Application of Fuzzy Logic Controller for Intensive Insulin Therapy in Type 1 Diabetic Mellitus Patients by Subcutaneous Route

Laleh Kardar *, Ali Fallah, Shahriar Gharibzadeh, Fatollah Moztarzadeh
Biomedical Engineering
Amirkabir University Of Technology
P.O.Box 15875- 4413, Tehran
IRAN
Laleh_kardar@aut.ac.ir

Abstract: - The work we describe here is aimed at assisting out-patients affected by insulin dependent diabetes mellitus with an advisory/control algorithm. This advisory/control algorithm incorporates expert knowledge about the treatment of this disease by using Mamdani type fuzzy logic controllers to regulate the blood glucose level (BGL) when the diabetic patient is subjected to a glucose meal disturbance or fluctuations in the measured glucose level due to error in the measuring instrument. We proposed two-level architecture for control system. The goal of the Low Level Module is to suggest the next insulin dosage of both short and intermediate acting insulin (Regular and NPH) formulation that are programmed in a three-shot daily basis before meals, depending on the blood glucose measurement. The combined preparation is then injected by the patient through a subcutaneous route. The High Level Module adjusts the maximum amounts of insulin provided to the patient in a time-scale of days. This module aims to work as a supervisor of the low level module. Simulations are illustrated, using a flow-limited model for diabetes mellitus based on the work of Puckett.

Key-Words: - Diabetes mellitus, Fuzzy logic controller, Intensive insulin therapy

1 Introduction

Several organs, hormones and enzyme systems are involved in the regulation of the blood glucose levels in human body. Insulin, a hormone secreted by pancreatic beta cells, is the most important hormone in the regulation of blood glucose levels. It influences the rates of glucose utilization by the tissues and regulates the storage of the fuel, therefore helps to keep blood glucose concentrations within a narrow range of about 90-130 mg/dl. Diabetes mellitus is an endocrine metabolic disorder in which the body does not produce or properly use insulin.

Based on insulin dependency, diabetes is classified into two types, I and II. Type I is insulin-dependent diabetes mellitus (IDDM) and type II is referred to as noninsulin dependent diabetes mellitus (NIDDM). Type I diabetes represents approximately 10% of all American diabetes [1] and is usually caused by loss of control of blood glucose levels. This loss of control is usually caused by a malfunction of the pancreas leading to a decrease in insulin production. It should be mentioned that this type of diabetes has a rapid onset and is most frequently apparent in children and adolescents (juvenile onset). Type II diabetes is characterized by insulin being appropriately produced by the pancreas but inappropriately absorbed and handled by body cells. This kind of diabetes is more common than type I, and is characterized by late occurrence (adult stage) [2].

The results of the Diabetes Control and Complications Trial (DCCT) [3] showed that an intensive insulin therapy can reduce the incidence of these illnesses in the long term. Consequently, an intensive therapy is encouraged for type 1 diabetic mellitus (TIDM) patients prescribed either by a continuous subcutaneous insulin infusion (CSII) pump, or a multiple daily injections regimen (MDIR). In this contribution, the latter one is studied, which is the most common scenario in chronic patients, due to the high cost and availability of portable CSII pumps. With this consideration, if an intensive therapy is followed by the patient, the prescribed insulin treatment must be carefully selected by the physician. It is then appealing to have an advisory/control system for the patient in order to update each daily dose of insulin [4], [5], [6], [7], [8], [9]. In the control theory field, the fuzzy logic has emerged as a powerful tool to incorporate expert knowledge about the systems into the controllers design [10], [11], in particular, the ability of synthesizing expert knowledge in the fuzzy logic

framework has raised a lot of attention in the biomedical engineering field.

Meanwhile several research efforts have been focused on the mathematical modeling of the glucose- insulin dynamics [12]. Modeling the glucose-insulin interaction requires an understanding of the physiological and metabolic processes that determine the observable behavior. Chemical reactions and transport processes form an integrated network when modeling the glucose-insulin interaction in human body. A number of mathematical models of the insulin-dependent (type-I) diabetes mellitus have been previously reported in the literature [13], [14].

The control strategy presented in this work formalizes expert knowledge in the fuzzy logic framework. This paper is organized as follows. Section 2 gives an overview of the mathematical modeling of the insulin-glucose dynamics in a TIDM patient. Section 3 introduces the synthesis of the knowledge-based (Mamdani-type) fuzzy controllers. Finally, section 4 introduced the simulation results. Section 5 presents concluding remarks and future work.

2 Diabetic patient modeling

The model to be presented here is a flow-limited model for diabetes mellitus based on the work of Puckett [15]. The glucose diagram (Fig.1) contains tissues including heart, brain, liver, kidney and muscle where the glucose is used for energy. Glucose excretion by kidney and gastrointestinal tract where the exogenous glucose enters the blood, are also included. The diagram for insulin (Fig.2) includes subcutaneous tissue as a source for insulin. It is assumed that the pancreas is completely lacking insulin production. Removal and degradation of insulin occurs mostly in liver, kidney and peripheral tissue. They degrade one-half, one-third and one-sixth, respectively, of the insulin presented to them, regardless of the plasma concentration.

A mass balance equation is written for each compartment in the model. The compartments here represent actual body regions. The advantage of this type of modeling is that the model design is based on an understanding of the physiology and simulations that can yield insight into the physiological processes [18]. The main disadvantage of these models is that the personal variations in physiological parameters are not taken into account. Therefore, the outputs are average values thus, the simulator should be used for only educational purposes rather than providing medical advice.

It is assumed that changes in blood glucose and insulin concentrations for each tissue are fast and the balances are in a quasi-steady state (i.e. $dG/dt \approx 0$) shortly after a disturbance (i.e. the carbohydrate intake).

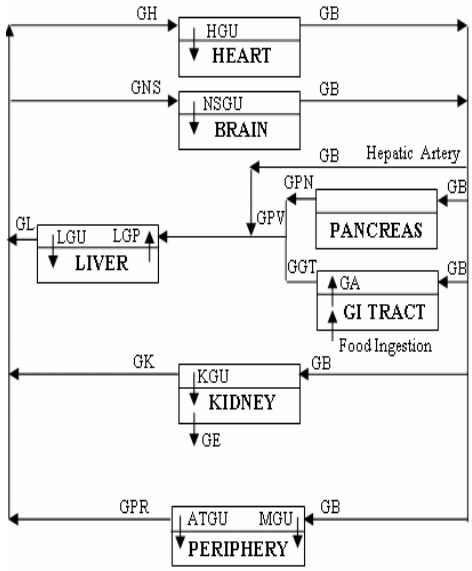


Fig.1.Pharmacokinetic Diagram of Glucose [15]

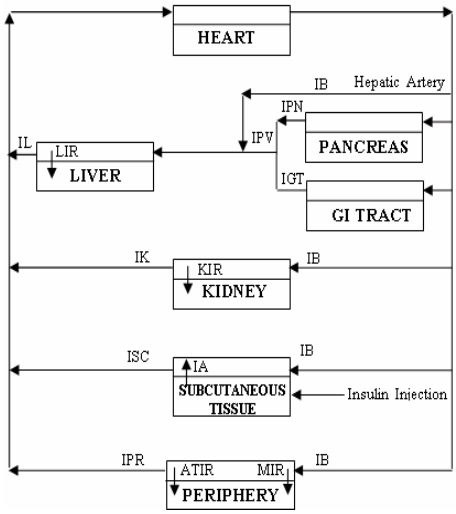


Fig.2. Pharmacokinetic Diagram of Insulin [15]

2.1 Insulin sub-model

Insulin travels through several regions of the body as it moves from the injection depot to the target cells. Diabetic educators usually teach patients to inject insulin into the subcutaneous tissue in such a way as to put it in the interstitial fluid and not a blood vessel. The insulin must then diffuse through the interstitial environment to nearby capillaries. After crossing the capillary wall, it is carried to the main circulation. The circulating hormone crosses the capillary wall in various tissues and diffuses through the interstitial milieu to the cell walls. Insulin's binding with receptors in the cell membrane then

cause intracellular signals which activate appropriate changes in the cell's metabolism. After initiating the signal, the hormone dissociates from the receptor, or the complex is internalized. The internalized insulin is released unaltered or degraded. The following three pool model has been found to produce an adequate fit to patient data and describes the absorption from an injection of short acting insulin (regular) at t=0:

$$\frac{d[I_p]}{dt} = -k_p[I_p] \qquad [I_p](t=0) = [I_p]_0 \qquad (3)$$

$$V_s \frac{d[I_s]}{dt} = k_p[I_p] - k_s[I_s] \qquad [I_s](t=0) = [I_s]_0 \qquad (4)$$

$$V_B \frac{d[I_B]}{dt} = k_s[I_s] - k_B[I_B] + k_B[I_B]_0 \qquad (5)$$

$$[I_B](t=0) = [I_B]_0$$

$$\tau_p = k_p^{-1}, \tau_s = V_s / k_s, \tau_B = V_B / k_B$$

Where, $[I_p]$ is total amount of insulin in pocket, k_p is rate constant for the transport of insulin from the pocket into the surrounding interstitial fluid, $[I_p]_0$ is injected insulin, $[I_s]$ is insulin concentration in interstitial fluid, $[I_B]$ is concentration of insulin in the capillary blood, k_s is rate constant for the transport from the interstitial region to the capillary blood, V_s is effective volume of the interstitial fluid, V_B is effective volume of circulating blood, k_B is rate constant for removal of insulin in the liver and kidney, τ_p, τ_s, τ_B are time constants. The insulin sub-model parameters are tabulated in Table 1.

Table 1.Constant parameters of insulin Sub-model [15]

Parameter	Value
$\tau_p\,(min)$	63
$\tau_s\,(min)$	63
$\tau_B\,(min)$	16
$[I_B]_0\ (\mu U)$	17.5
$[I_s]_0\ (\mu U)$	0

2.2 Glucose sub-model

Setting dG/dt =0 in all tissues we get

$$V_B \frac{d[G_B]}{dt} = -TGU - GE + GA + LGP \qquad (6)$$

In summary, we present the different sub-models making up the glucose portion of the overall model here:

*Total Glucose Uptake (**TGU**)*

$$TGU = k[I_A][G_B] + CNU \qquad (7)$$

$$\frac{d[I_A]}{dt} = \frac{1}{T_{IA}}([I_B]_D - [I_A]) \qquad (8)$$

Where, k is a constant value, $[I_A]$ is effective insulin concentration, $[G_B]$ is circulating blood glucose concentration, CNU is glucose and insulin independent uptake which is approximately a constant, $[I_B]_D$ is circulating blood insulin concentration delayed by the pure time delay $T_{D,TGU}$.

Glucose Excretion (***GE***)

$$GE = 1.25\frac{dl}{\min}([G_B] - 176\frac{mg}{dl})U([G_B] - 176\frac{mg}{dl}) \qquad (9)$$

Where, U([G_B]-176mg/dl) is step function indicating the threshold at approximately 176 mg/dl.

Glucose Absorption from the small intestine (***GA***)

$$\frac{dGA}{dt} = -\frac{1}{T_A}GA + \frac{F}{T_A T_{GE}}[G_G] \qquad GA(t < t_M) = 0 \qquad (10)$$

$$\frac{d[G_G]}{dt} = -\frac{1}{T_{GE}}[G_G] + [CHO_G] \quad [G_G](t < t_M) = 0 \qquad (11)$$

$$[CHO_G] = \frac{1}{4\min}CHO_M(t - t_M)u(t - t_M) - \qquad (12)$$

$$\frac{1}{4\min}CHO_M(t - t_M - 1)u(t - t_M - 1) -$$

$$\frac{1}{4\min}CHO_M(t - t_M - 4)u(t - t_M - 4) +$$

$$\frac{1}{4\min}CHO_M(t - t_M - 5)u(t - t_M - 5)$$

Where, $[CHO_G]$ is total amount of hydrolyzed meal carbohydrate that have entered the stomach, CHO_M is carbohydrate content of the meal (in *mg/kg*) , t_M is time of meal (in minutes), $[G_G]$ is total amount of glucose in the stomach, F is fraction of meal carbohydrates that actually absorb into the blood.

*Rate of Liver Glucose Production (**LGP**)*

$$LGP = a_1\left(1 - \frac{a_2([GI]_D - a_3)}{|[GI]_D - a_3| + a_4}\right) \qquad (13)$$

$$\frac{d[GI]_D}{dt} = \qquad (14)$$

$$\begin{cases} k_A([G_L]_D[I_B]_D - [GI]_D) & if\ \frac{d}{dt}[G_L]_D[I_B]_D \geq 0 \\ k_A([G_L]_D[I_B]_D - [GI]_D) & if\ \frac{d}{dt}[G_L]_D[I_B]_D < 0 \\ [GI]_D(t=0) = [G_B]_0[I_B]_0 \end{cases}$$

$$[G_L] = [G_B] + \frac{GA}{Q_L} \qquad (15)$$

Where, $[G_L]_D$ is average glucose concentration entering the liver delayed by the pure time delay $T_{D,LGP}$, $[I_B]_D$ is circulating blood insulin concentration delayed by the pure time delay $T_{D,LGP}$, $[GI]_D$ is $[G_L]_D[I_B]_D$ delayed in a first order

manner with a time constant $1/k_A$ or $1/k_D$, Q_L is a constant value. The glucose sub-model parameters are tabulated in table 2.

Table 2.Constant parameters of glucose sub-model [15]

Parameter	Value
V_B (dl/kg)	1.0754
$T_{D,TGU}$ (min)	30
T_{IA} (min)	21.3
k $(1/min)$	0.000382
CNU $(mg/kg\text{-}min)$	1.67
T_{GE} (min)	156.59
T_A (min)	34.66
F	1
Q_L (ml/min)	810
a_1 $(mg/kg\text{-}min)$	1.13
a_2	0.43
a_3 $(mg-\mu U/dl-ml)$	7259
a_4 $(mg-\mu U/dl-ml)$	765
$T_{D,LGP}$ (min)	30
k_A $(1/min)$	0.3671
k_D $(1/min)$	0.0036

Fig.3, 4, 5 represent the simulation results of this sub-model for glucose absorption, total glucose uptake and liver glucose production rates for a set of initial conditions respectively.

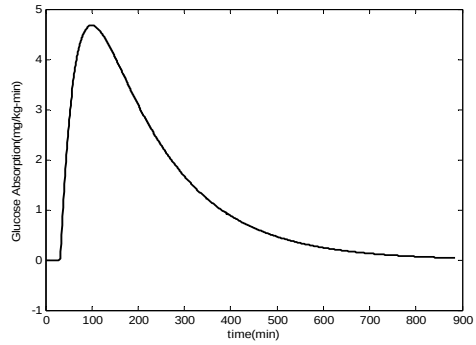


Fig.3. Time Course of Glucose Absorption Rate

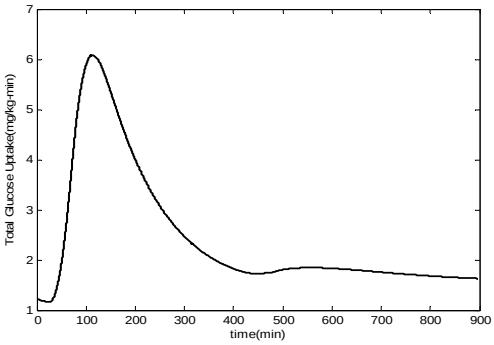


Fig.4. Time Course of Total Glucose Uptake Rate

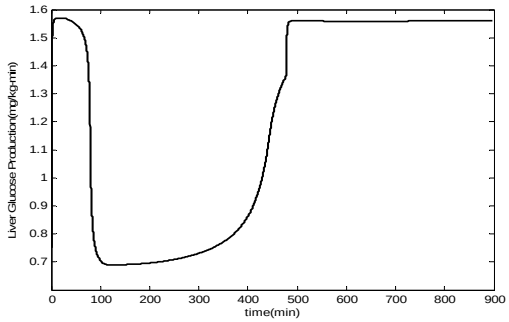


Fig.5. Time Course of Liver Glucose Production Rate

3 Problem statement and control method

Three meals are considered per day: breakfast (7-10 h), lunch (13-15 h) and dinner (20-22 h); where the lunch is the major one of the day. Roughly, there is a time interval of 6 h between each meal. In the proposed injection plan, the insulin doses are programmed previous to each meal, where the NPH provides the basal insulin, and the transient effects after each meal (post-prandial peaks) are regulated by the regular. Because of slow basal insulin absorption, the morning and lunch doses for NPH are skipped, and only regular are injected. The control objective is then stated in Table 3.

Table 3.Control objective

Plasma Glucose	Normal	Target
Before eating	Less than 110	90 to 130
Two hours After eating	Less than 110	Less than 180
Bedtime	Less than 120	110 to 150

It is important to mention that the control problem posed is very demanding, since the doses given by a physician vary from patient to patient. Furthermore, the glucose-insulin dynamics of for type 1 diabetic patients are highly nonlinear and they can be modified by different parameters like diet, exercise, stress, etc.

Therefore the advisory/control scheme presented in this work is based on two-level architecture; see Fig.6, where the high level module has the purpose of supervising the low level module performance in a time-scale of days.

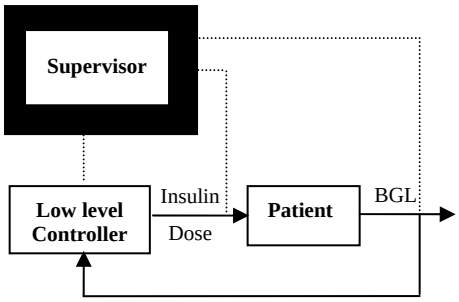


Fig.6. the overall scheme for two-level control system

3.1 Low Level Module

The low level module is structured with a Mamdani type fuzzy architecture and computes the regular (I_r) and NPH (I_{nph}) insulin doses given to the patient before each meal. The input variables to this module are:

- Time of the day (t): the information of time is used to determine whether a NPH insulin dose is injected next or not.
- Glucose measurement (G): the information of the BGL is used for the euglycemic analysis.
- Previous regular dose (I_{rd}): the regular dose calculated in the previous meal is used to analyze the glycemic control.
- Previous NPH insulin dose (I_{nphd}): due to the absorption process of the NPH, its dose in the morning is considered to evaluate also the glycemic control.

The two outputs regular (I_r) and NPH doses (I_{nph}) are normalized to the interval [0,1], and the actual injection preparation (I_r^a ; I_{nph}^a) is calculated when the amplitudes are scaled according to the values $I_r^{\max}$ (Maximum regular insulin dosing) and $I_{nph}^{\max}$ (maximum NPH insulin dosing) provided by the high level module.

$$I_r^a = I_r^{\max} \times I_r$$
$$I_{nph}^a = I_{nph}^{\max} \times I_{nph} \qquad (16)$$

The input and output characteristics are shown in Table 4 and 5 respectively, including the interval of variation for each variable and the fuzzy sets associated with the type of membership function used (fuzzication method). By the definition of the input fuzzy set, a total of 108 IF-THEN rules were defined. These rules were of AND (minimum) type antecedent. The output (defuzzification method) is calculated by the centroid method. The major trends in the rules description are:

- The morning and lunch doses of NPH insulin are skipped.
- The regular doses increases as the BGL increases.
- If the previous dose of insulin is small and the BGL is above normal, then increase the doses.

A sample of the proposed rules for the low level module is detailed next:

IF Time=Morning and Glucose=Low and I_{rd}=Large and I_{nphd}=Large **THEN** I_r=Small and I_{nph}=Medium.

3.2 High Level Module

The high level module is synthesized using physician knowledge [16], [17] by applying a Mamdani type fuzzy logic structure and regulates the amounts of insulin given to the patient by evaluating the glycemic control in a time-scale of days. According to control objective listed in Table 3, the systemic glucose deviation from the target glucose level (TGL) can be measured as:

$$J = \frac{1}{n}\sum_{k=1}^{n}\theta(k) \qquad (17)$$

Where n is the number of measurements used for evaluation, and $\theta(k)$ (point wise deviation from TGL) is defined as:

a) For BGL measured before eating:

$$\theta(k) = \begin{cases} G(k) - 130 \ mg/dl & G(k) > 130\, mg/dl \\ \Gamma.[G(k) - 90]\, mg/dl & G(k) < 90\, mg/dl \\ 0 & 90 \le G(k) \le 130\, mg/dl \end{cases} \qquad (18)$$

b) For BGL measured 2 hours after eating:

$$\theta(k) = \begin{cases} G(k) - 180\, mg/dl & G(k) > 180\, mg/dl \\ 0 & Otherwise \end{cases} \qquad (19)$$

c) For BGL measured at bedtime:

$$\theta(k) = \begin{cases} G(k) - 150 \ mg/dl & G(k) > 150\, mg/dl \\ \Gamma.[G(k) - 110]\, mg/dl & G(k) < 110\, mg/dl \\ 0 & 110 \le G(k) \le 150\, mg/dl \end{cases} \qquad (20)$$

Where Γ is a constant that includes an additional weight for low glucose concentrations (hypoglycemic scenarios). Consequently, the high level module must adjust the insulin dosing in three global scenarios:

- Increase it, if an hyperglycemic condition is detected.
- Decrease it, in the case of an hypoglycemic condition.
- Maintain it, for a normal condition.

These dosing adjustments are performed in a time-scale of days, where they could be specified per day or week according to the physician's advice. The adjustment is done the next morning by modifying the scaling factors $I_r^{\max}$ and $I_{nph}^{\max}$ using an integral type of updating rule:

Table 4.Inputs characteristics for low level module

Input	Interval	Membership Function			
t	[0,24] h	Morning (SMF)	Lunch (GBCMF)	Evening (SMF)	
G	[40,400] mg/dl	Low (SMF)	Normal (GBCMF)	Medium (GBCMF)	High (SMF)
I_{rd}	[0,1]	Small (SMF)	Medium (GBCMF)	Large (SMF)	
I_{nphd}	[0,1]	Small (SMF)	Medium (GBCMF)	Large (SMF)	

Table 5.Outputs characteristics for low level module

output	Interval	Membership Function				
I_r	[0,1]	None (TMF)	Small (TMF)	Medium (TMF)	Large (TMF)	Very Large (TMF)
I_{nph}	[0,1]	None (TMF)	Small (TMF)	Medium (TMF)	Large (TMF)	Very Large (TMF)

$$I_r^{\max}(i) = I_r^{\max}(i-1) + \Delta I_r$$
$$I_{nph}^{\max}(i) = I_{nph}^{\max}(i-1) + \Delta I_{nph} \quad (21)$$

Where ΔI_r and ΔI_{nph} are the adjustments given by the high level module. The index i-1 refers to the old scaling factor, and i to the new adjusted one. The input information used by the high level module includes details of the glycemic control during the previous days, and the previous insulin adjustments, this is:

- The glucose deviation (J) in (17).
- Memory of the previous deviation (J_d).
- The previous adjustments ΔI_r and ΔI_{nph}.

The input and output characteristics are shown in Table 6 and 7 respectively, including the interval of variation for each variable and the fuzzy sets associated with the type of membership function used (fuzzication method). By the definition of the input fuzzy set, a total of 81 IF-THEN rules were defined. These rules were of AND (minimum) type antecedent. The output (defuzzification method) is calculated by the centroid method. The premise of these rules can be summarized in three points:

- If there is a tendency for the glucose deviation to increase above the TGL, then increase the scaling factors.
- If there is a tendency to decrease below the TGL, then reduce the scaling factors.
- If the glucose deviation is in the TGL, then try to decrease the scaling factor without leaving the TGL.

A sample of the proposed rules for the low level module is detailed next:

IF J_d=Negative and J=Negative and ΔI_{rd}=Zero and ΔI_{nphd}=Zero **THEN** ΔI_r=Negative and ΔI_{nph}=Negative.

4 Simulations

The numerical simulation was implemented in MATLAB/Simulink using the Fuzzy Logic Toolbox. A total of 25 days (T = 36000 min) were simulated with three meals per day: **breakfast**: 8 h, **lunch**: 14 h, and **dinner**: 20 h. Three boluses of insulin are programmed per day by a subcutaneous injection, where a combination of Regular and NPH insulin is programmed. The high level module supervises intensively the low level module every day to adjust the scaling factors. During the simulation period (25 days), a total of 100 doses are computed. The hypoglycemic weight Γ in (18) and (20) was selected to 5 [7] during the computation of glucose deviation J.

At the first case of our simulation, the patient starts with small scaling factors for both types of insulin, producing small insulin doses and high glucose levels. The algorithm adjusts the insulin dosages in order to reach the TGL. For this scenario, a $\pm$ 15 % error (typical error in commercial devices) in each of the glucose measurements is assumed.

At the second case, in order to analyze the effect of heavy variations in the meal intakes, the patient varies his carbohydrate intake during meals by 25% from the nominal ones, using a uniform distribution.

The insulin-glucose dynamics can vary drastically from patient to patient. In previous studies [15], it was shown that the parameters related to the body's sensitivity to insulin (k) presented the largest impact in the blood glucose concentration. Thus in order to analyze this scenario, at the third case the values of this parameter was perturbed 20 %, and 25 combinations were selected that achieved the largest sensitivity in the BGL.

At the last case, a 40 days simulation is also presented, in order to analyze the stability of the advisory/control for a longer period of time despite measurement errors.

Table 6.Inputs characteristics for high level module

Input	Interval	Membership Function		
J	[-20,20] mg/dl	Negative (SMF)	Zero (GBCMF)	Positive (SMF)
J_d	[-20,20] mg/dl	Negative (SMF)	Zero (GBCMF)	Positive (SMF)
ΔI_{rd}	[-2,2] U	Negative (SMF)	Zero (GBCMF)	Positive (SMF)
ΔI_{nphd}	[-4,4] U	Negative (SMF)	Zero (GBCMF)	Positive (SMF)

Table 7.Outputs characteristics for high level module

Output	Interval	Membership Function				
ΔI_r	[-2,2] U	Very Negative (SMF)	Negative (TMF)	Zero (TMF)	Positive (TMF)	Very Positive (SMF)
ΔI_{nph}	[-4,4] U	Very Negative (SMF)	Negative (TMF)	Zero (TMF)	Positive (TMF)	Very Positive (SMF)

Fig.7, 8, 9 and 10 present simulations for the case 1, 2, 3 and 4 respectively: meal carbohydrates intakes, blood glucose concentration, insulin doses, insulin scaling factors and glucose deviation function. Hypoglycemia was detected when the BGL decreased below 60 *mg/dl* during simulations. It is observed that there is no instability in the system although the measurement error can be as high as 15%, and meal intakes can have up to 10% variation and no hypoglycemic conditions are detected. For all cases studied, the advisory/control algorithm is able of regulate the plasma glucose around the TGL despite initially low scaling factors and measurement errors, variable carbohydrates intake and variability in the glucose-insulin dynamics. .

5 Conclusion

In this study, a fuzzy logic controller has been proposed to maintain the normoglycaemic for diabetic patient of type I. The treatment strategy is based on a four-daily dose of regular and NPH insulin and which is applied through a subcutaneous route. In order to incorporate knowledge about patient treatment, the controllers are designed using a Mamdani-type fuzzy scheme. Simulation results with a physiological model of the TIDM patient show the effectiveness of structure for blood glucose regulation. Hence the results presented are encouraging for clinical studies, however in that case, some other physiological factors not addressed in the TIDM mathematical model could affect the actual performance, and further tuning could be necessary according with the results achieved in each patient. As shown in this paper, the fuzzy logic framework has the potential to synthesize expert knowledge to treat diseases. Therefore, the approach and methodology introduced could be a valuable tool for educational purposes. Moreover, in future work, the inclusion of an exercise regime in the overall model of the TIDM patient in order to have a more realistic simulation will be considered.

References:

[1] [Online] Available: www.who.int/mediacentre/factsheets/fs236/en/

[2] ENDOCRINE WEB INC., 1998, The Diabetes Center. http://www.endocrineweb.com

[3] DCCT, .The effect of intensive treatment of diabetes on the development and progression of long-term complications in insulin-dependent diabetes mellitus,. *N. Engl. J. Med.*, vol. 329, pp. 977.986, 1993.

[4] J. M. Bailey and W. M. Haddad, .Drug dosing control in clinical pharmacology,. *IEEE Control Systems Magazine*, vol. 25, no. 2, pp. 35.51, 2005.

[5] R. Bellazzi, .Electronic management systems in diabetes mellitus: Impact on patient outcomes,. *Disease Management & Health Outcomes*, vol. 11, no. 3, pp. 159.171, 2003.

[6] R. Bellazzi, G. Nucci, and G. Cobelli, .The subcutaneous route to insulin-dependent diabetes therapy,. *IEEE Engineering in Medicine and Biology*, vol. 20, pp. 54.64, junuary/february 2001.

[7] D. U. Campos-Delgado, R. Femat, M. Hern´andez-Ordonez, and A. Gordillo-Moscoso, Self-tuning insulin adjustment algorithm for type I diabetic patients based on multi-doses regime,. *Applied Bionics & Biomechanics*, vol. 2, no. 2, pp. 61.72, 2005.

[8] D. U. Campos-Delgado, R. Femat, E. Ruiz-Vel´azquez, and A. Gordillo-Moscoso, Knowledge-based controllers for blood glucose regulation in type I diabetic patients by subcutaneous route,. in *Proc. of the Int. Symp. on Inteligent Cont.*, Houston, USA, october 2003.

[9] K. Miyako, R. Kuromaru, H. Kohno, and T. Hara, .Improved diabetes control by using close adjustment algorithms,. *Pediatrics International*, vol. 46, pp. 678.684, 2004.

[10] D. Driankov, H. Hellendoorn, and M. Reinfrank, *An Introduction to Fuzzy Control*, 2nd ed. Springer-Verlag Berlin Heidelberg, 1996.

[11] L. X. Wang, *A Course in Fuzzy Systems and Control*. Upper Saddle River, New Jersey: Prentice Hall Inc., 1997.

[12] J. T. Sorensen, .A physiologic model of glucose metabolism in man and its use to design and assess improved insulin therapies for diabetes, *Ph.D. Thesis, Chemical Engineering Department, MIT, Cambridge*, 1985.

[13] M.S. Leaning and M.A. Boroujerdi. A system for compartmental modeling and simulation. *Comp Meth Prog Biomed*, 35:71-92, 1991.

[14] R.N. Bergman, Y.Z. Ider, C.R. Bowden, and C. Cobelli. Quantitative estimation of insulin sensitivity. *Am J Physiol*, 236:E667-77,1979.

[15] W.R. Puckett. Dynamic modeling of diabetes mellitus. *PhD Thesis, University of Wisconsin - Madison*, 1992.

[16] ADA, .Standards of medical care for patients with diabetes mellitus, *Diabetes Care*, vol. 25, supplement 1, pp. 533.549, 2002.

[17] K. Miyako, R. Kuromaru, H. Kohno, and T. Hara, .Improved diabetes control by using close adjustment algorithms, *Pediatrics International*, vol. 46, pp. 678.684, 2004.

[18] R.S Hillman, The dynamics and control of glucose metabolism, *PhD Thesis, MIT*, 1976.

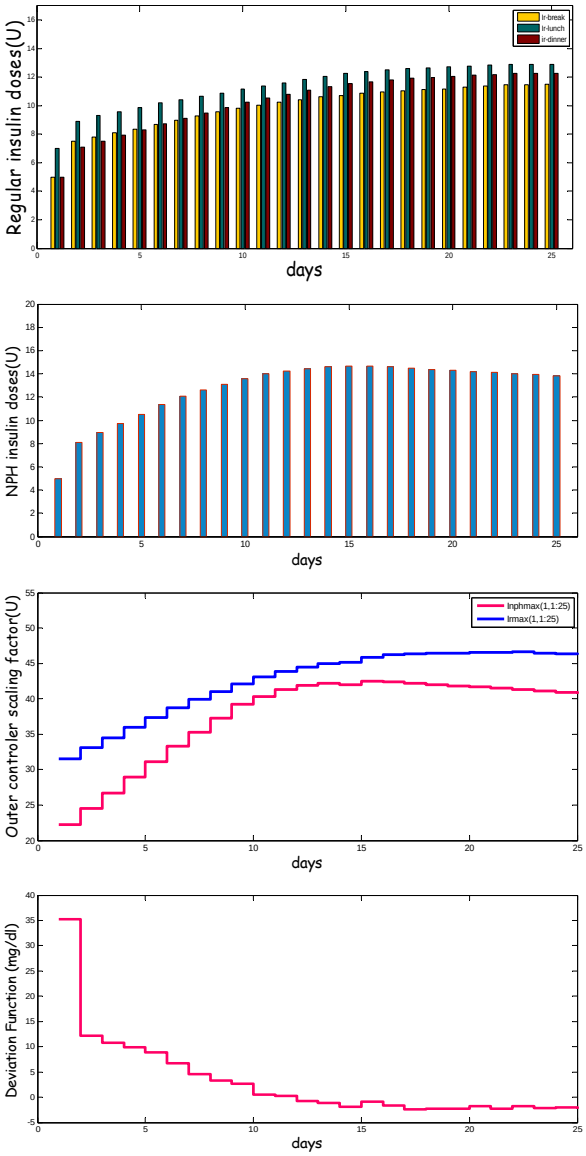
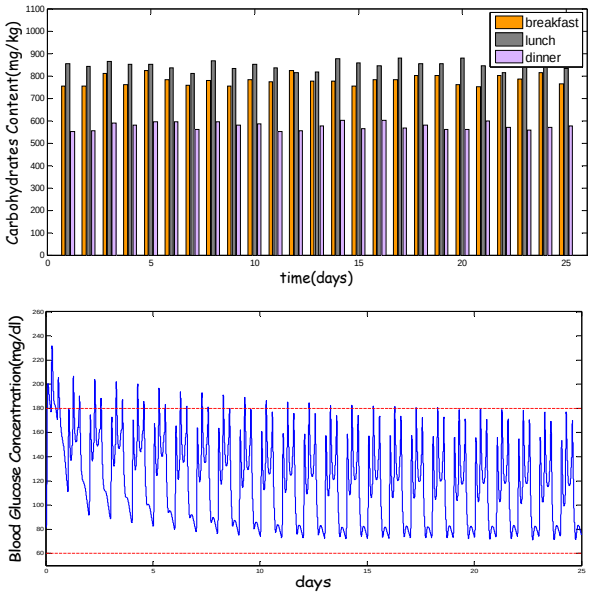
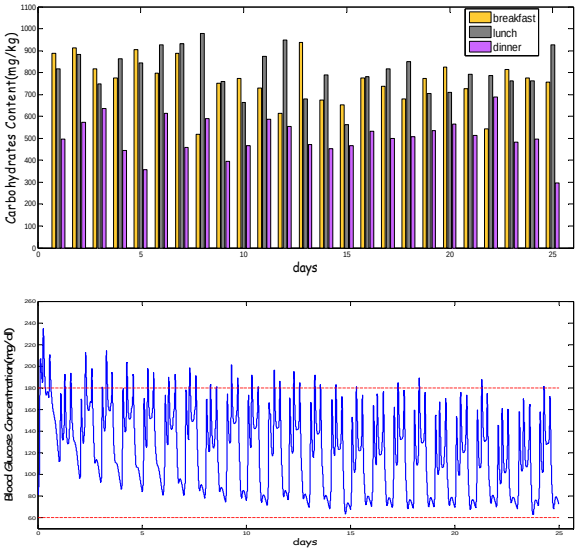


Fig.7. Simulation for a 25 days period: case 1





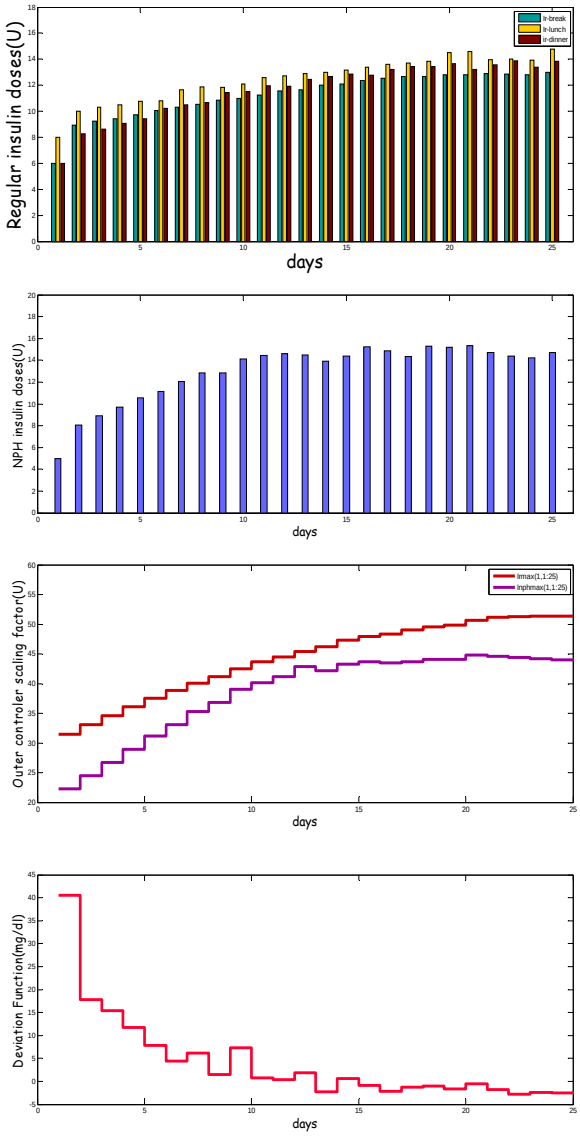


Fig.8. Simulation for a 25 days period: case 2

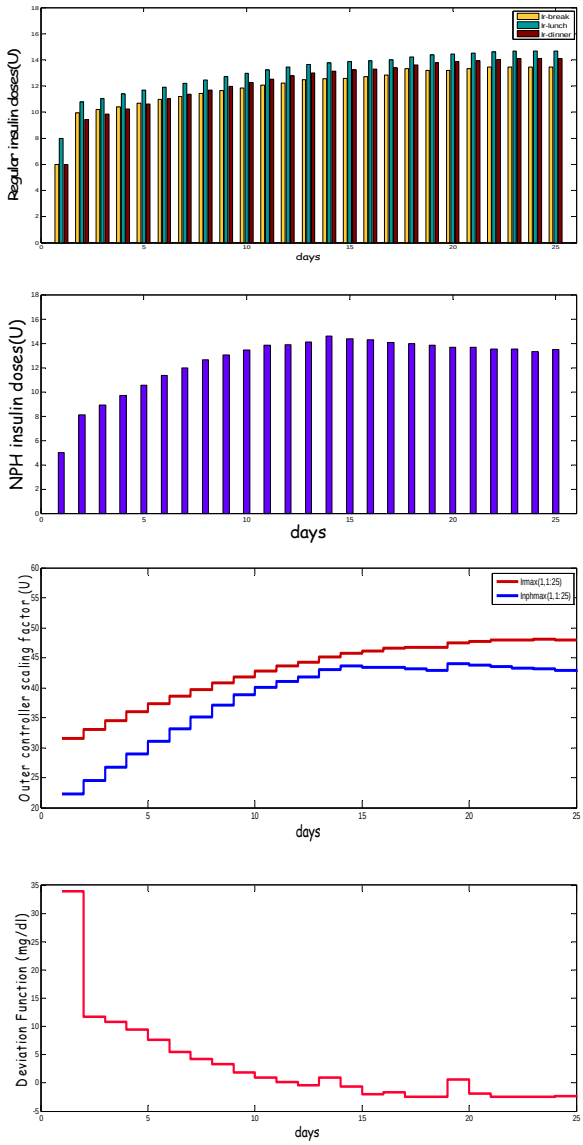
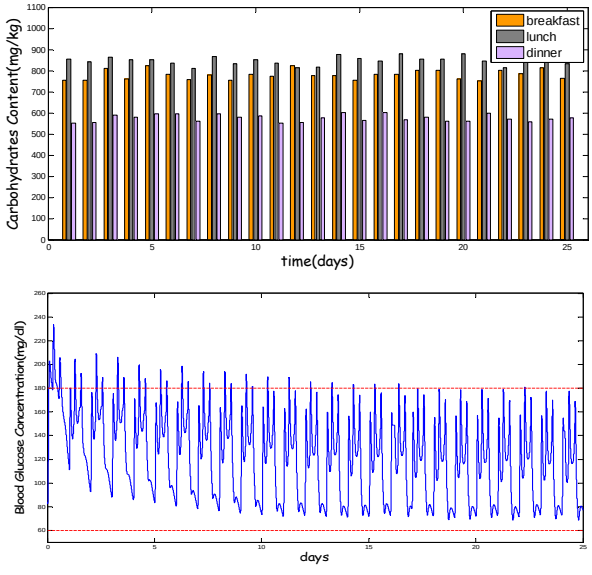
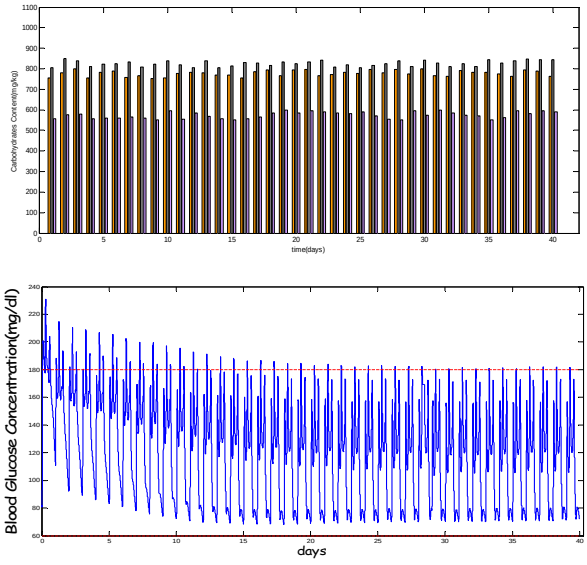


Fig.9. Simulation for a 25 days period: case 3





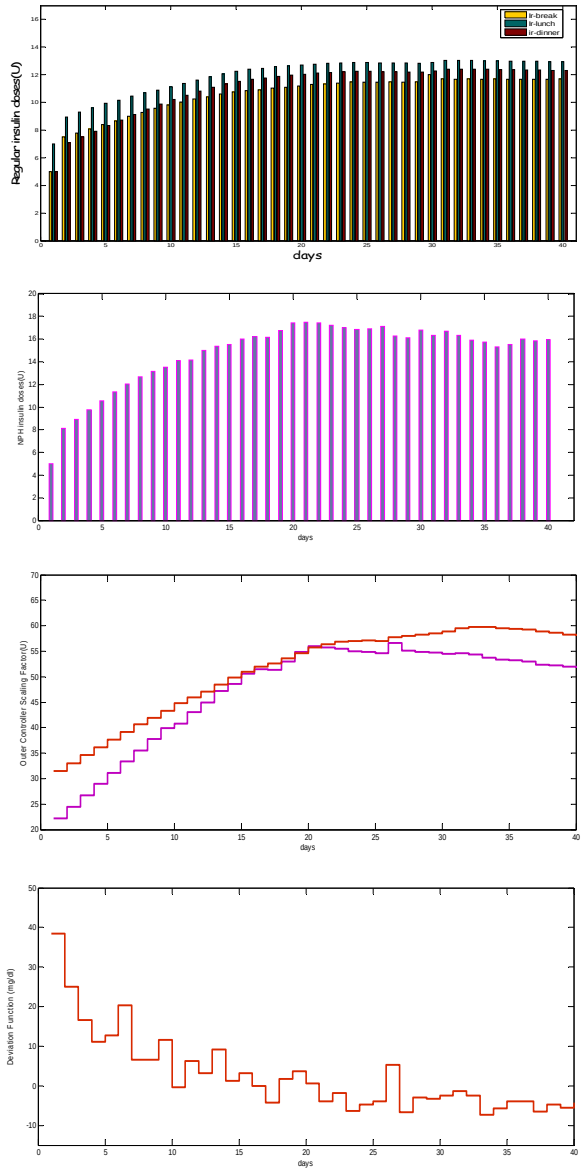


Fig.10. Simulation for a 40 days period: case 4