GLUCOSE REGULATION IN TYPE 1 DIABETIC PATIENTS BY A MULTI-DOSES REGIMEN

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Abstract: In this paper several multi-doses control regimens are suggested for type 1 diabetic patients. The suggested regimes are proposed based on different insulin formulations. The insulin doses are assumed to be infused by a subcutaneous injection in a three daily regimen prior to each meal. Mixing two types of insulin: rapid or short, and intermediate or long action, the basal and postprandial insulin productions of the pancreas are reproduced. The performance in the glucose regulation is evaluated during a 10-day trial by open-loop and closed-loop simulation with a compartmental model.

Keywords: Diabetes, Biomedicine, Glucose Regulation.

1. INTRODUCTION

The insulin is a hormone in charge to promote the processing of glucose (energy) by the body cells. As a result, this hormone has a regulatory effect in the blood glucose, and prevents high (hyperglycemia) glucose concentrations beyond the euglycemic (normal) level $70 - 120\ mg/dl$ (Sorensen 1985), (Puckett 1992). The type 1 diabetes is a desease characterized by the destruction of the β-cells in the pancreatic islets of Langerhans. Since the β-cells produce the insulin in the pancreas, external insulin infusions are needed by the patient in order to maintain regulated his/her blood glucose. Due to continuous variations in the blood glucose concentration (BGC), the diabetes can produce short and long term illnesses (nephropathy, retinopathy, and other tissue damage) (DCCT 1993). In a healthy pancreas, a constant basal rate of insulin is produced 22 mU/dl (Sorensen 1985), but in order to assimilate the glucose absorbed by the gut through meals, the basal rate is increased (postprandial peaks) temporary. Therefore, this insulin release pattern should be imitated externally in order to reduce the risk of future deseases.

As a first step in the treatment of this illness, it is necessary to understand the insulin-glucose dynamics in diabetic patients. For this reason, several research efforts have focused on the mathematical modeling of these interactions (Puckett 1992), (Sorensen 1985). These models can also be used as educational simulators for demonstration and self-learning (Lehmann and Deutsch 1998). There are two overall approaches for glucose control, and they depend on the location of the insulin infusions: (a) subcutaneous (Bellazzi *et al.* 2001) and (b) intravenous (Parker *et al.* 2001). For the intravenous approach, a continuous pump

is used to deliver a variable insulin infusion rate to the patient, according with a control algorithm that processes the glucose measurements. Several control methodologies have been suggested: H_∞ robust control (Ruiz-Velazquez *et al.* 2004), optimal control and model predictive (Lynch and Bequette 2002). However, due to the size of mechanical pumps, this approach is now limited to patients under a hospital treatment. On the other hand, the subcutaneous approach relies on several therapeutic regimes based on combinations of different types of insulin (American Diabetes Association 2002), (APhA Special Report 2001), (Dickerson 1999), (Hirsch 1999); delivered to the patient through a subcutaneous route on multiple daily dosing regimes. The doses are programmed according with the information gathered by implanted glucose sensors (MiniMed ®), picks of blood glucose concentration (Accu-Chek ®) or non-invasive blood glucometers (GlucoWatch ®) (Tamada *et al.* 2002), and physician advice. Thus, algorithms for the optimal time and amount of insulin have been suggested in (Doyle *et al.* 2001), (Shimauchi *et al.* 1988). The subcutaneous approach is indeed a challenging control problem since the insulin absorption has to be considered, and consequently a time-lag is present in the plasma insulin concentration. Nevertheless, this is the most common therapeutic regime for type 1 diabetic patients in a chronical stage.

The rest of the paper is organized as follows. Section 2 describes the types and characteristics of different comercial insulins, and the control problem framework is defined in Section 3. The multi-doses regimens are illustrated in Section 4. Section 5 outlines the mathematical model for a type 1 diabetic patient. The implementation of the control strategies by simulation is shown in Section 6, and some conclusions and final remarks are introduced in Section 7.

2. INSULIN TYPES AND CHARACTERISTICS

If the insulin is injected subcutaneously to the patient, there is an absorption process from the periphery toward the blood stream. As a result, there is an inherent delay time in the insulin action. Now, in some cases to reproduce the basal insulin rate, it is desired to reduce the absorption rate of the injected insulin. For this purpose, to the insulin formulations is added protamine or zinc to delay the absorption and the biological activity of the insulin (Dickerson 1999). In general, the insulin is classified according with its origin: bovine, porcine, and human; and with its action: rapid (Aspart and Lispro), short (Regular), intermediate (NPH and Lente), and long (Ultralente and Glargine) (APhA Special Report 2001). Human insulin is synthesized by chemical modification of pork insulin, or through a recombinant DNA technology. Since the human insulin is less antigenic than animal insulin, and it also has a more rapid onset of action and shorter absorption process, human insulin is preferred in therapeutical regimes. Table 1 illustrates the dynamic characteristics of the different types of human insulin. For some types of insulin, Berger y Rodbard (1989) proposed a mathematical model to reproduce the assimilation pattern after a subcutaneous injection. The time evolution of Lispro, Regular, NPH, Lente and Ultralente insulin after a 10 U infusion is shown in Figure 1.

Table 1. Insulin Characteristics After Subcutaneous Infusion.

Type	**Action (hours)**		
	Onset	**Peak**	**Duration**
Rapid			
Aspart	$0.17 - 0.33$	$1 - 3$	$3 - 5$
Lispro	$0.25 - 0.50$	$0.25 - 0.5$	$3 - 4$
Short			
Regular	$0.5 - 1$	$2 - 3$	$3 - 6$
Intermediate			
NPH	$2 - 4$	$4 - 10$	$10 - 18$
Lente	$3 - 4$	$4 - 10$	$16 - 24$
Long			
Ultralente	$6 - 10$	$8 - 24$	$18 - 30$
Glargine	$1 - 2$	$2 - 20$	$20 - 24$

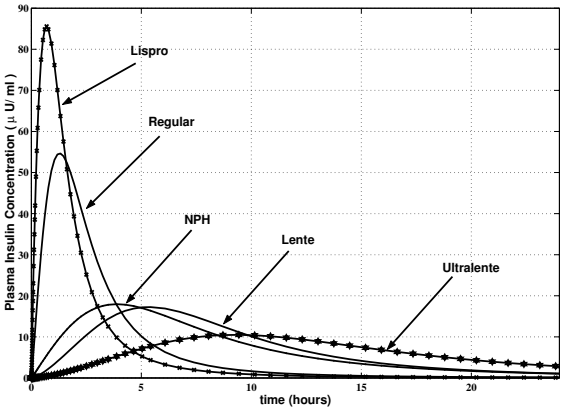

Fig. 1. Time Evolution of Plasma Insulin Concentration after a Subcutaneous Insulin Infusion of 10 U.

3. CONTROL PROBLEM DESCRIPTION

According to Mexican customs, three major meals are taken per day: breakfast (*desayuno*) (7:00-10:00 hrs), lunch (*comida*) (13:00-15:00 hrs) and dinner (*cena*) (20:00-22:00 hrs); where the *comida* meal is the major one of the day. Roughly, there is a time interval of 6 hrs among each meal of the day. Using this meal description, the approach presented in the paper relies in a three daily

injections using rapid or short, and intermediate or long action types of insulin. These doses are programmed $10-15$ minutes before taking a meal for rapid insulin, and $30-60$ minutes for short action insulin. Due to the delayed action of the intermediate or long action insulin, the doses for lunch-time are omitted, and only rapid or short action insulin is injected.

In order to prevent log-term illnesses (DCCT 1993), the **control objective** is defined as to regulate the BGC around an euglycemic concentration (EC) interval, defined as

$$EC = [70, 120] \text{ mg/dl} \quad (1)$$

using three daily doses of a preparation of two types of insulin. In this control scheme, several glucose measurements are available daily which could be derived from blood samples, in-vivo sensors or non-invasive means (Tamada *et al.* 2002). The control problem posed is very demanding since the doses given by a physician can vary abruptly from patient to patient. Moreover, the insulin-glucose dynamics for a type 1 diabetic patient are highly non-linear and can be modified by different parameters like diet, exercise, etc. (Puckett 1992), (Sorensen 1985). Note that a diet is assigned by the physician according with age and weight, however in most of the cases, the patient cannot follow tightly the amount of carbohydrates per meal assigned. So, the insulin regime should be robust enough to maintain the BGC regulated despite these issues.

In a systems point of view, a type 1 diabetic patient can be viewed a SISO (single-input single-output) system, where the control output is the subcutaneous BGC and the control input is the external insulin. It is important to point out that in the absence of a control input (insulin), the system is unstable since the BGC rises continuously. On the other hand, the control objective is difficult to tackle with classical control theory, since the strategy with multiple daily infusions can be thought as discrete impulses with variable sampling time given by the meal times. So, control strategies that rely on knowledge-based techniques as fuzzy-logic (Campos-Delgado *et al.* 2003) and neural networks, or self-tuning algorithms (Campos-Delgado *et al.* 2004) and adaptive control (Bellazzi *et al.* 2001) have been suggested.

4. MULTI-DOSES THERAPEUTICAL REGIMENS

According with the pharmacological effect of each insulin, several combinations of fast and slow action insulin can be suggested (APhA Special Report 2001), (American Diabetes Association 2002). Consequently, Lispro o Regular insulin are combined with NPH, Lente or Ultralente insulin. Five therapeutic regimes are illustrated in Table 2. These regimens are also known as *flexible insulin regimens or basal-bolus insulin therapy* (Hirsch 1999), since they allow the patient to adjust the timing and amount of insulin in accordance with changes in meal carbohydrate content or exercise. Note that the mixing of short-acting (Regular) and lente insulin is not recommended, since the absorption dynamics of the mixture can be seriously delayed (American Diabetes Association 2002), so this strategy is not considered in the paper. At the time of this study, there was not accurate data and models to identify the absorption dynamics of the (rapid-acting) Aspart and (long-acting) Glargine insulin (see Table 1), hence their performance was not investigated and will be objective of future research. Initially, in type 1 diabetic patients, the amount of insulin is calculated based on the patient weight, as 0.3 to 0.8 U per kilogram. This amount is continuously updated by the physician in collaboration with the patient in order to reach an euglycemic control, and it could change according with food consumption, exercise, illness, stress, hormonal changes, traveling and any change of routine (APhA Special Report 2001), (American Diabetes Association 2002). Hence it looks promising and rewarding the idea of an automated insulin adjustment algorithm for diabetic patients.

Table 2. Three Daily Doses Control Regimens.

Breakfast	**Lunch**	**Diner**
Lispro+NPH	Lispro	Lispro+NPH
Lispro+Lente	Lispro	Lispro+Lente
Lispro+Ultralente	Lispro	Lispro+Ultralente
Regular+NPH	Regular	Regular+NPH
Regular+Ultralente	Regular	Regular+Ultralente

5. TYPE 1 DIABETIC MATHEMATICAL MODEL

In this section, the mathematical model of a type 1 diabetic patient is described. Due to space limitation, only references are given for a detailed mathematical description. The model can be presented in three parts:

Insulin-Glucose Compartmental Model : the insulin-glucose model used in this work has a physiological structure based on a compartmental technique (Sorensen 1985). This model departs from experimental evidence to formulate and validate metabolic processes on the whole organ and tissue level, including counter-regulatory effects. Thus, the insulin-glucose model is governed by 19 nonlinear ordinary differential equations, and is divided into three

subsystems (i) Glucose, (ii) Insulin, and (iii) Glucagon. The first two subsystems were modeled for the brain, arterial system (heart/lungs), liver, gut, kidney, and periphery (muscle and adipose tissue) compartments. The glucagon was modeled as a single blood pool compartment. The system output is the peripheral interstitial glucose, that permits to obtain accurate glucose levels.

Glucose Input via Gastric Emptying : The amount of glucose in the gut following the ingestion of a meal, containing Ch milimoles of glucose equivalent carbohydrate, is modeled as a first order differential equation (Lehmann and Deutsch 1992). In this model, the rate of gastric emptying due to a meal is a function of the amount of carbohydrates intake Ch. Finally, the glucose input for a meal intake is given by a proportion of the glucose in the gut.

Subcutaneous Insulin Injection : it assumes that an insulin dose is injected subcutaneously. Hence the velocity of absorption can be described by a first order non-linear differential equation that depends on the different types of insulin: Lispro, Regular, NPH, Lente or Ultralente (Berger and Rodbard 1989). Finally, the plasma insulin concentration due to the subcutaneous injection is proportional to the absorbed insulin. It is also assumed that the insulin effect of previous injections is additive, *i.e.* the insulin plasma concentration depends on the combined effect of the actual and previous dosages. This consideration is not significant for rapid and short action insulin since its duration is approximately from 3 to 4 hrs, and the doses are programmed in periods of 6 hours during the day and 12 hrs at night. However, it is important for intermediate and long action insulin since their duration are from 10 to 18 hrs.

6. PERFORMANCE ANALYSIS THROUGH SIMULATION

First the performance of an open-loop strategy for insulin infusions was tested. The five therapeutic regimens in Table 2 were analyzed based on a performance index that measured the error in maintaining an euglycemic control ($BGC \in [70, 120]$ mg/dl). Next, the best regimens were simulated with a closed-loop strategy using a self-tuning algorithm for doses adjustment (Campos-Delgado *et al.* 2004). The numerical simulation were implemented in MATLAB/Simulink ©. A total of 12 days (284 hrs.) were simulated with three meals per day:

- **Breakfast**: 8:00 hrs.,
- **Lunch**: 14:00 hrs.,
- **Dinner**: 20:00 hrs.

The meals carbohydrate intakes were calculated according with the following profile: male, 30 years old, 80 kg, 1.75 m, number of hours of sleep per day: 7, number of hours of very light activity: 4, number of hours of light activity: 9, number of hours of intense activity: 4, amount of calories per day: 3734 Cal/day. It is considered that 50 % of the calories are coming from carbohydrates, and that 4 calories are equivalent to 1 gr. of carbohydrates (CH). Consequently, it is needed 467 gr. of carbohydrates per day. Assuming a distribution of this amount of carbohydrates in three meals: 30 % breakfast, 45 % lunch and 25 % dinner, results in the next meal distribution of carbohydrates:

- **Breakfast**: 140 gr. CH,
- **Lunch**: 210 gr. CH, and
- **Dinner**: 117 gr. CH.

Therefore, the lunch is the heaviest meal of the day according to Mexican customs. During the simulation time, the amount of carbohydrate intake per meal was varied around the nominal values calculated previously ±15%, but looking to add up to ≈ 3734 Cal/day in average during the simulation interval. Consequently, a variable meal carbohydrate intake was tested during simulation.

6.1 Open-Loop Simulation

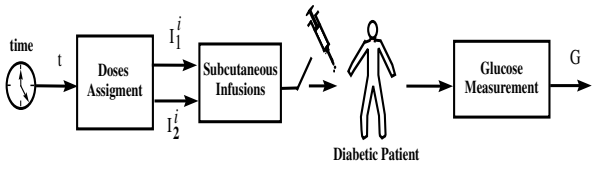

Fig. 2. Open-Loop Doses Assignment.

A total of 29 U/day ($\approx 0.36\ U/kg$) were assigned for each insulin formulation, the distribution was different in every case but the total per day maintained. In some cases, an increase in the total amount of insulin per day will improve the BGC regulation, however in some others (formulations with NPH insulin), this could induce an hypoglycemic scenario ($BGC < 60\ mg/dl$) due to the dynamics of the insulin. So, it was decided to maintain the total insulin per day to 29 U/day for the initial open-loop comparison. A total of six insulin dosages are defined:

(1) I_1^b: breakfast dose of rapid or short acting insulin.
(2) I_1^l: lunch dose of rapid or short acting insulin.
(3) I_1^d: dinner dose of rapid or short acting insulin.
(4) I_2^b: breakfast dose of intermediate or long acting insulin.

Table 3. Open-loop Regimens for Performance Analysis.

Formulation	I_1^b/I_2^b (U)	I_1^l (U)	I_1^d/I_2^d (U)	**J**
Lispro/NPH	2.75/10	3.5	2.75/10	20.46
Lispro/Lente	3.0/10	3.0	3.0/10	**8.87**
Lispro/Ultralente	3.0/10	3.0	3.0/10	**5.99**
Regular/NPH	2.5/10.5	3.25	2.5/10.25	22.28
Regular/Ultralente	2.75/10.75	2.5	2.5/10.75	**7.00**

(5) I_2^d: dinner dose of intermediate or long acting insulin.

The diagram in Figure 2 was followed. The performance index (blood glucose deviation) was measured during simulation

$$J = \frac{1}{T}\int_0^T \phi^2(t)dt \tag{2}$$

where T represents the total simulation time, and $\phi(t)$ (pointwise deviation from EC) is defined as

$$\phi(t) = \begin{cases} G(t) - 120\ mg/dl & G(t) > 120\ mg/dl \\ G(t) - 70\ mg/dl & G(t) < 70\ mg/dl \\ 0 & 70 \leq G(t) \leq 120\ mg/dl \end{cases} \tag{3}$$

with $G(t)$ representing the continuous glucose concentration. During the simulation, T was set to 10 days (240 hours) in order to avoid the effect of initial conditions in the performance analysis. The results are presented in Table 3. This table shows that the best formulation uses Ultralente or Lente insulin as basal insulin for either Lispro or Regular insulin. Consequently, these three combinations will be tested during closed-loop simulation in the next subsection.

6.2 Closed-Loop Simulations

The best three formulations obtained during the open-loop test: (a) Lispro-Lente, (b) Lispro-Ultralente, and (c) Regular-Ultralente will be analyzed in a closed-loop fashion (see Figure 3). The doses adaptation is performed by reducing the error in the BGC from euglycemics (Campos-Delgado *et al.* 2004). In this control scheme, several glucose measurements are assumed to be available daily which could be derived from blood samples, in-vivo sensors or non-invasive means (Tamada *et al.* 2002), in order to compute a cost function for the doses adaptation. Since the objective of the paper is not to introduce the tuning algorithm, rather to analyze the different insulin formulations, the details of the algorithm are omitted and the reader is referred to (Campos-Delgado *et al.* 2004). The results are summarized in Table 4. It is noticeable that the the BGC is almost regulated to the EC during the evaluation time with Ultralente as basal insulin, with either Regular or Lispro as fast-acting insulin. There is not significant difference between the Lispro/Ultralente or Regular/Ultralente formulation. Note that the best strategies require more insulin per day, but due to the properties of insulin mixture, there is no occurrence of hypoglycemia. Thus the self-tuning algorithm improves the previous performance with the open-loop strategy, and it accomplishes a better BGC regulation.

Table 4. Closed-Loop Performance Analysis with Self-Tuning.

Formulation	**Total Insulin per Day** (U)	**J**
Lispro/Lente	29.5	7.0
Lispro/Ultralente	30.8	1.7
Regular/Ultralente	31.5	0.84

7. CONCLUSIONS AND FINAL REMARKS

In this paper several therapeutic regimens based on multi-doses strategies were analyzed. Flexible insulin schemes were presented, where a combination of a rapid or short-acting insulin is used to cover the postprandial glucose peaks due to meals, and an intermediate or long-acting insulin is used to provide a basal insulin concentration. Their performance was evaluated in open-loop and closed-loop schemes. The best formulations used an Ultralente type as basal insulin in combination with either Lispro or Regular insulin. The results showed in simulation that a closed-loop scheme can provide an almost perfect BGC regulation into the euglycemic concentration despite variable meal carbohydrate intake.

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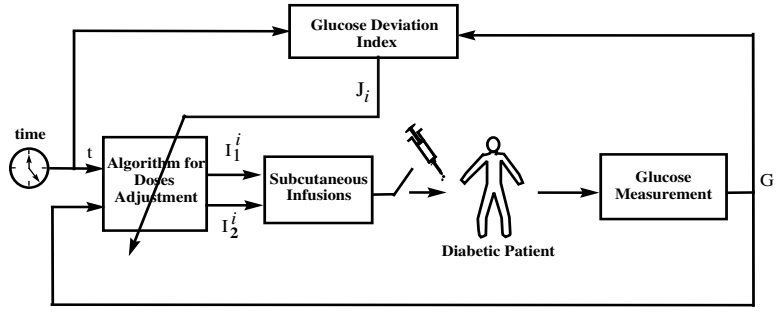

Fig. 3. Closed-Loop Adjustment Algorithm.

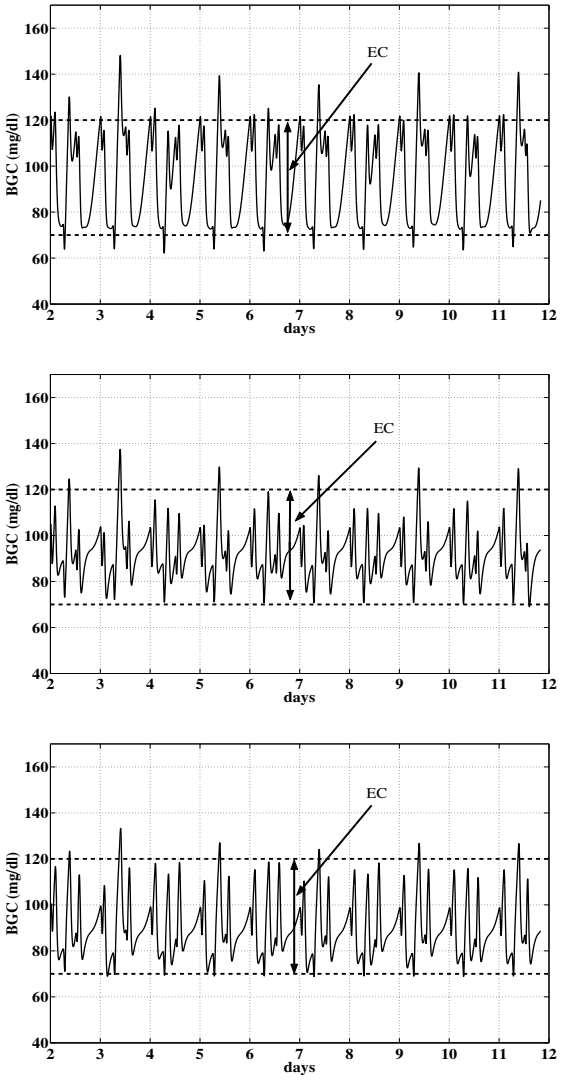

Fig. 4. Closed-Loop Simulations (TOP) formulation Lispro / Lente, (MIDDLE) formulation Lispro / Ultralente, (BOTTOM) formulation Regular / Ultralente.

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