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

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Abstract:
In this paper several control regimes 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 patient 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 in order to avoid high (hyperglycemia) glucose concentrations from its euglycemic (normal) level 70 – 120 mg/dl (Sorensen 1985), (Puckett 1992). The type 1 diabetes is a disease 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 (diabetes coma, nephropathy, retinopathy, and other tissue damage). 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 (Belazzi 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: $H_{\infty}$ 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 paper is organized as follows. Section 2 describes the types and characteristics of different commercial 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, Berge 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.

<table>
<thead>
<tr>
<th>Type</th>
<th>Onset (hours)</th>
<th>Action (hours)</th>
<th>Duration (hours)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rapid</td>
<td>0.17 - 0.33</td>
<td>1 - 3</td>
<td>3 - 5</td>
</tr>
<tr>
<td>Aspart</td>
<td>0.25 - 0.50</td>
<td>0.25 - 0.5</td>
<td>3 - 4</td>
</tr>
<tr>
<td>Lispro</td>
<td>0.5 - 1</td>
<td>2 - 3</td>
<td>3 - 6</td>
</tr>
<tr>
<td>Short</td>
<td>NPH</td>
<td>2 - 4</td>
<td>10 - 18</td>
</tr>
<tr>
<td>Intermediate</td>
<td>Lente</td>
<td>3 - 4</td>
<td>16 - 24</td>
</tr>
<tr>
<td>Long</td>
<td>Ultralente</td>
<td>6 - 10</td>
<td>18 - 30</td>
</tr>
<tr>
<td>Glargine</td>
<td></td>
<td>1 - 2</td>
<td>20 - 24</td>
</tr>
</tbody>
</table>

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. 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. In Figure 1, the plasma insulin concentration for different types of insulin are shown for a subcutaneous injection of 10 U. 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, the control objective is defined as to regulate the BGC around an euglycemic concentration (EC), defined as

\[ EC = 70 - 120 \text{ mg/dl} \]  

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 alternative techniques as fuzzy-logic (Campos-Delgado et al. 2003), self-tuning algorithms (Campos-Delgado et al. 2004), neural networks, and adaptive control (Belazzi 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.

<table>
<thead>
<tr>
<th>Table 2. Three Daily Doses Control Regimens.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Breakfast</td>
</tr>
<tr>
<td>Lispro+NPH</td>
</tr>
<tr>
<td>Lispro+Lente</td>
</tr>
<tr>
<td>Lispro+Ultralente</td>
</tr>
<tr>
<td>Regular+NPH</td>
</tr>
<tr>
<td>Regular+Ultralente</td>
</tr>
</tbody>
</table>

Five therapeutic regimens 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 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.

5. TYPE 1 DIABETIC MATHEMATICAL MODEL

In this section, the mathematical model of a type 1 diabetic patient is described. For simplicity, this model is 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 of the compartmental model 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 inges-
tion 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**: Assume 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 of the different types
of insulin: Lispro, Regular, NPH, Lente or Ul-
tralente (Berger and Rodbard 1989). Finally, the
plasma insulin concentration due to the subcutaneous injection is proportional to the
absorbed insulin. It is assumed that the in-
sulin 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 hours, and the
doses are programmed in periods of 6 hours
during the day and 12 hours at night. However,
it is important for intermediate and long action
insulin since their duration are from 10 to 18
hours.

### 6. PERFORMANCE ANALYSIS THROUGH SIMULATION

First the performance of an open-loop strategy
for insulin infusions was tested. The five therapeu-
tic 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 dose 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 take 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 in-
take per meal was varied around the nominal
values calculated previously $\pm 15\%$, but looking to
add up to $\approx 3734$ 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.](image)

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 main-
tained. 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. $I^b_1$: breakfast dose of rapid or short acting
   insulin.
2. $I^l_1$: lunch dose of rapid or short acting insulin.
3. $I^d_1$: dinner dose of rapid or short acting in-
   sulin.
4. $I^b_2$: breakfast dose of intermediate or long
   acting insulin.
5. $I^l_2$: lunch dose of intermediate or long
   acting insulin.
6. $I^d_2$: dinner dose of intermediate or long
   acting insulin.
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 self-tuning algorithm improves the previous performance with the open-loop strategy, and it accomplishes a better BGC regulation.

Table 3. Open-loop Regimens for Performance Analysis.

<table>
<thead>
<tr>
<th>Formulation</th>
<th>(I_1^0/I_2^0) (U)</th>
<th>(I_1^0) (U)</th>
<th>(I_2^0/I_2^0) (U)</th>
<th>J</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lispro/NPH</td>
<td>2.75/10</td>
<td>3.5</td>
<td>2.75/10</td>
<td>20.46</td>
</tr>
<tr>
<td>Lispro/Lente</td>
<td>3.0/10</td>
<td>3.0</td>
<td>3.0/10</td>
<td>8.87</td>
</tr>
<tr>
<td>Lispro/Ultralente</td>
<td>3.0/10</td>
<td>3.0</td>
<td>3.0/10</td>
<td>5.99</td>
</tr>
<tr>
<td>Regular/NPH</td>
<td>2.5/10.5</td>
<td>3.25</td>
<td>2.5/10.25</td>
<td>22.28</td>
</tr>
<tr>
<td>Regular/Ultralente</td>
<td>2.75/10.75</td>
<td>2.5</td>
<td>2.5/10.75</td>
<td>7.00</td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th>Formulation</th>
<th>Total Insulin per Day (U)</th>
<th>J</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lispro/Lente</td>
<td>29.5</td>
<td>7.0</td>
</tr>
<tr>
<td>Lispro/Ultralente</td>
<td>30.8</td>
<td>1.7</td>
</tr>
<tr>
<td>Regular/Ultralente</td>
<td>31.5</td>
<td>0.84</td>
</tr>
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</table>
REFERENCES


