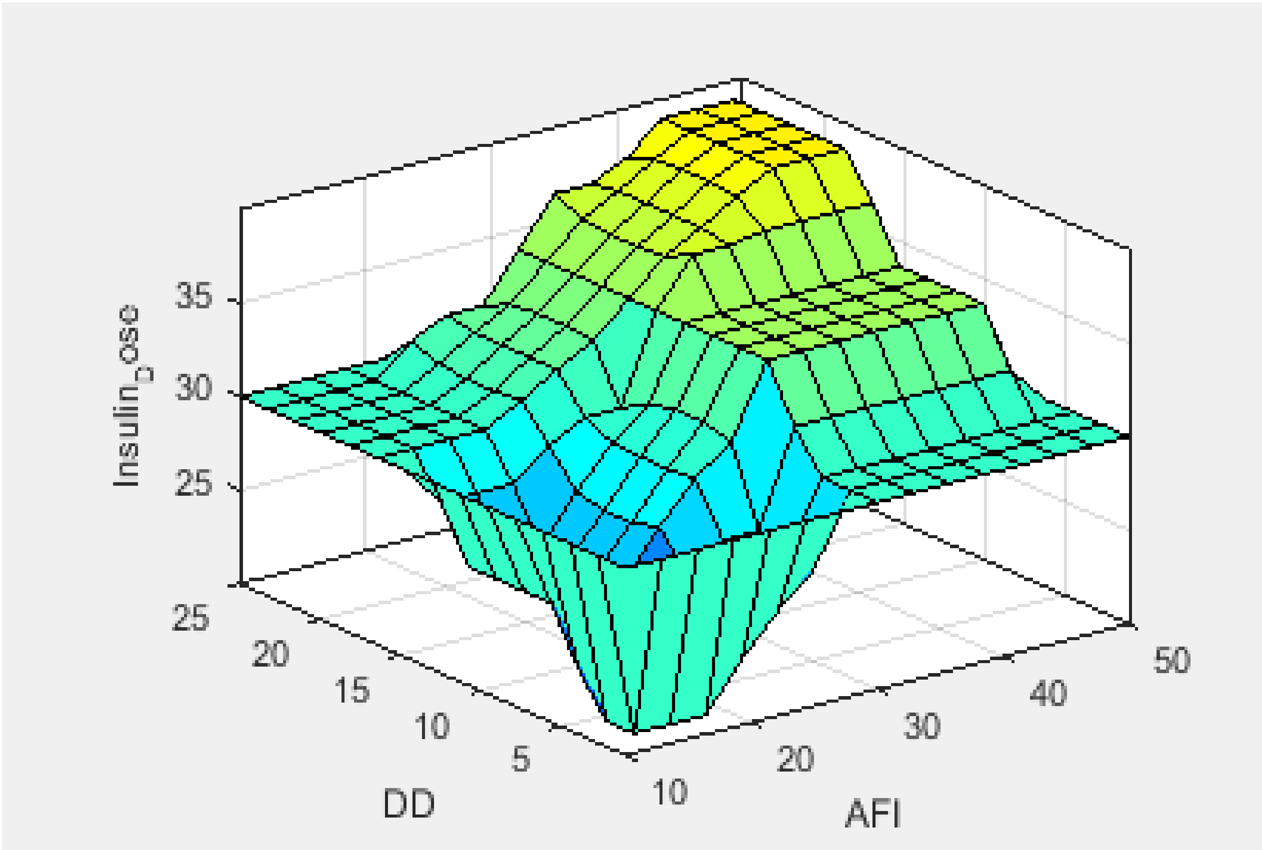

Figure 2.4B: Surface diagram of insulin dose against DD (x-axis) and AFI (y-axis).

Two different surface diagrams are generated in this study by repositioning the axis of the inputs to get a different three-dimensional view on the data. The Plot points and the grid value is automatically set by default. The Output variable (Insulin Dose) is fixed to the Z-axis, only the input variables are interchanged between the x-axis and y-axis.

Chapter 3

Result and Discussion

3.1 Result

All of the 18 patients included in this study were chosen randomly and were admitted to BIRDEM and BSMMU with ongoing insulin treatment during the time of survey. All patients are known to have Type 2 diabetes as well as other health complications as reported during the interview period. These patients had insulin dose prescribed by the physicians beforehand. Here, the output of predicted insulin dose from the Fuzzy-logic system provided insulin doses is compared with the patients prescribed insulin dose. Table 3.1.1 below illustrates the prescribed insulin dose and the Predicted insulin dose and shows the numerical difference between the two for the 18 patients.

Table 3.1.1: Predicted Insulin dose (PID), Physician's prescribed insulin dose (PPID) and their numerical difference for 18 patients.

Patient Number	Predicted Insulin Dose (PID) by Fuzzy-logic system	Physician's prescribed Insulin Dose (PPID)	Numerical Difference
1	30	32	-2
2	30	26	4
3	38.3	34	4.3
4	25	17	8
5	28.6	34	-5.4
6	38.3	34	4.3
7	30	25	5
8	27.7	22	5.7
9	30	39	-9
10	31.7	30	1.7
11	36	29	7

12	40	20	20
13	30	31	-1
14	24.9	32	-7.1
15	26.6	34	-7.4
16	25	30	-5
17	37.5	42	-4.5
18	35	22	13

The fuzzy logic based system provided a prescribed insulin dose, which has numerical differences of varying degrees from the physician's prescribed insulin dose (PPID) for each patient. The predicted insulin dose (PID) has been subtracted from the physician's prescribed insulin dose (PPID) which gives the numerical difference. In case, where the numerical difference is positive, it shows that the fuzzy-logic predicted insulin dose (PID) is greater than the physician's prescribed insulin dose (PPID) and the patients is most likely to suffer from hyperglycemia. When the numerical difference is negative that is the PID is less than the PPID, it shows that the patient is most likely to suffer from hypoglycemia.

The numerical differences are illustrated in a 3D bar chart below:

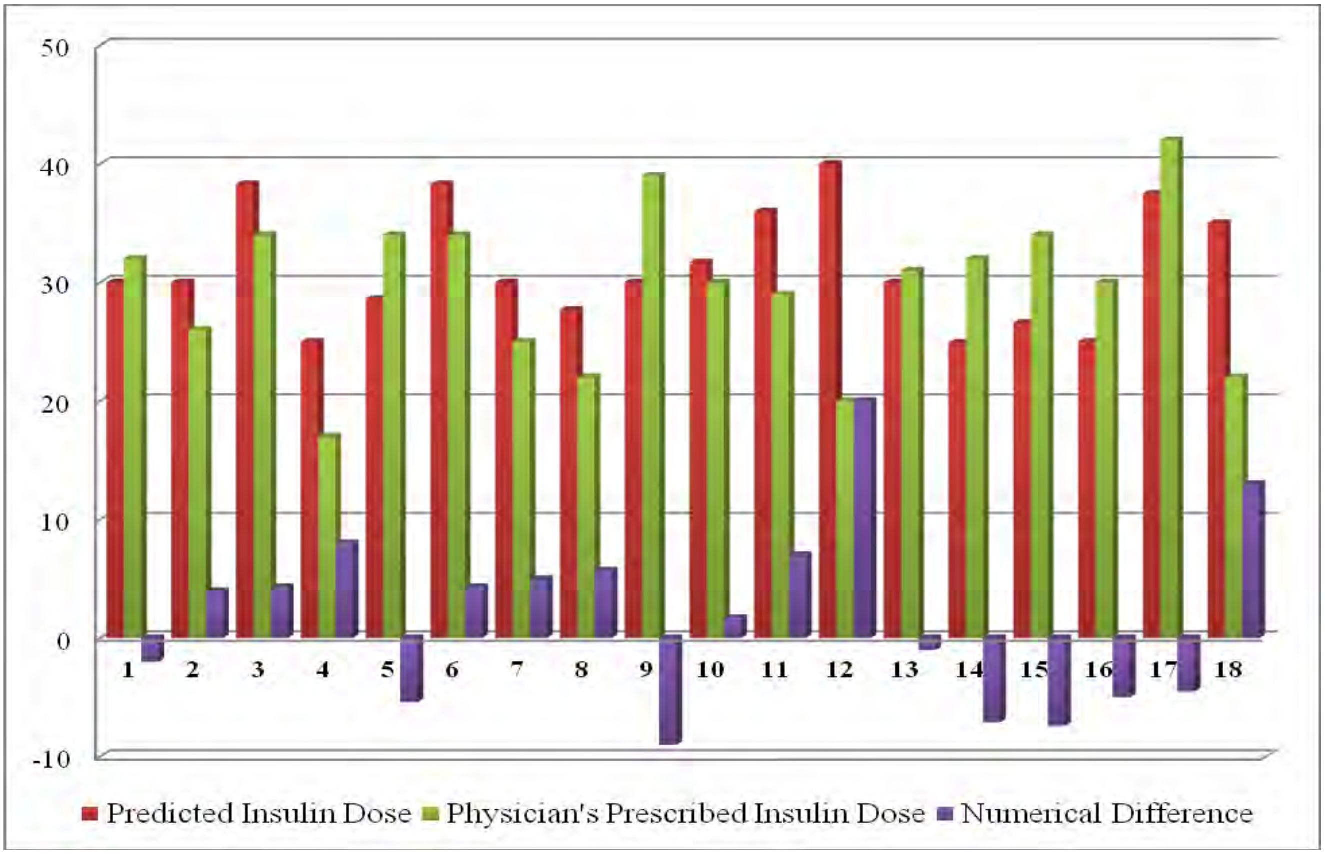

Figure 3.1A: 3D bar column showing the numeric difference between prescribed and predicted insulin dose.

The x-axis shows the patient's number while the y-axis represents the numeric value for the physician's prescribed insulin dose, predicted insulin dose and the numerical difference between them. Patient number 12 has the greatest numerical difference of + (ve) 20, followed by patient 18 and patient 9 of numerical difference of + (ve) 13 and – (ve) 9 respectively.

The graphical representation in figure 3.1A gives an idea on the extent of differences of the PID and PPID for the 18 patients. Here, eight patients out of eighteen patients show negative numerical difference whereas the rest shows positive numerical difference. No patient has been found with the same PID and PPID.

3.2 Discussion

The main purpose of this study was to get superior insulin dose for patients with type 2 diabetes to reduce the events of hyperglycemia and hypoglycemia. Using the fuzzy-logic system, a predicted insulin dose has been developed with has different degrees of numerical differences from the physicians' insulin dose. In the study, the numerical differences in dose of some patient are significantly high compared to those of others. Out of the 18 patients, a majority of patients has a positive numerical difference that suggests that patients are more likely to experience hyperglycemic events. Experiencing hypoglycemic events is also common within the patient population. The positive numerical difference means the patient is most likely to suffer from hyperglycemia as the patients is administering less units of insulin dose. Likewise, negative numerical difference means the patient requires fewer units of insulin dose and he/she is in risk of hypoglycemic events.

When observed carefully at the patient's medical history, the predicted insulin dose (PID) is found to give an insulin dose, which is better fit with the patient's condition when compared with the PPID. For instance, patient number 12 was found to have PPID of 20 units with an average daily fat intake (AFI) of 40.86 grams and duration of 20 years of diabetes. The fuzzy logic predicted an insulin dose of 40 units, which according to the patient's medical history goes better with providing a healthy life in the long run. Patient 12 had faced many incidents of hyperglycemic events in the past, with an average blood glucose level of 16.8mmol/L, 19.1mmol/L and 18.1mmol/L after breakfast, after lunch and after dinner respectively. The patient has a high fat intake with a long duration of diabetes, which made him more susceptible to hyperglycemic events. Thus, an insulin dose of 40 units would prevent such hyperglycemic conditions in that patient. The fuzzy-logic system also suggested a higher insulin dose for patient number 2, 3 and 4 of a numerical difference of 4, 4.3 and 8 respectively. The medical history of these patients (patient number 2, 3 and 4) also suggests that previously, they all had continuous events of hyperglycemia. Their blood glucose level stayed elevated after breakfast, after lunch and after dinner with the administration of the physician's prescribed insulin dose. A sustained hyperglycemic condition can result into many long-term complications. All three patients were found to have other health complications. Patient number 3 has dyslipidemia, which is an abnormal amount of lipid present in the blood that further contributes to insulin resistance and high risk of cardiovascular diseases (CVD) (Rader, 2007). It is extremely important to prevent and mitigate the consequences of CVD risk and other life threatening conditions through medical interventions of accurate dose of insulin (Ahern et al., 1993). Thus, the suggestive dose from this study is a better fit for the patient number 3. Likewise, the predicted insulin dose in our study will lead to better regulation of blood glucose level for patient number 2 and 4. Then again, the numerical difference for patient 5, 6 and 7 is +4.3, +5 and +5.7 units respectively; as in the physician's prescribed insulin dose is lower than the predicted insulin dose. The patients' medical history also suggests them to be hyperglycemic during all events after having food. Medical history of patient 5 suggests to be hyperglycemic during the entire course of this study. Patient 6 was found to have an average blood glucose level of 12.3mmol/L, 19.7mmol/L, and 17.5 mmol/L after breakfast, after lunch and after dinner respectively. In this case, even after administration of the prescribed insulin dose, the patient was hyperglycemic on a regular basis. This patient has a history of heart problem and hypertension. Continuous hyperglycemic condition would even result into additional health problems. Patient 7 was found to have average blood glucose level of 15.2 mmol/L, 11.9mmol/L, and 17.5mmol/L after breakfast, after lunch and after dinner with elevated lipid and cholesterol level. For all these patients, a higher dose of insulin as suggested by the fuzzy-logic in this study may reduce the chances of hyperglycemic effects and will prevent long-term health complications. Patient number 10, 11 and 18 also experienced hyperglycemic events and should increase the insulin dose as suggested in this study. However, is a high dose of insulin is administered; the patient is most likely to suffer from hypoglycemic events. In case of patient number 15, the predicted dose from this study is 26.6 units whereas the patient was taking 34 units of insulin. It has been seen that the patient was undergoing continuous hypoglycemic events, which is as low as 3.2mmol/L average blood glucose level after lunch and 3.8mmol/L average blood glucose level after dinner. The patient is also suffering from other health complications such a retinopathy, nephropathy, anemia and many others. In this case, the patient must reduce the insulin dose in order to prevent hypoglycemia. The predicted insulin dose might result into a normal blood glucose level for patient number 15 for increasing the quality of life. In this study, few results were seen, where the fuzzy logic system suggests a low dose of insulin but the patient shows history of hyperglycemic events. For example, in case of patient number 1, the predicted insulin dose is 30 units and the physician's prescribed dose is 32 units with a numerical difference of -2. The patients is 70 years old male with 1 year duration of diabetes, having medical history of stroke, mild anemia, decreased blood pressure, vitiligo, sore mouth, decreased appetite and weakness. The increase in blood glucose level before and after meal might result due to his decrease physical activity and other health conditions. This fuzzy output provided by this system solely depends on the two factors only whereas insulin dose also depends on different other factors related to the patient. This might be the reason for this anomalous result. The predicted dose of insulin for this study shows a low insulin dose compared to the prescribed insulin dose for patient number 14, where the patient had past events of hyperglycemic conditions. Patient 14 was found to have few health problems, which made the patient unable to walk at all. This might be one of the reasons to have previous events of slight hyperglycemia after meal.

The results of the predicted insulin dose proposed by the fuzzy logic system, when compared with the current health condition of the patients shows superiority over the conventional way of undertaking insulin dose prescribed by the physician alone. Optimized insulin dosage adjustments were made possible through this AI system of precision dosing.

Chapter 4

Conclusion and Future Scope

4.1 Conclusion

Diabetes is a long-term health condition and a mounting problem not only in the western world but also in the developing countries. The long term complication of diabetes mellitus include retinopathy with potential permanent blindness, neuropathy with risk of foot ulcers that can lead to amputations of the limbs, nephropathy associated with permanent renal failure and other autoimmune disorders (Vicini, Avogaro, Spilker, Gallo, & Cobelli, 2002). The effect of diabetes mellitus on the patients' everyday lifestyle can sometimes be serious when the glucose concentration in plasma goes beyond the normal blood glucose level, an average of 4.5mmol/L (Verma et al., 2006). In order to prevent both present and future health complications, proper maintenance of insulin therapy needs to be maintained and a healthy lifestyle needs to be adapted. Many factors influence the state of diabetes where it is difficult for a physician to look at all the factors such as hereditary characteristics, diet, workout, occupation, age, body mass, weight blood pressure and other health conditions and prescribe a certain insulin dose; customized for an individual patient (Bell et al., 2016). Even a single change in any of the factors may result into a different insulin dose for the patient. Then again, the problem also lies with changing stage of the disease where the insulin dose needs to be upgraded in accordance with the disease condition for better maintenance of blood glucose level. Maintaining a precise accurate dose of insulin difficult as diabetes mellitus is dependent on a number of different factors and need good exerts' knowledge. During the last three decades, practical model of non-linear dynamics of blood glucose level and insulin dose has been developed which comprises of a set of non-linear differential equations which needs to be calculated numerically (Verma et al., 2006). These types of conventional methods often prove to be insufficient to control such complex biological systems (Verma et al., 2006). Studies study conducted, demonstrated that the fuzzy based controllers showed superiority other conventional methods when biological systems are involved (Basher, 2017; Chowdhury et al., 2017; Grant, 2007; Verma et al., 2006). Fuzzy-logic based system provides simple but approach can be made to very sensitive and critical problems by adjusting various parameters and an output using linguistic rules can be accomplished (Lalka & Jain, 2015).

In this study, a fuzzy logic based system has been proposed to maintain the blood glucose level for diabetic patients of type 2. Fuzzy logic controllers takes uncertainties into account and considering all possible parameters and inputs derived from experimental data or expert knowledge, a precise value is derived (Verma et al., 2006). Fuzzy-logic based system are robust in nature and accuracy is never compromised. In this paper, the fuzzy logic enabled to recommend accurate precise value of insulin dose depending to patients' average fat intake and duration of diabetes. The recommended insulin doses were evaluated based on the patients' past medical reports and have showed justified logical reasons in its preciseness over the physician's insulin dose. The development of an automated 'artificial intelligent' system is more reliable than manual interventions as they ate not prone to miscalculations or stressful environments. Human error would most likely to be eliminated if such system based controller are introduced in case of such a complicated disease like diabetes mellitus. Since, this fuzzy logic based system provides a more precise, personalized calculation for daily insulin dose administration, it may to a better future for the diabetes patients. A self- customized or personalized tool for the adjustment of insulin dose could serve as a valuable object to enhance awareness among the diabetes patients. The diabetes patients will better understand how their body responds to insulin, how other physiological and external factors affects the insulin dose and how sight adjustment of insulin dose can prevent avoidable events of hyperglycemia and hypoglycemia.

Few challenges observed so far includes situations where the fuzzy-logic system might fail to match the standard of human performance due to the lack of inadequate data. Fuzzy also acts within its fixed rules but human possess the ability to act beyond rules. However, problems like this can easily be overcome through proper feeding of experts' knowledge and real-time data into the fuzzy-logic system. Fuzzy-logic has the ability to understand, learn and adapt accordingly to the programming, showing far potential than we can even imagine.

4.2 Future Scope

By using technologies involving 'artificial intelligence', not only problems associated with diabetes mellitus can be combat but also such new technologies have the potential to combat never-ending problems associated with other diseases. Various Clinical Decision Support Systems have been developed by the aid of Artificial Intelligence and is now widely used in clinics and hospitals (Prasath, Lakshmi, Nathiya, Bharathan, & Neetha, 2013). Artificial Neural networks is one of the most powerful AI tool used for the clinical diagnosis, analysis and data interpretation of the biological system (Ramesh, Kambhampati, Monson, & Drew, 2004). This system has been used to interpret ultrasound, radio-scope scan, analysis of electro-enchalograms (ECG), and diagnosis of epilepsy (Ramesh et al., 2004) . Other artificial intelligent (AI) techniques such as the fuzzy logic system have also been used in different field of medicine (Ramesh et al., 2004). The most wide field of application of fuzzy control system is the field of an aesthesia, which involves monitoring various vital parameters of the patient and controlling drug infusion in order to maintain a constant an aesthetic level within the body (Mahfouf, Abbod, & Linkens, 2001). Fuzzy-logic controller has been also implemented for controlling the heart pump rate depending on the body perfusion demand in case of artificial heart (Mahfouf et al., 2001). Then again, fuzzy-rule based system has been developed which serves as a decision making support for the diagnosis of tuberculosis, the evaluation of lung cancer, prostate cancer and skin cancer (Prasath et al., 2013). Moreover, the application of fuzzy-logic based system have been made in the diagnosis of acute leukemia, pancreatic cancer, breast cancer and for the administration of controlling blood pressure (Ramesh et al., 2004; Schneider et al., 2002). In a study conducted by Nguyen, fuzzy-logic system based algorithms has been used for mechanically controlling the ventilation in patients with acute respiratory syndrome and this system showed potential capacity of making sensible decisions (Nguyen, Bernstein, & Bates, 2014). In a recent study, a novel approach has been made for predicting the mortality rate of cardiovascular-patients in Intensive Care Unit (ICU), using the fuzzy logic method (Moridani, Setarehdan, Nasrabadi, & Hajinasrollah, 2018). In this case of predicting insulin dose, due to the unavailability of universal and fixed sets of data for diabetes, research using fuzzy is quite limited till date. Further study, which involves other parameters of diabetes, can be formulated using fuzzy logic and the corresponding changes of the output can be studied along with studying the relationship among the parameters itself. Such expert systems can be collaborated with an appropriate diet management system for a better, more accurate and a complete system for the control of diabetes.

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