A Method to Early Detect Blood Glucose Variations Using Continuous Glucose Monitoring System

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Abstract: - The modern research in the field of the treatment for type I diabetes mellitus include the artificial pancreas. In this paper the authors have used the mathematical analysis of the blood glucose time series recorded through continuous glucose monitoring system in order to reveal the internal structure of the blood glucose control system and to synthesise the control laws of the insulin pump. It was calculated and evaluated the histogram and the first and second order derivates of blood glucose concentration.

Key-Words: - diabetes mellitus, continuous glucose monitoring, computer assisted diagnosis, blood glucose control.

1 Introduction
During the last decade, research in the area of diabetes and its complications has been concentrated on specific aspects such as glucose-insulin dynamics, mathematical models, treatment control and cost. One solution for type I diabetes patients and patients undergoing intensive care is the artificial pancreas consisting of a continuous glucose monitoring system, an insulin pump and control and command algorithms for the pump.

The artificial pancreas built as a closed-loop system [1] must integrate in its structure time delay blocks, in accordance to the kinetics of meal and insulin administration. The short-acting insulin needs around 50 minutes to be absorbed and around 30 minutes to take effect. The peak of insulin concentration in plasma occurs after 40 to 50 minutes after subcutaneous injection of short-acting insulin such as lispro and aspart. The effects of insulin administration ensure the next two hours and consist in the reduction of the blood glucose concentration. The meal produces an increase in the blood glucose concentration after 10 to 40 minutes. The time glucose diffusion from plasma to the interstitial fluid is around 10 minutes.

Blood glucose oscillations during a period of 24 hours are the result of the blood glucose control system, external perturbations such as meals, insulin treatment, exercise, stress, extreme temperatures and other diseases [2].

In type I diabetes patients the great variability of the blood glucose values leads to large and damaging periods of hyperglycemia as well as hypoglycemia. The most important perturbations responsible for this behavior are: inappropriate nutrition (schedule, composition or quantity), inappropriate insulin administration or both. For a good prediction of proper dosage of insulin, the detection of meal or other external perturbations is indispensable as time and amplitude of their effects. Because blood glucose variability is a sum of these effects in time and amplitude, it is very difficult or even impossible to detect only the meal, for example, with the purpose of estimating the necessary insulin [3].

We therefore have proposed a method for the analysis moment by moment of the blood glucose evolution, recorded through continuous glucose monitoring system (CGMS) and to predict the trend of glucose concentration using the rate of change - ROC (speed and acceleration). Insulin could be administrated through insulin pump in accordance with the glucose’s rate of change.

A particular feature of the increase in blood glucose could predict the hyperglycemia as a consequence of meal administration in discordance
with the nutrition schedule, or in the case of neglected insulin administration.

2 Mathematical Methods

In statistics, a histogram is a graphical display of a table that shows what proportion of cases fall into each of several or many specified categories. In a mathematical sense, a histogram is a mapping that counts the number of observations that fall into various disjoint categories (known as bins). There is no "best" number of bins, and different bin sizes can reveal different features of the data. In the present paper the authors propose the usage of histograms in order to characterize the time-series coming from the continuous glucose monitoring system.

Also, due the fact that we are dealing with measurements that can be corrupted by errors, we have calculated a Gaussian distribution for these data. The Gaussian distribution, also called the normal distribution, is an important family of continuous probability distributions, applicable in many fields. Each member of the family may be defined by two parameters:

- The mean (average, \( \mu \))
- The variance (standard deviation) squared) \( \sigma^2 \), respectively.

The importance of the normal distribution as a model of quantitative phenomena in the natural science is due to the central limit theorem. Many physiological measurements can be approximated well by the normal distribution. In addition, the normal distribution maximizes information entropy among all distributions with known mean and variance, which makes it the natural choice of underlying distribution for data summarized in terms of sample mean and variance. Using numerical methods of processing we have been calculated first and second order derivatives of blood glucose concentration.

3 Human Experimental Study

For this study we have selected 22 adult subjects (12 female and 10 male), patients with insulin dependent diabetes mellitus and 8 healthy humans. Sixteen patients underwent treatment with rapid and semi-lent types of insulin, at different times of the day, according to the classic method of treatment and clinically supervised. Patients maintain a satisfactory or poorly control of the blood glucose concentration for a long period of time. Six patients have received a proper dosage of insulin from a device called insulin pump. This offers a continuous basal rate of insulin and facilitates the administration of insulin bolus related to meals, exercise or other particular states. These patients maintain a very good control over the blood glucose concentration for a long period of time. The blood glucose was recorded for each patient at five minute intervals, continuously for three days, using the Real-Time Guardian Continuous Glucose Monitoring System – CGMS, in unrestrained conditions. Each patient had a normal life, with usual meals and activities at work and at home.

The continuous blood glucose records represent for this study time-series of the blood glucose concentration. To increase the accuracy of the measurements we use the interpolation methods. It is possible to use for the reconstruction of the time evolution of glycaemia, dedicated filters. Nyquist filters are attractive for interpolation purposes. The spectral analyses reveal the frequency band edge and offer the basic information to correct determination of Nyquist sample period.

For exemplification we choose the following individual cases:

- Three patients (P1, P2 and P3) with insulin dependent diabetes (type I) under intermittent treatment with insulin injections. The CGMS displays high variability of the glucose values as an expression of an insufficient control of diabetes (Fig. 1, Fig. 3 and Fig. 5). This aspect is revealed in a statistical manner by the corresponding histograms (Fig. 2, Fig. 4 and Fig. 6).

- One patient (P4) with insulin dependent diabetes under insulin treatment administrated by insulin pump. The CGMS displays a less variability of glucose values, expression for an improved control of diabetes (Fig. 7). This aspect is revealed in a statistical manner by the corresponding histogram (Fig. 8).

![Fig. 1. Time evolution of the glucose concentration for the P1 patient. (INS–insulin treatment, M–meal)](image-url)
- One healthy human (P5) with normal food administration and activity. The CGMS displays a low variability of the glucose values, expression of an efficiently blood glucose control (Fig. 9). This aspect is revealed in a statistical manner by the corresponding histogram (Fig. 10).

The graphics are marked records moments in which patients have eaten (intake of glucose) and the moments in which they administered insulin. Given the disorderly program of patients, and due to their refusal to follow a certain rhythmic treatment and nutrition, you can see a great variability of blood glucose values.

The authors have used a low-pass filter with a pass band 0-0.5 Hz. In this way a part of measurement noise is removed from the experimental data and the time series are not affected. It is worth mentioning that the authors took care not to affect through filtering the harmonic content of the recorded signal. In the paper Nyquist Sample Period Determination for Continuous Glucose Monitoring System [4] the upper limit of the bandwidth is indicated to be 0.026 Hz.
Fig. 7. Time evolution of the blood glucose concentration (BGC) for the P4 patient (insulin pump) (INS—insulin treatment, M—meal).

Fig. 8. Histogram of the blood glucose concentration for the P4 patient. (insulin pump)

Fig. 9. Time evolution of the glucose concentration for the P5 subject. (healthy subject)

Fig. 10. Histogram of the glucose for the P5 subject.

Using numerical methods of processing we have been calculated first and second order derivates of BGC.

Fig. 11. First order derivate of blood glucose for P1 patient.

Fig. 12. Second order derivate of BGC for P1 patient.

The results for the patients P1-P5 are presented in Figures 11-20.
By analysing the first order derivate, we are able to notice its capacity to anticipate the tendency of blood glucose variation. An increase in blood glucose, measured in mg/dl/min, is marked by positive segments of the rate of change (ROC).

In the case of hypoglycaemia, ROC values become negative. If we compare these developments with the evolution of the glucose concentrations, we are able to notice that events mostly overlap each other in time. These are the moments that mark the intake...
of food as well as the positive, larger segments of
the ROC.

Fig.19. First order derivate of blood glucose for P5
patient (healthy subject).

Fig.20. Second order derivate of blood glucose for
P5 patient (healthy subject).

The ROC expressed as first (D1) and second (D2)
derivative have had the statistics parameters
which are presented in Table 1.

Table 1.

<table>
<thead>
<tr>
<th>Statistics parameters</th>
<th>Patient P2</th>
<th>Patient P4</th>
<th>Patient P5</th>
</tr>
</thead>
<tbody>
<tr>
<td>D1 (mg/dl/min)</td>
<td>Maximum</td>
<td>+4.2000</td>
<td>+2.4000</td>
</tr>
<tr>
<td></td>
<td>Minim</td>
<td>-3.8000</td>
<td>-2.0000</td>
</tr>
<tr>
<td>Standard deviation of D1</td>
<td>+1.0840</td>
<td>+0.6160</td>
<td>+0.3872</td>
</tr>
<tr>
<td>D2 (mg/dl/min²)</td>
<td>Maximum</td>
<td>+1.0400</td>
<td>+0.4800</td>
</tr>
<tr>
<td></td>
<td>Minimum</td>
<td>-0.8400</td>
<td>-0.4800</td>
</tr>
<tr>
<td>Standard deviation of D2</td>
<td>+0.2453</td>
<td>+0.1251</td>
<td>+0.09417</td>
</tr>
</tbody>
</table>

4 Conclusion

This method has great implication in the
surveillance of a diabetes patient’s nutrition
schedule and treatment, especially in the case of
children and teenagers with type I diabetes. The
hyperglycemia and hypoglycemia occur in several
cases such as:
- The patient hides a supplementary meal admi-
nistration or a larger dose of carbohydrates.
- The patient forgets to administrate the needed
injected insulin dose or bolus of insulin in the case
of insulin pumps
- The patient is not cooperative (young or old age,
psychic disorders, suffering from life-altering
afflictions, having serious social and economical
issues etc.).

This method can be used as an alternative that
allows the determination of food intake. The
degree of confidence increases if we use first
order derivate and second order derivate together.
This is the reason why we recommend the use a first
and second order derivates for the insulin pump’s
law control synthesis.

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