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Intensive Insulin Therapy of Type-1 Diabetes by Fuzzy-Based Controller

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Abstract

This paper presents a control algorithm for a type-1 diabetes mellitus (TIDM) patient under an intensive insulin treatment (IIT) based on an hourly injections regimen. The control algorithm incorporates expert knowledge about the treatment of this disease by using

Table 1- Summarizes the 2006 World Health Organization recommendations for the diagnostic criteria for diabetes and intermediate hyperglycemia [5].

	Fasting plasma glucose	**2–h plasma glucose***
Diabetes	≥7.0mmol/l (126mg/dl)	≥11.1mmol/l (200mg/dl)
Impaired Glucose Tolerance (IGT)	<7.0mmol/l (126mg/dl)	≥7.8 and <11.1mmol/l (140mg/dl and 200mg/dl)
Impaired Fasting Glucose (IFG)	6.1 to 6.9mmol/l (110mg/dl to 125mg/dl)	<7.8mmol/l (140mg/dl)

*** Venous plasma glucose 2–h after ingestion of 75g oral glucose load**

Mamdani-type fuzzy logic controllers to regulate the blood glucose level (BGL). The overall control strategy is based on one function and one loop feedback strategy to overcome the variability in the glucose-insulin dynamics from patient to patient. A fuzzy-loop provides the amount of rapid-acting insulin (e.g. insulin Lispro, insulin Aspart or insulin Glulisine) formulations that are programmed in an hourly. Meanwhile, a basal-function adjusts the amounts of intermediate-acting insulin (e.g. insulin NPH) stabilize the BGL of patient in low glucose level. The fuzzy-loop works as an expert and decide the insulin dose in high BGL and the basal-loop adjusts dose of intermediate-acting insulin for low BGL.

Keywords: Diabetes mellitus, Mamdani fuzzy-based control, glucose regulation, intensive insulin therapy.

INTRODUCTION

Diabetes is a disorder that affects the way your body uses food for energy. Normally, the sugar you take in is digested and broken down to a simple sugar, known as glucose. The glucose then circulates in your blood where it waits to enter cells to be used as fuel. Insulin, a hormone produced by the pancreas, helps move the glucose into cells. A healthy pancreas adjusts the amount of insulin based on the level of glucose. But, if a person has diabetes, this process breaks down, and blood sugar levels become too high. There are two main types of full-blown diabetes. People with Type 1 diabetes are completely unable to produce insulin. Type 1 most often occurs before age 30, but may strike at any age. Type 1 can be caused by a genetic disorder. The origins of Type 1 are not fully understood, and there are several theories. But all of the possible causes still have the same end result: The pancreas produces very little or no insulin anymore. Frequent insulin injections are needed for Type 1. People with Type 2 diabetes can produce insulin, but their cells don't respond to it. In either case, the glucose cannot move into the cells and blood glucose levels can become high. Over time, the high blood glucose levels of uncontrolled diabetes can be toxic to virtually every system of the body. Neuropathy–nerve damage, nephropathy-kidney damage, retinopathy-vision problems, blindness, Cardiovascular Disease-heart disease and increased risk of strokes, depression, and amputation [1-4]. Concentration of blood glucose for diabetes and intermediate hyperglycemia was announced by WHO in 2006. These values are shown in Table 1.

Trials of intensive insulin therapy with rapid-acting insulin showed that it can prevent or slow the progression of long-term diabetes complications so it will supply better life to patients with continuous injection systems [6]. However, the side affect of IIT cause the hypoglycemia which is the medical term for a state produced by a lower than normal Blood Glucose Concentration (BGC). *Basal* is type of insulin that you need in your body 24/7 regardless of when you eat and *Bolus* insulin refers to the dose you take to cover food you've eaten with short acting insulin [7]. Intensive insulin therapy using a basal-bolus approaches [8], whether as multiple daily injections or pump therapy, is considered the best treatment for individuals with type-1 diabetes regardless of age. This is because it provides greater glycemic control and has been shown to reduce the risk of complications compared with conventional fixed-dose regimens, most recently shown in the Diabetes Control and Complications Trial analysis. While achieving good glycemic control is important in all age groups, it is of particular importance in children with type-1 diabetes, as they face the longest duration of the disease.

Early model of control algorithm based on mathematical modeling of insulin-glucose dynamics [9-13]. In the control theory, the fuzzy logic has emerged as a powerful tool to employ expert knowledge about the systems for implementing an appropriate control law [14]. Delgado *et al*. [15] and Ting and Quek [16] developed a controller using fuzzy method for regulating of glucose level, but they used rate of change technique in their algorithm. Rate of change glucose or insulin technique is good in some values. On the other hand, some researchers do not attention to rate of change in different level of Blood Glucose Concentration (BGC) giving different meanings (e.g. at 200mg/dl and rate of change %20, at 300 mg/dl and rate of change %20) and also those systems behave as a discrete function because of considering meal times. These models have ranged from linear to nonlinear with increasing the levels of complexity, since the parameters of these models are not constant and vary from patient to patient. In this paper we proposed to develop a fuzzy based optimal controller that is control the glucose level of the patient via an infusion device. It will control BGL full linguistically and it does not depend on rate of change BGC.

INSULIN TYPES AND CHARACTERISTICS

There are many forms of insulin to treat diabetes. They are classified by how fast they start to work and how long their effects last. Different insulin is listed in below according to whether they serve primarily as bolus or basal insulin [17].

Bolus Insulin
- Aspart (Novolog®)
- Glulisine (Apidra®)
- Lispro (Humalog®)
- Regular

Basal Insulin
- Detemir (Levemir®)
- Glargine (Lantus®)
- NPH*

Table 2 lists the types of injectable insulin with details about **onset** (the length of time before insulin reaches the bloodstream and begins to lower blood sugar), **peak** (the time period when the insulin is the most effective in lowering blood sugar) and **duration** (how long insulin continues to lower blood sugar). These three factors may vary, depending on your body's response. The final column provides some insight into the "coverage" provided by the different insulin types in relation to mealtime [18].

SYSTEM DESCRIPTION

There are plenty factors which effect the insulin requirement of the patient for holding desired BGL and also these can be various patient to patient. Because of this, any mathematical model which consists all factors effect insulin requirement have not been realized. Designed insulin controller block diagram is shown in Fig 1. As can be seen from this figure, blood glucose sensor measures BGC and memory keep this data then transmits the data to control algorithm which behave like a brain. It has basal function for basal insulin and fuzzy controller for bolus insulin. It secretes basal or bolus insulin(s) hourly because rapid-insulin peak time is about an hour. When it secretes insulin less then an hour, the system may cause the instability in BGC; this can also cause hypoglycemia. In addition, giving rapid-acting insulin between 90-130 mg/dl can cause hypoglycemia so that

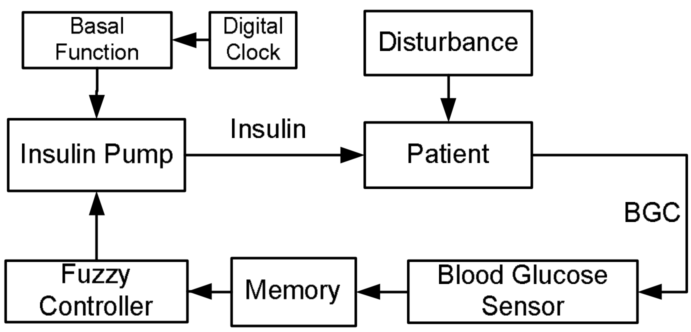


Fig. 1-Insulin Regulation System Block Diagram

Table 2- Characteristics of Insulin types

Type of Insulin & Brand Names	Onset	Peak	Duration	Role in Blood Sugar Management
Rapid-Acting				
Humalog or Lispro	15-30 min.	30-90 min	3-5 hours	Rapid-acting insulin covers insulin needs for meals eaten at the same time as the injection. This type of insulin is used with longer-acting insulin.
Novolog or Aspart	10-20 min.	40-50 min.	3-5 hours	
Apidra or Glulisine	20-30 min.	30-90 min.	1-2½ hours	
Short-Acting				
Regular (R) humulin or novolin	30 min. -1 hour	2-5 hours	5-8 hours	Short-acting insulin covers insulin needs for meals eaten within 30-60 minutes
Velosulin (for use in the insulin pump)	30 min.-1 hour	2-3 hours	2-3 hours	
Intermediate-Acting				
NPH (N)	1-2 hours	4-12 hours	18-24 hours	Intermediate-acting insulin covers insulin needs for about half the day or overnight. This type of insulin is often combined with rapid- or short-acting insulin.
Lente (L)	1-2½ hours	3-10 hours	18-24 hours	
Long-Acting				
Ultralente (U)	30 min.-3 hours	10-20 hours	20-36 hours	Long-acting insulin covers insulin needs for about 1 full day. This type of insulin is often combined, when needed, with rapid- or short-acting insulin.
Lantus	1-1½ hour	No peak time; insulin is delivered at a steady level	20-24 hours	
Levemir or detemir(FDA approved June 2005)	1-2 hours	6-8 hours	Up to 24 hours	
Pre-Mixed*				
Humulin 70/30	30 min.	2-4 hours	14-24 hours	These products are generally taken twice a day before mealtime.
Novolin 70/30	30 min.	2-12 hours	Up to 24 hours	
Novolog 70/30	10-20 min.	1-4 hours	Up to 24 hours	
Humulin 50/50	30 min.	2-5 hours	18-24 hours	
Humalog mix 75/25	15 min.	30 min.-2½ hours	16-20 hours	

the system gives basal insulin (NPH) at this interval. A control algorithm processes the information of the glucose sensor in real-time, and updates the insulin injection rate by the pump. The controller implementation was carried out using the Fuzzy Logic Toolbox of MATLAB©.Fuzzy-loop works with two inputs; one is instant BGC2 at that time and the other input BGC1 is that supplied by memory which measured it an hour before. Calculation of daily insulin dose is basically between 0.2 – 0.5U/kg/day × weight of patient but the patient must consult to his doctor or any expert for calculation and divide the total daily dose into the basal dose and the bolus doses by simply dividing it in half [19].

Table 3-Input characteristic of fuzzy-loop

Inputs	Intervals	Membership functions				
BGC1 (measured at that time)	[120;500]mg/dl	Medium (ZMF)	High (GAUSSMF)	Very-high (GAUSSMF)	Extreme-high (GAUSSMF)	Danger (SMF)
BGC2 (measured an hour before)	[120;500]mg/dl	Medium (ZMF)	High (GAUSSMF)	Very-high (GAUSSMF)	Extreme-high (GAUSSMF)	Danger (SMF)

Table 4-Output characteristic of fuzzy-loop

Output	Intervals (different patient to patient)	Membership functions				
Insulin	[0;10] Unit	Less (ZMF)	Average (GAUSSMF)	High (GAUSSMF)	Very-high (GAUSSMF)	Extreme-high (SMF)

Table 5-Characteristic of bolus-loop for LPH (peak time 4 hours)

	Intervals	Morning	Afternoon	Night
Inputs	[0:24]h	4<=t<12	12<=t<20	otherwise
Outputs	[0:24]h	(K_m*daily-dose/2)/24	(K_a*daily-dose/2)/24	(K_n*daily-dose/2)/24

K_m, K_a, and K_n are the correction factor of daylight-time for patient. (E.g. K_m=0.8, K_a=1, and K_n =1.2)

U is the biological equivalent of about 45.5 μg pure crystalline insulin (1/22mg exactly). This corresponds to the old USP insulin unit, where one unit (U) of insulin is equal to the amount required to reduce the concentration of blood glucose in a fasting rabbit to 45 mg/dl (2.5 mmol/L) [20]. In addition, at night our metabolism is minimum level and we do not need to energy so that more glucose concentration in blood than daylight, we can use some ratio which is also determined by experts. We developed the algorithm for basal function with related to the time factor. These factors are shown in Table 5 and values are selected by a doctor from Istanbul Sur Hospital. Fuzzy controller (FC) is the main control unit of the system behaves as an expert and the supplier of bolus insulin. FC comment inputs then decide the insulin requirement like a doctor. However, the most important part of FC is the rule base. These rules are created by an expert (doctor). Characteristics of input and output membership functions are given Table 3 and 4, respectively. The Z-shaped (ZMF), S-shaped (SMF), and Gaussian curve (GAUSSMF) definition of the input and output fuzzy sets, a total of 25 IF-THEN rules were defined. These rules were of AND (minimum) type antecedent. The output (defuzzification method) is calculated by the CENTROID method. The linguistic rules are generated by the doctor. Some rules from fuzzy-controller (This rule based is created according to a Type 1 diabetes patient who is 80 kg male with athletic body) are given below:

<**Rule 4: if** BGC1 is medium and BGC2 is extreme-high **then** insulin is very-high>
<**Rule 14: if** BGC1 is very-high and BGC2 is extreme-high **then** insulin is extreme-high>
<**Rule 21: if** BGC1 is danger and BGC2 is medium **then** insulin is less>

EXPERIMENTS AND RESULTS

The patient is 32 years old male. His weight 80 kg and his height is 1.78 meter. Starting time to simulation is 8:00 a.m. Data was received hourly. Fuzzy membership and rule are created by the doctor's experiences. Surface of the fuzzy loop is shown that in Fig 2. In this figure, the horizontal planes have BGC1 and BGC2 which are inputs and BGC1 means BGC measured an hour before, the other is BGC measured at that time, the vertical direction is requirement insulin dose and its max output value is 10 units. The blood glucose concentration behavior of the patient with insulin injections by using our algorithm in two days is shown in Fig. 3a. According to this patient data, the program generated the data and received the Fig.3b. It shows bolus and basal injection in a time. There is one hypoglycemia value at 27 hour; it is good news because the biggest problem of the intensive insulin therapy is risk of being plenty of hypoglycemia and also mean of BGC is 116.0408 mg/dl. This value in target level but it can be better. The fuzzy-rules and the other data have some error but it will show us a way for overcoming diabetes in future. More data we receive after using this algorithm and with new type of insulin which have shorter peak time we can keep blood glucose level easier in acceptable values. The program is very useful but also patients must be careful when selecting food. In addition, he/she must give up smoking and alcohol if not he gain resistance of insulin and it is very complex and uncontrollable situation with algorithm.

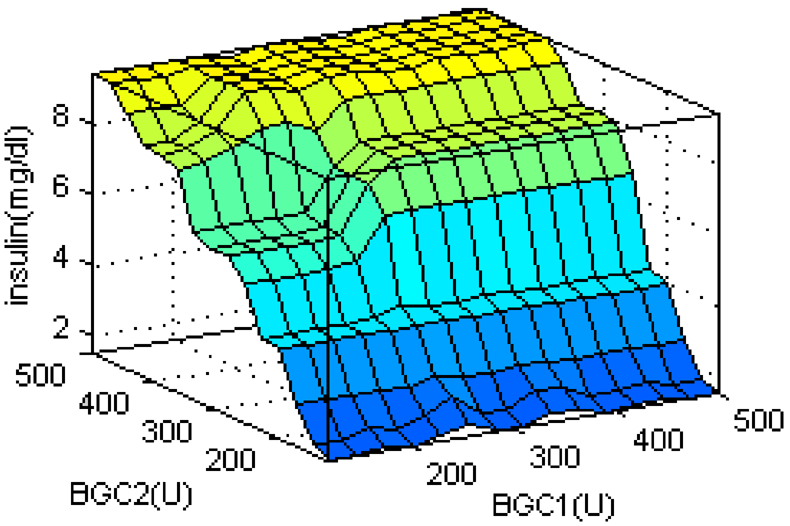
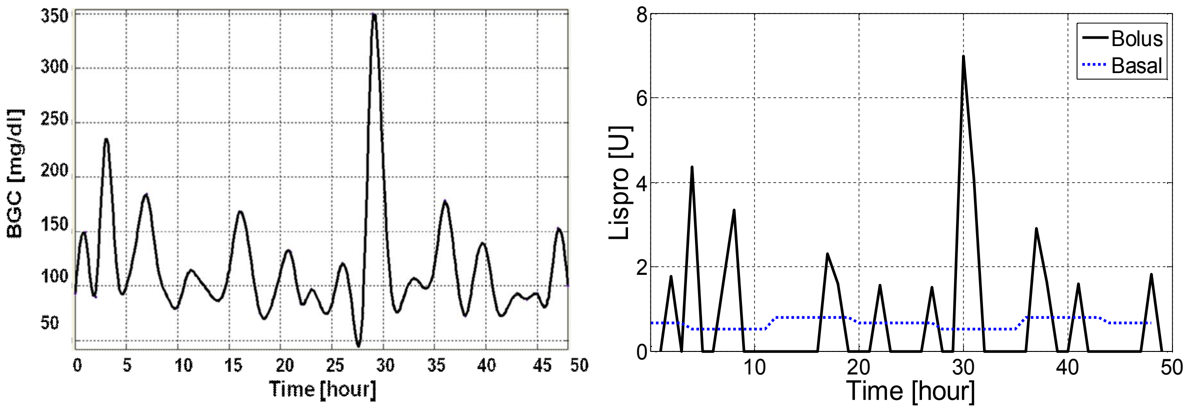


Fig. 2- Surface of the fuzzy-loop

CONCLUSIONS

Basal-bolus insulin is one of the most advanced approaches to diabetes care, offering a way to closely simulate natural insulin delivery. The basal insulin address the glucose the liver makes, while the bolus insulin address the sugar in the foods that are eaten. Because some people need more basal insulin and others need more bolus insulin, this regimen can be custom fit to the needs of each individual. The algorithm will be better in future with receiving more data from patients and also easy to understand for experts, especially doctor who works on diabetes. We can add some correction factors for membership function like age factor, exercise factor, stress factor, temperature factor, and so on so that we can create algorithm with these correction factor and patient can program the device. On the other hand, they will have better life standards.



(a) (b)

Fig. 3- (a) Blood glucose concentration of the patient in two days, (b) Bolus and basal injection

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