Predictive Blood Glucose Control Using Exponential Smoothing Method

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Abstract: Diabetes mellitus is a disease with a constant, significant increase in the number of patients, low quality of life and high medical care costs. In this moment we have many diabetes patients with poor control of blood glucose. Some authors consider that the closed-loop system, (artificial pancreas) is the best solution. An extra-corporeal blood glucose sensor is coupled to a computer, which controls the rate of infusion of insulin so as to maintain normal glycaemia. This paper presents the structure of predictive algorithm that can remove most erroneous values. In addition, several numerical simulation results are given where the proposed predictive method outperforms well-known average and median voters. The results of this study can be also applied, to other physiological systems; it offers important data for the medical practice. These findings may have significant clinical implication in diagnosis of the diabetes mellitus, in blood glucose monitoring and in the management of the diabetes therapy.

Keywords: Continuous glucose monitoring, exponential smoothing method, insulin pump, control of blood glucose.

1. INTRODUCTION

Diabetes mellitus is a disease with a constant, significant increase in the number of patients, low quality of life for patients and high medical care costs. Self monitoring blood glucose, continuous glucose monitoring system, insulin pumps and new specific drugs have radically changed life quality and expectance in diabetes patients. These new devices have allowed the technical realisation of the closed-loop artificial pancreas. Optimal glycaemia control in medical practice is being evaluated on the level of HbA1c and the amount of hypoglycaemic episodes. To ensure to the patients with diabetes a lifestyle as close to normal are required:

- Monitoring of blood glucose.
- Providing the necessary amount of insulin for maintaining the blood glucose to normal values for the human body.

Recent advances (Cauter, Kenneth, 1997), (Troisi, Cowie et al., 2000), reveal the oscillator behaviour of the insulin secretion and consequently the intrinsic dynamics of blood glucose control in healthy human and diabetic patients. The systems used for continuous glucose monitoring offer the recordings of time series of blood glucose values for 72 hours. The information about physiological blood glucose control and the physiopathology of diabetes mellitus could be subtracted with proper mathematical methods from the experimental data acquisition. The sources of blood glucose are: the gut in the digestive states, post absorptive of the meal and the liver in the inter-digestive states. The blood glucose is used in all cells under the absolute control of the insulin (exceptions: red blood cells and neurons). So, the medical concept in the diabetes management was focused on the insulin dynamics and insulin therapy. Physiologically, insulin stimulates glucose uptake by insulin sensitive tissue (mainly skeletal muscle and adipose tissue) and inhibits hepatic glucose production. Insulin secretion is an important oscillatory process and insulin oscillations are followed by plasma glucose oscillations. The glucose values are registered in a discrete manner by intermitted measurements. The sample rate must be adapted for the specific dynamics of the biological parameters used for the experimental recordings. The actual protocols used in diagnosis and management of the diabetes mellitus include the classical clinical trials and the physicians' experience, but they do not account by the dynamics of the blood glucose and insulin. So, it is natural to have many diabetes patients with poor control of blood glucose values. The blood glucose dynamical pattern ascertained by mathematical methods (Iancu, 2003), (Makroglou et al., 2006) for each patient could significantly improve the diabetes treatment in the future.

2. CONTINUOUS MONITORING OF GLYCAEMIA

The continuous glucose monitoring system (CGMS) uses a sensor for the measuring of the blood glucose, placed under or on the skin. The tested methods are of great diversity: the oxidation reaction of glucose, reverse ionophorese, micro dialyse, spectroscopy, techniques based on the laser and fluorescent lights. The sensors measure the glucose concentration at 5, 15 or 60 minute intervals. Basically, the system can realise the monitoring of the glycaemia with exceptional results:

- The continuous recording of the glycaemia values and their tendencies.
- The recording of all hypoglycaemia or hyperglycaemia episodes.

Measurements given by the CGMS are affected by perturbations (movement of the sensor, incomplete contact, etc.). Because of this, it is necessary to introduce a filter for the acquired data. The authors propose the algorithm described in the following, known as exponential smoothing.

3. HUMAN EXPERIMENTAL STUDY

For this study we have selected adult subjects, patients with insulin dependent diabetes mellitus and healthy humans. We have patients underwent treatment with rapid and semi-lent types of insulin (injections), 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. Other 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* 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. The following figures present 3 examples for the blood glucose representation of the records over 24 hours (Iancu, 2008), (Iancu, 2010).

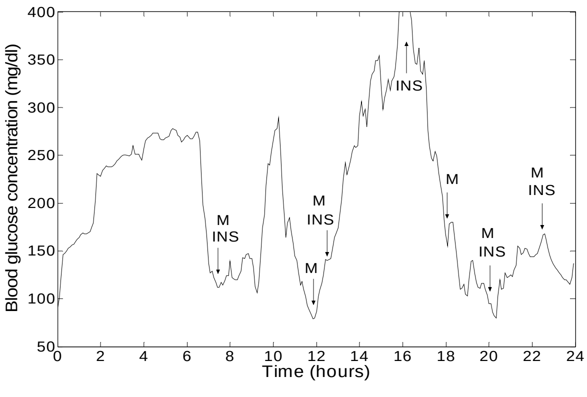

Fig. 1. Time evolution of the glucose concentration for a patient P1 with insulin injections. (INS – insulin treatment, M – meal).

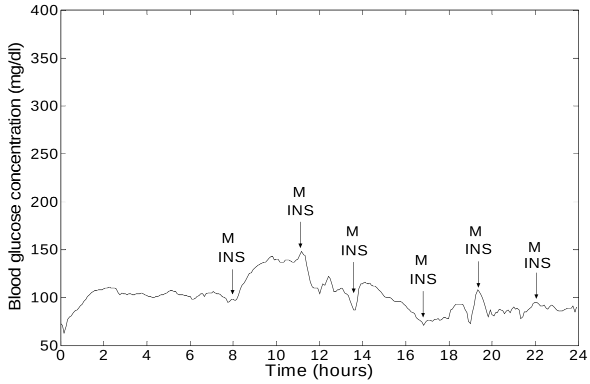

Fig. 2. Time evolution of the glucose concentration for a patient P2 with insulin pump. (INS – insulin treatment, M – meal).

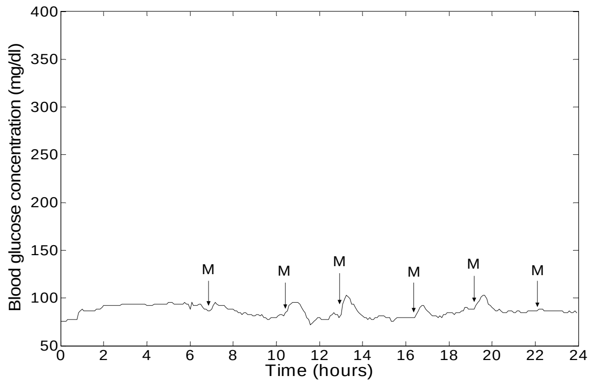

Fig. 3. Time evolution of the glucose concentration for a normal subject. (M – meal).

4. ARTIFICIAL PANCREAS

The modern concept on the artificial pancreas has been put across in 1983 with the appearance of the first commercial variant of the insulin pump. Numerous project and studies have had the purpose of designing equipment capable of substituting the physiological system for the glycaemia control in the human organism.

Presently, there are two main research directions with the artificial pancreas as a main purpose:

- The insulin pump.
- The continuous glucose monitoring system (CGMS).

The insulin pump is a small device that is placed outside the body or is implanted into the body containing an insulin reservoir and a catheter for the introducing of insulin into the body. The use of insulin pump avoids hypoglycaemic episodes. Hypoglycaemia is a severe, acute complication of the insulin treatment at insulin dependent patients and influences, through itself, any protocol of insulin administration. Moreover, hypoglycaemia is a frequent occurrence during sleep, in type I diabetes patients and imposes a special algorithm for blood glucose control in order to avoid and reduce nocturnal hypoglycaemic risks. Furthermore, the unexpected and irregular oscillations of glycaemia have been constantly observed in the blood glucose dynamic at diabetes patients. The limits of the insulin pump consisted in the medical point of view in possible complications (infections, detachments or false readings) and the necessity of replacement at relative small periods. From the precision point of view, a high dispersion of measurements has been seen. For every administration way there is an absorption curve specific for insulin, time constants and action periods that impose the particularisation of the glycaemia control algorithms.

5. CONTROL OF BLOOD GLUCOSE

Monitoring systems have revealed rapid changes in glycaemia, which requires a sophisticated control structure. The generalised structure of the control system for blood glucose is shown in the Figure 4.

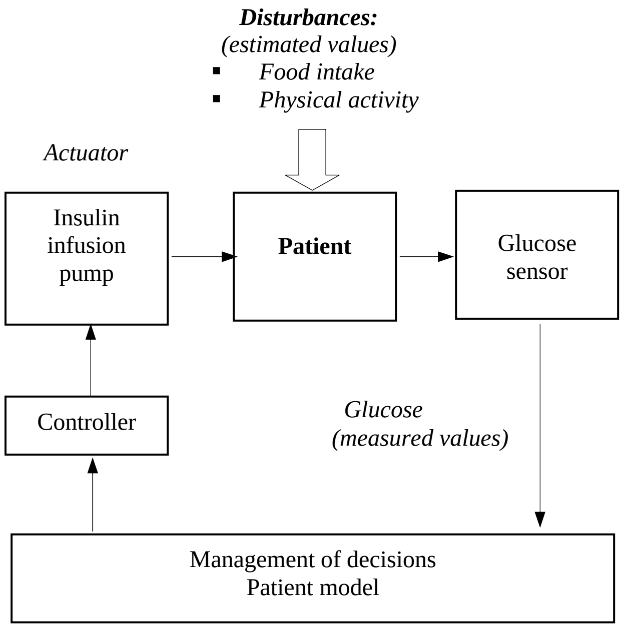

Fig. 4. The structure of the predictive system for blood glucose control (Iancu, 2010).

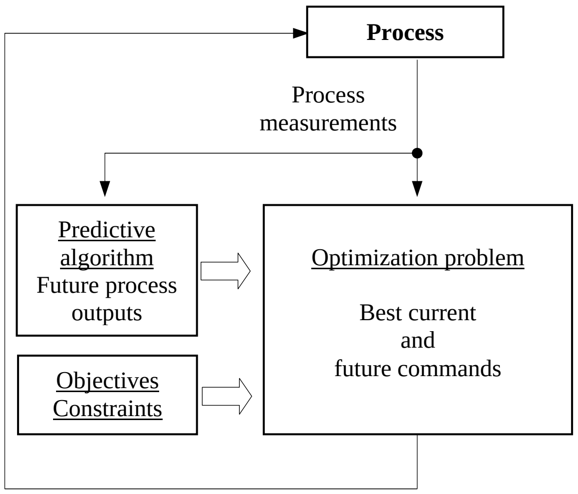

Fig. 5. The structure for the predictive control system.

The control system for blood glucose must face perturbations.

Using the predictive control theory we can minimize deviations of blood glucose from normal levels, while penalizing the use of large amounts of infused insulin for safety.

The insulin infusion pump allows a constant and predictable delivery rate of insulin into a subcutaneous site. The efficiency of the predictive control system is to keep the blood glucose levels as close to normal as possible. This behaviour is essential for preventing diabetes related complications. Ideally this level is between 60 and 120 mg/dl before meals and less than 180 mg/dl two hours after starting a meal.

The more popular scheme for control processes affected by time delay was proposed by O. J. M. Smith (Smith, 1959). This algorithm requires a minimal knowledge of the process to describe it through a transfer function (model):

$$P(s) = G(s)e^{-s\tau} \tag{1}$$

Unfortunately, the knowing of the mathematical model attached to the patient is a difficult problem. Using Smith predictors leads to good results in controlling blood glucose concentration. These results can be severely affected by the errors of estimation of model parameters and especially by the incorrect determination of dead time. This can lead to instability of control system, with serious consequences for the patient's life.

Given this situation, the authors propose to use an algorithm based on exponential smoothing (Fig. 6). In this way we can get in real-time feedback information from the patient, which can be used by the controller to synthesis the commands for the insulin pump.

The complex and highly non-stationary nature (Kovatchev, Clarke et al., 2005), (Zick, Petersen et al., 2007) of the blood glucose time series, especially in diabetic patients and the permanent influence of the external perturbations (meal, sleep, exercise, other treatments etc.) require a complex series of mathematical study methods.

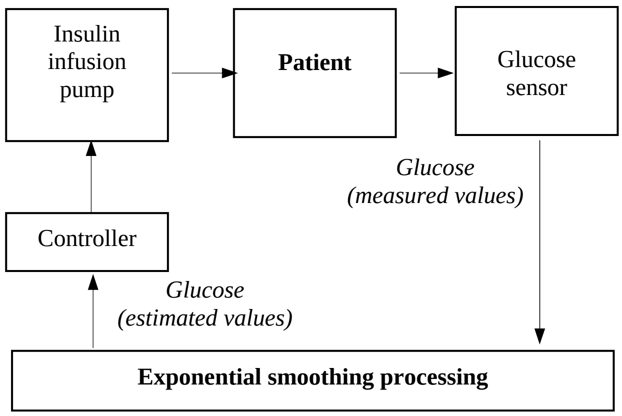

Fig. 6. The structure of control system with exponential smoothing.

However, statistical methods have the advantage to be accurate and robust, simple enough to be implemented with low costs.

6. EXPONENTIAL SMOOTHING METHOD

Single exponential smoothing is used for smoothing discrete time series. The efficiency of this algorithm can be attributed to its simplicity and to the capacity to adjust its responsiveness to changes in the process and its reasonable accuracy.

Let be an observed time series $X = \{x_1 \quad x_2 \quad ... \quad x_n\}$. Formally, the simple exponential smoothing equation takes the form (Ostertagová, 2011):

$$\tilde{x}_{i+1} = \alpha x_i + (1-\alpha)\tilde{x}_i \qquad (2)$$

where x_i is the actual, known series value at moment time i, $\tilde{x}_i$ is the forecast value of the variable X at time i, $\tilde{x}_{i+1}$ is the forecast value at time i+1 and α is the smoothing constant.

Smoothing constant α is a selected number between zero and one, 0 <α <1 (Brown, Meyer, 1961). When α =1, the original and smoothed version of the series are identical. At the other extreme, when $\alpha = 0$, the series is smoothed flat (Ostertagová, 2011). In the literature it is demonstrate the next relation (Brown, Meyer, 1961):

$$\begin{aligned}\tilde{x}_{i+1} &= \alpha x_i + \alpha(1-\alpha)x_{i-1} + \alpha(1-\alpha)^2 x_{i-2} + ... \\ &... + \alpha(1-\alpha)^{i-1}x_1 = \alpha \sum_{k=0}^{i-1}(1-\alpha)^k x_{i-k}\end{aligned} \qquad (3)$$

In scientific papers are presented also *double exponential smoothing* and *triple exponential smoothing*.

From (2) we obtain:

$$\tilde{x}_{i+1} = \tilde{x}_i + \alpha(x_i - \tilde{x}_i) = \tilde{x}_i + \alpha\varepsilon_i \qquad (4)$$

where ε_i represent the forecast error at time *i*.

Using this error it is possible to define the following parameters (Ostertagová, 2011):

- Mean square error - *MSE*

$$MSE = \frac{1}{n}\sum_{i=1}^{n} e_i^2 \qquad (5)$$

- Root mean square error - *RMSE*

$$RMSE = \sqrt{MSE} \qquad (6)$$

The objective is to find an appropriate smoothing constant so that *MSE* and *RMSE* to be minimum.

7. APPLICATION OF EXPONENTIAL SMOOTHING METHOD FOR BLOOD GLUCOSE ESTIMATION

The authors applied the method single exponential smoothing to the time series obtaining from CGMS for each patients represented in Fig. 1-3. The sensors measure the blood glucose concentration at 5 minute intervals, over 24 hours. So, we have 288 values distributed in a time series for each patient. For the time series presented in Fig. 1, 2 and 3, we have been calculated the mean and the standard deviation (Table 1). Also, using statistical prediction, it was possible to calculate the confidence intervals for 95% and 99% of blood glucose values. The following figures present 3 examples for the application of the single exponential smoothing for blood glucose records over 24 hours

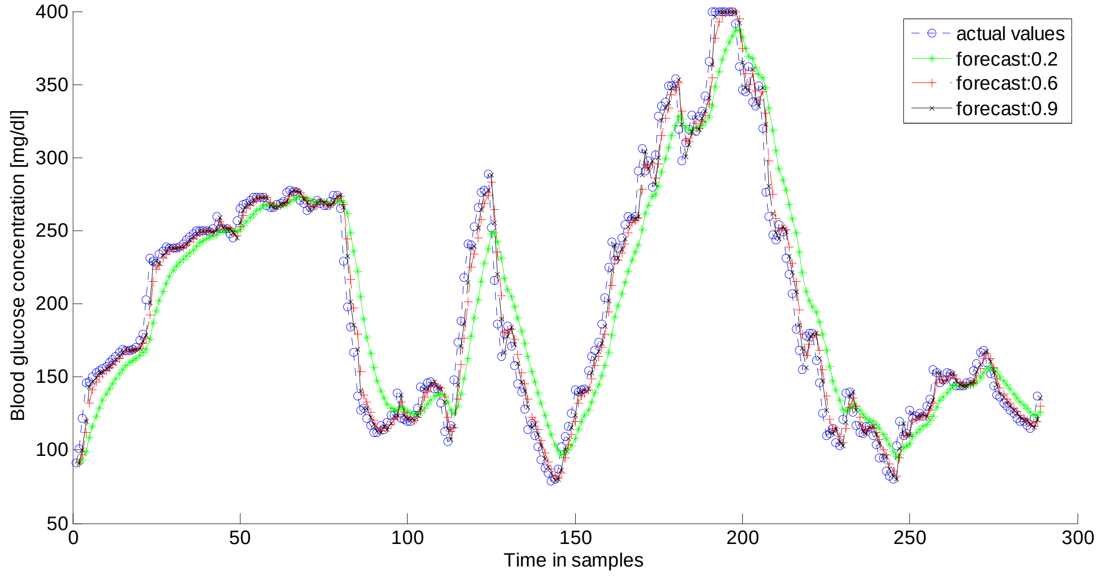

Fig. 7. The result of single exponential smoothing for a record from P1 patient, with insulin injections.

Table 1. Statistic parameters

Statistic parameters		**Patient P1** (injections)	**Patient P2** (pump)	**Healthy subject**
Mean of blood glucose values - μ (mg/dl)		199.31	101.28	86.56
Standard deviation - σ		81.02	17.29	6.14
Confidence interval for 95%	Minimum	189.91	99.27	85.85
	Maximum	208.71	103.28	87.27
Confidence interval for 99%	Minimum	186.93	98.63	85.62
	Maximum	211.69	103.92	87.50

8. CONCLUSIONS

Clinical studies have shown a high correlation between glucose variability and chronic complications of diabetes. Glycaemia variability has also indicated, along the studies, unsatisfactory treatment and management of the disease.

In medical practice, the mean glucose was accepted as the only significant and relevant measure of glycaemia variability. Despite these, predictive control of the closed loop control system, based on a mathematical model, is difficult to accomplish because these oscillations have an unknown and unpredictable source.

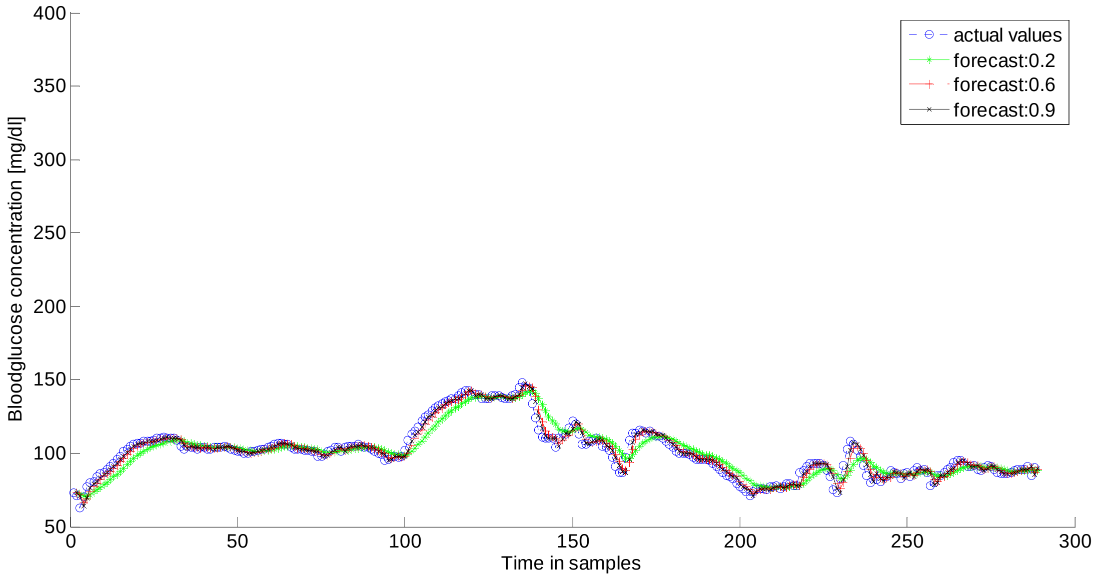

Fig. 8. The result of single exponential smoothing for a record from P2 patient, with insulin pump.

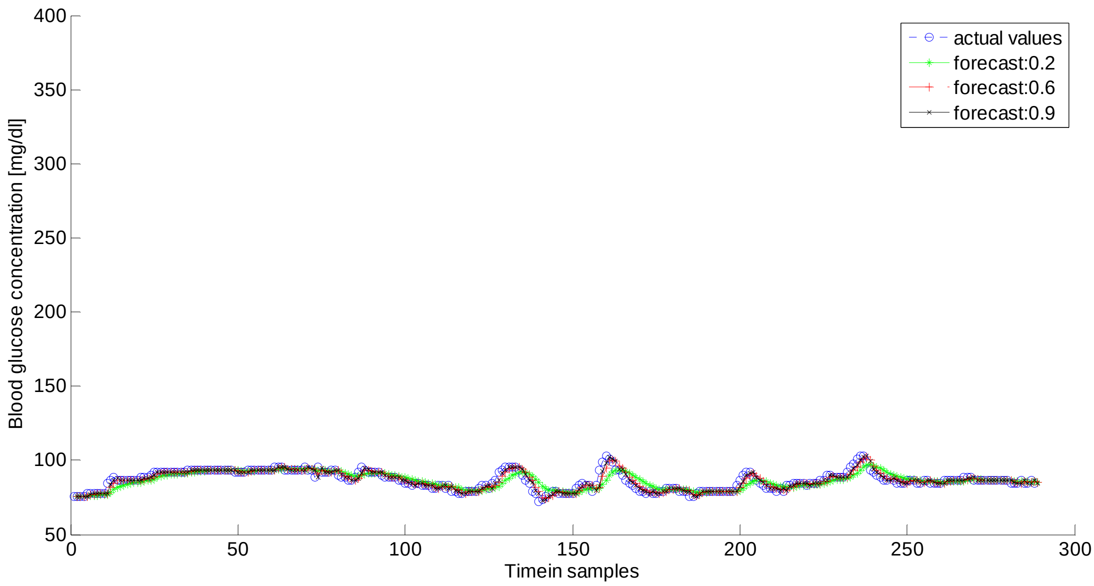

Fig. 9. The result of single exponential smoothing for a record from the healthy subject.

It can be seen the efficiency of this algorithm. The single exponential smoothing for blood glucose records can be used in predictive control because it offers in real time the forecast values, it is easy to use and affordable, it has the capacity to adjust its responsiveness to changes in the process and has reasonable accuracy.

REFERENCES

Brown, R. G., Meyer, R. F. (1961), The fundamental theory of exponential smoothing, *Operations Research*, 9, pp. 673-685.

Iancu, Ionela, E. Iancu, *Modeling and Simulation in Physiology*, (2003) Ed. Universitaria Craiova, pp.146-158, ISBN 973-8043-406-5.

Iancu E., Ionela Iancu, Maria Mota (2008) Statistical analysis of the blood glucose data for automated diagnosis, International Conference on Mathematics & Computers in Biology & Chemistry (MCBC'08), Bucuresti, România, *Proceedings of the conference* ISBN 978-960-6766-75-6, pp. 17-21.

Iancu Ionela, Maria Mota, E. Iancu, (2008) Method for the analysing of blood glucose dynamics in diabetes mellitus patients, The 2008 IEEE International Conference on Automation, Quality and Testing, Robotics – AQTR 2008, THETA 16, Cluj-Napoca, România, *Proceedings of the conference,* IEEE Catalog number: CFP08AQT-PRT, ISBN: 978-1-4244-2576-1, vol.3, pp. 60-65.

Iancu Ionela, Maria Mota, E. Iancu (2010) *Computer-assisted monitoring and diagnosis in patients with diabetes. Contributions to the development of automated systems for blood glucose control*, Ed. SITECH, ISBN 978-606-11-0743-8.

Kovatchev, Boris P., William L. Clarke, Marc Breton, K. Brayman, A. McCall, (2005), Quantifying Temporal Glucose Variability in Diabetes via Continuous Glucose Monitoring: Mathematical Methods and Clinical Application, *Diabetes Technology & Therapeutics* ;7 (6), pp.849-862.

Makroglou, Athena, Jiaxu Li, Yang Kuang, (2006) Mathematical models and software tools for the glucose-insulin regulatory system and diabetes: an overview, *Applied Numerical Mathematics* 56 pp. 559–573, www.elsevier.com/locate/

Ostertagová, E., Oskar Ostertag (2011) The simple exponential smoothing model, The 4th International Conference on Modelling of Mechanical and Mechatronic Systems, Technical University of Košice, Slovak Republic, *Proceedings of conference*, pp. 380-384.

Smith, O. J. , (1959) A controller to overcame dead time, *ISA Journal*, Vol. 6, No.2, pp.28-33.

Troisi J. Rebecca., Catherine C. Cowie, Maureen I. Harris, (2000) Diurnal variation in fasting plasma glucose, *JAMA*, 284, pp.3157-3159.

Van Cauter, Eve, Kenneth S. Polonsky, André J. Scheen, (1997) Roles of circadian rhythmicity and sleep in human glucose regulation, *Endocrine Reviews* 18 (5): pp. 716-738.

Zick, Reinhard, Bettina Petersen, Mario Richter, Cornelia Haug, (2007) Comparison of Continuous Blood Glucose Measurement with Conventional Documentation of Hypoglycemia in Patients with Type 2 Diabetes on Multiple Daily Insulin Injection Therapy, *Diabetes Technology & Therapeutics*, 9(6), pp. 483-492.