A Novel Index to Evaluate the Blood Glucose Controllability of Type I Diabetic Patients

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Abstract: The development of the Artificial Pancreas has been growing rapidly during the last 10 years with the advent of Glucose Monitoring Systems and insulin delivery pumps. Several works have appeared testing different control algorithms for defining the proper insulin dosage in type I diabetic patients, focused on driving them into a healthy range of blood glucose (BG) concentration. However, practically none of them has previously considered to quantify the inherent degree of difficulty in achieving normal glycaemic values. Hence, in this work a novel index, named “Glucose Controllability” (GC), is presented using the parameters of simplified models and easily measurable patients data. It allows performing a certain classification procedure before the implementation of any control algorithm. To test this methodology, Predictive Functional Control (PFC) is applied for insulin dosage computation. After that, through the well-known Control Variability Grid Analysis (CVGA) plot, it is evaluated if the GC index is able to anticipate how “controllable” each diabetic person could be. The validation was performed with a database of 30 virtual type I diabetic patients. The final simulation results are shown here together with the conclusions and future works.

Keywords: Artificial Pancreas, Diabetes Mellitus, control algorithm, controllability, safety, index.

1. INTRODUCTION

Diabetes Mellitus is a disorder of the metabolism where either insufficient insulin is produced by the beta cells in the pancreas, or the body is unable to effectively utilize that insulin. As a result, glucose cannot be transported to the cells, leading to dangerously high BG levels. Untreated over time, high BG levels can lead to costly complications and low BG can lead to death. It is a very frequent chronic disease that in the last years has reached the proportion of an epidemic. The prevalence of diabetes for all age-groups worldwide was estimated to be 7.8% in 2030 by the International Diabetes Federation (IDF Diabetes Atlas). The total number of people with diabetes is projected to rise from 171 million in 2000 to 439 million in 2030.

To diagnose this disease, there are lots of indexes that help doctors come to a conclusion. All of them are based on the overall glucose tolerance, which is determined by three major physiological factors: insulin secretion, insulin sensitivity ($S_I$), and insulin-independent effect, namely glucose effectiveness ($S_G$) (Ader et al., 1985). Some of these indexes can be estimated in a very simple manner only using fasting plasma glucose and insulin values. However, to have a more accurate value of them a clinical intervention is needed, which is both expensive and difficult to perform by a non-specialist.

There are other indexes that give different information. For example, the Glycaemic Index or $G_I$, is a measure of the effects of carbohydrates on BG levels. The Insulin Index ($I_I$) is a measure used to quantify the typical insulin response to various foods. These indexes are useful for a patient who already has diabetes mellitus.

In the past, several works have presented the results of using different control algorithms tested on well recognized in silico diabetic patients in computer-based environments. PID (proportional integral derivative) (Ramprasad et al., 2004) and MPC (model predictive control) (Hovorka et al., 2004a; Magni et al., 2009) control laws are among the most well-known methodologies proposed in literature for determining the correct insulin dosage for regulating the BG levels. However, practically none of these works analyzed previously the inherent difficulty associated to each patient to be efficiently controlled. This is the principal topic analyzed here and constitutes the main contribution of this paper.

Up to now, several closed loop experiments have been carried out in vivo (Hovorka et al., 2004b; Brutomesse et al., 2009; El-Khatib et al., 2010; Hovorka et al., 2010). All of them were inspired by the studies done by Pfeiffer et al. (1974) in the so called Biostator. It was a closed-loop experiment where a type I diabetic patient was subjected to intravenous BG measurements...
with real time intravenous insulin infusion. Lately, the Juvenile Diabetes Research Foundation (JDRF) Artificial Pancreas Project, a consortium of groups, has been doing clinical trials at different institutions like University of Virginia (Clarke et al., 2009) to accelerate the development of the so dreamed artificial pancreas. Even though these interventions are performed under very strict safety conditions, it would be of great help to know a priori if a specific control algorithm will cause hazard to a diabetic patient’s health.

In this context, a novel index called “Glucose Controllability” is proposed here whose purpose is to estimate how easy to control is the BG level of a specific type I diabetic patient. This characteristic could be valuable for selecting the proper control algorithm to be run for deciding more accurately the insulin dosage, acting as an artificial pancreas. Therefore, the aim of this index is to predict a priori which would be the real capacity of a diabetic person to stay inside the healthy glycaemia range. The index can be computed through conventional tests by recording the time responses of BG when an exogenous insulin step is injected as well as a specific meal intake. This data is useful for doing the identification of simplified models such as first order with time delay for both inputs. Then, after defining an intermediate index called Severity, its prediction capability is evaluated through the implementation of PFC on 30 in silico patients. Hence for each of them the controller is designed for recommending the insulin dosage during 24 hs. In this period the patients have a standardized breakfast, lunch and dinner at typical times and the BG evolution is measured. This allows to do a classification in terms of the CVGA. Then, the obtained results through this methodology are compared to the predictions given by the GC for the 30 patients. Finally, at the Conclusions Section the evaluation of these results is given.

2. INDEXES FOR EVALUATING DIABETIC PATIENTS

In this section a brief review of current indexes used in diabetes is presented so as to give an overview of what is available these days. These are generalizations, there exist many different methods to determine each index.

- Glycated Hemoglobin, HbA1c: it is a form of hemoglobin used primarily to identify the average plasma glucose concentration over prolonged periods of time. The 2010 American Diabetes Association Standards of Medical Care in Diabetes added the A1c = 6.5 as a criterion for the diagnosis of diabetes (American Diabetes Association, 2010).

- Insulin Sensitivity, $S_I$: it represents the increase in net fractional glucose clearance rate per unit change in serum insulin concentration after an intravenous glucose load.

\[
S_I = -\frac{\partial^2 \dot{Q}}{\partial Q \partial I} |_{SS}
\]

(1)

where $Q$ is BG mass and $I$ is plasma insulin. This index is determined at steady state but there are modifications that contemplate the non-steady state. There are different ways to determine this index, for example by means of the Bergman Minimal model (Bergman et al., 1979), an Intravenous Glucose Tolerance Test (IVGTT), HOMA2-%S (Wallace et al., 2004), etc.

- Glucose Effectiveness, $S_G$: it represents the net fractional glucose clearance rate due to the increase in glucose itself without any increase in circulating insulin concentration above baseline. To determine this index a study with tracers should be done as shown in Bergman et al. (1979).

\[
S_G = -\frac{\partial \dot{Q}}{\partial Q} |_{SS}
\]

(2)

- Index of Pancreatic $\beta$-Cell Function: to see the percentage of insulin secreted by the pancreas. For example the index HOMA2-%B.

- Glycaemic Index, $G_I$: it shows how much glucose is present in the blood as a result of a particular food.

- Insulin Index, $I_I$: it shows how much insulin is present in people’s blood as a result of a particular food.

The first four indexes give qualitative information that helps doctors to diagnose diabetes or study the evolution of the disease of a particular patient. Some of them, like HOMA, are really useful to make epidemiological studies (Bermúdez Rojas et al., 2009). The last two indexes help diabetic patients with their diets and those who are insulin dependent can determine the required insulin doses for them.

However, these indexes are not useful since the control point of view because they do not give any information about the time evolution of BG of patients under specific treatment with insulin. In the next section the GC index will be defined and its usefulness for studying the controllability of a type I diabetic patient will be evaluated.

3. SEVERITY INDEX

The main idea for defining the GC index is based on the real need of having a priori knowledge about the difficulty degree of a particular patient in accordance with his response to a specific treatment with insulin. It is considered that it would be recommendable before deciding if a particular patient could undergo a closed loop experiment.

In Automatic Control, the term Controllability refers to the ability to move a system around in its entire configuration space using only certain admissible manipulations. The exact definition varies slightly within the framework or the type of models applied (Ogata, 2002). Having this definition in mind, the GC is made to carry this idea over into the diabetes problem.

The calculation of the GC index is based on data easily obtainable in any common laboratory. The first thing to do is to record the BG dynamic behavior when insulin dosage changes and as a response to a specific meal intake. Then, identification techniques are applied so as to obtain simplified models that capture the dynamic behavior of the endocrine system. It was found that the two first order with time delay models were able to capture the interaction between plasma insulin and glucose ($G_m$) and a meal dose, assumed as a perturbation, with plasma glucose...
be used to test the control algorithm to see how normalized the BG profiles of each patient are.

The database of 30 type I virtual diabetic patients were loaded for running the so called UVa Simulator. It is a well-known mathematical model of the physiology of type I diabetic patients. It is based on the early works of Claudio Cobelli (Carson et al., 1982) with some modifications incorporated by Dalla Man et al. (2007) (See Fig. 2 for a schematic view). It has been validated against clinical and experimental data and has been approved by the FDA in 2008 as a substitute to animal trials in the pre-clinical testing of closed-loop control algorithms (Kovatchev et al., 2009). The full model consists of 20 equations with 33 parameters. The developers have got a database of 300 patients (100 adults, 100 adolescents and 100 children).

Here, only some of the most important equations of the model are presented. These equations represent the glucose fluxes (i.e. rate of appearance, endogenous glucose production, etc.) postulated by the Glucose-Insulin Model:

\[
G_p(t) = EGP(t) + Ra(t) - U_p(t) - E(t) - k_1 G_p(t) + k_2 G_i(t);
\]

\[
G_i(t) = k_1 G_p(t) - k_2 G_i(t) - U_id(t);
\]

\[
G(t) = \frac{G_p(t)}{V_G};
\]

with \(G_p(0) = G_{ph}, G_i(0) = G_{ih}, G(0) = G_0\).

Here \(G_p\) and \(G_i\) (mg/kg) are glucose masses in plasma and rapidly-equilibrating tissues, and in slowly-equilibrating tissues, respectively, \(G\) (mg/dl) is plasma glucose concentration, suffix \(b\) denotes basal state, \(EGP\) is endogenous glucose production (mg/kg/min), \(Ra\) is glucose rate of appearance in plasma (mg/kg/min), \(E\) is renal excretion (mg/kg/min), \(U_p\) and \(U_id\) are insulin-independent and dependent glucose utilizations, respectively (mg/kg/min), \(V_G\) is the distribution volume of glucose (dl/kg), and \(k_1\) and \(k_2\) (min\(^{-1}\)) are rate parameters.

In addition to glucose fluxes, the detailed model contains equations of insulin kinetics, as well as a compartmental representation of glucose intestinal absorption and the glucose transit through the stomach and intestine. Glucose excretion by the kidney, which occurs if plasma glucose exceeds a certain threshold, is modeled as well.

Using this simulation environment, the internal models mentioned in Section 3 were determined as will be explained with more details in Section 5.1.1. Once the gains of both models were available, the Severity index and the GC were determined for each patient as can be seen in Table 1.

### 5. VALIDATION

The next step is to analyze if this index is useful as a tool for classifying the type I diabetic patients in categories according to their responses to insulin treatment. Based on this, the controller individually designed for each patient will present different performances. The test is done by implementing PFC tuned for each patient where the internal models were identified in Section 3 (the ones used to construct the Severity Index). After that, every patient undergoes an \textit{in silico} preclinical trial (Section 5.2) and a CVGA plot (Section 5.3) is constructed to see the suitability of such a control algorithm. It is important to note that the CVGA gives the same information that the...
Table 1. Internal models gains, Severity Index, BW and Glucose Controllability (G. C.)

<table>
<thead>
<tr>
<th>Patient</th>
<th>$K_{mi}$</th>
<th>$K_{di}$</th>
<th>Severity</th>
<th>BW</th>
<th>G. C.</th>
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<tbody>
<tr>
<td>1</td>
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<td>34.961</td>
<td>37.608</td>
<td>58.86</td>
<td>11.187</td>
</tr>
<tr>
<td>2</td>
<td>-3.666</td>
<td>28.039</td>
<td>7.650</td>
<td>24.76</td>
<td>-5.537</td>
</tr>
<tr>
<td>3</td>
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<td>25.236</td>
<td>20.934</td>
<td>46.85</td>
<td>8.848</td>
</tr>
<tr>
<td>4</td>
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<td>39.768</td>
<td>51.60</td>
<td>2.674</td>
</tr>
<tr>
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<td>13.729</td>
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<tr>
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</tr>
<tr>
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</tr>
<tr>
<td>8</td>
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</tr>
<tr>
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<tr>
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<tr>
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<tr>
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<tr>
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<tr>
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<td>41.778</td>
<td>77.167</td>
<td>66.63</td>
<td>-3.987</td>
</tr>
</tbody>
</table>

Index presented here. The main difference is that the CVGA is a closed loop method whereas the GC index is determined before closing the loop and in a very easy way.

5.1 Predictive Functional Control (PFC)

The PFC technique is the third generation of a family of Model Algorithmic Control. PFC basically consists of four main elements such as a process dynamic model, a reference trajectory $y_r(n)$, a self-compensation of the predicted error and a specific structure for the manipulated variable. The future error between $y_r(n)$ and the predicted output over the coincidence horizon $[H_1,H_2]$ is estimated. A self compensation is done accounting for the actual mismatch between real data and model output. The estimation of the future error at the coincidence horizon by specific kind of extrapolation, allows to improve the model prediction. Within PFC, feed-forward and feedback control actions can be jointly designed and constraints are taken into account in a very natural way.

Here just a brief summary of the PFC technique is presented. For more details about the implementation of PFC, the reader should see Jacques and O’Donovan (2009). The authors have previously tested its performance with type I diabetic patients with promising outcomes (Campetelli et al., 2010b).

Models for the PFC controller

The PFC has three inputs, the glucose measurement, the glucose set point (100 mg/dl in our case) and the glucose rate of appearance into the glucose compartment (Ra). The last input is only present if the meal is announced. To avoid the nonlinearities in the stomach compartment, the model for the controller was linearized without

Fig. 3. In silico preclinical trial for adult patient

this compartment present. As a consequence of this, the meal disturbance has to be given as a filtered response into the glucose compartment and not as a step response into the stomach compartment (Ellingsen, 2008).

To announce a meal, the mean of all model parameters for each group of patients was taken and the glucose rate of appearance of each group was saved in a matrix. Then, the controller receives a mean absorption profile. Another way of solving this problem could be detecting when a patient receives a meal as shown in Dassau et al. (2008).

In our case, the relationship between insulin infusion (manipulated variable) and BG (controlled variable) is called $G_{mi}$. Meanwhile $G_{di}$ refers to the relationship between exogenous glucose (Glucose rate of appearance Ra from a meal) and BG. Both models were set to be first order with time delay, (3) and (4), and their identification was done by means of a step excitation in the insulin delivery and in the meal ingestion at the nominal condition (See Fig. 1). The step used depends on the group studied. For the manipulated variable, having the information of the Total Daily Insulin (TDI [U]) consumed by each patient, the mean value of all patients was taken. For the perturbation, the $Ra = \sum R_{ai}$ was calculated. In Table 1, the gain of both models ($K_{mi}$ and $K_{di}$) identified for every patient can be seen.

5.2 The In Silico Preclinical Trial

The performance of our controller was tested on a 1-day virtual protocol (Fig. 3) based on Patek et al. (2009). For an adult patient:

1. Admit state: Patient BG steady at 100 mg/dl at 18:00 Day 1.
2. Control loop is closed at 21:00 Day 1.
3. At 7:30 Day 2, the patient has breakfast lasting about 2 min with a carbohydrate (CHO) content of 50 grams.
4. At approximately noon (12:00) Day 2, the patient takes a lunch meal containing 65 grams CHO. Meal duration is 15 min.
5. At 18:00 Day 2, the patient takes a dinner meal containing 80 grams CHO. Meal duration is 15 min.

This scenario changes for adolescents and children just in the amount of food they eat (Adolescents: 40/50/65 grams; Children: 25/30/40 grams).
5.3 Control Variability Grid Analysis (CVGA)

Control Variability Grid Analysis (Magni et al., 2008) is a graphical representation of minimum/maximum glucose values in a population of patients either real or virtual. CVGA provides a simultaneous visual and numerical assessment of the overall quality of glycemic regulation in the entire population of simulated or real patients. As such, it may play an important role in the tuning of closed-loop glucose control algorithms and also in the comparison of their performance.

Assuming that for each subject a time series of measured BG values over a specified time period (e.g., 1 day) is available, CVGA is obtained as follows: for each subject a point is plotted with an X coordinate -minimum BG- and a Y coordinate -maximum BG- within the considered time period. Note that the X axis is reversed as it goes from 110 mg/dl (left) to 50 mg/dl (right) so that optimal regulation is located in the lower left corner. The appearance of the overall plot is a cluster of points located in different regions of the X-Y plane that can be associated with different qualities of glycemic regulation.

In Fig. 4 the result of the CVGA evaluated during the in silico preclinical trial mentioned above is shown. Each point represent one virtual type I diabetic patient.

6. RESULTS

Based on the results of Fig. 4, it can be seen that the patients that have undergone the major risks are the ones situated in group B. The maximum value of their BG level and their minimum were in the risky zone. Even though the control algorithm could cope with their disease because in the CVGA they are in the green zone, comparatively they were more difficult to control. These patients should have a correspondingly high value of our Severity index.

Fig. 4. Control Variability Grid Analysis plot.

To see the relation between the index presented here and what is seen in the CVGA, the patients were divided in 3 groups based on the results of the CVGA. Group B are those patients which are definitely in zone B (red points), the same for those who are in group A (yellow points) and a third group was defined with those patients who are near the limit of zone A and B. This intermediate group was called AB (blue points). This division gave 7 patients in group A, 8 patients in group AB and 15 patients in group B.

After that, a plot was done showing the relationship of the BW of the patients and their Severity index. To see their relation with the CVGA they were marked with the groups and colors defined before, see Fig. 5. Even though there is a mixture of patients in the middle of this graph, it can be concluded that the extremities are well defined. It is evident that those patients with the highest values of Severity were the most difficult to lead to the healthy range. One can conclude as well that those patients with light BW (children in our case) were difficult to normalize regardless their Severity index value.

These results led us to define a line equation (Fig. 5) to separate among those patients who may run major risks and those who may not. The equation can be written as:

$$BW = 0.58 \times Severity + 25.86; \quad (9)$$

A better grasp of what this means and the definition of the GC is seen equating to zero:

$$GC = BW - 0.58 \times Severity - 25.86; \quad (10)$$

This term is a measure of the distance of any point to the separation line between the groups. The value of GC of the patients under study can be seen in Table 1. This table contains all the information used for determining the GC. The first ten patients are children with type I diabetes. From patient 11 to 20 they are adolescents and the rest are adults. Based on this, if the GC of a particular patient is positive, one can be quite sure that a control algorithm will give excellent results for him. On the other hand, if it is negative, he might be exposed to some hazard because of the inherent difficulty in estimating the right insulin dosage. The bigger the values of the GC, the more confident one can be of what it means. When the GC is near zero, it means that the response would be intermediate.

7. CONCLUSIONS AND FUTURE WORK

The new index, called Glucose Controllability, presented in this work is considered to be well posed according to the results shown in Fig. 5. By means of (10), one can detect a priori if a particular type I diabetic patient could experience a bad regulation of BG under specific insulin dosage estimated through a control algorithm. The results presented here were obtained with PFC. Testing with other control algorithm is expected to do as future work.

This finding was possible to do with the help of the FDA approved simulator of type I diabetic patients. It allowed to do some simplifications that need to be checked in biological
systems. Hence, the tests performed here will be then validated by means of experimental data obtained from diabetic Sprague Dawley rats in the laboratory as done in (Campetelli et al., 2010a). The final step is expected to do with human subjects.

The preliminary results from this technique suggest that could be taken into account before submitting a diabetic patient to the clinical closed loop trials, mentioned in the introduction of this paper, so common these days. With the knowledge of the GC of a diabetic patient, doctors will be able to know a priori how a closed loop mechanism would work with the treatment of this disease. Even though, the studies will be continued in order to evaluate if other parameters like BMI (not available for this work) improve the results presented here.

REFERENCES


