Spectral Analysis of the Blood Glucose Time Series for Automated Diagnosis

IONELA IANCU[*], EUGEN IANCU[**], MARIA MOȚA[***]
[*] Department of Physiology, Medical Informatics and Biostatistics
[** *]Department of Diabetes and Nutrition Diseases
University of Medicine and Pharmacy of Craiova
Petru Rares Street, no. 4, 200349 Craiova
[**] Department of Automation
University of Craiova
Decebal Street, no. 107, 200440 Craiova
ROMANIA

Abstract: - The control of uptake and release of hepatic glucose is a complex problem and has a relative physiological importance. The mellitus diabetes is a disease with serious social implications through the large number of people affected, complications and high costs that it involves. The introduction in the medical practice of the blood glucose continuous monitoring systems has made possible the automated analysis of the blood glucose dynamics. In this work the authors present an algorithm focused on the spectral analysis methods in order to detect the reliable characteristics, useful in the identification of standard aspects or automatic diagnosis in the diabetic patients monitoring with applications, especially in the intensive care units and telemedicine.

Key-Words: - Statistical analysis, diabetes mellitus, continuous glucose monitoring, spectral analysis, periodogram.

1 Introduction

The actual developpment of the blood glucose (BG) continous monitoring system has allowed the study of the blood glucose dynamics through a great number of mathematical methods. Their results have shown the complexity of the blood glucose control and the specific physiopathological response of every body system to pathological perturbations. The most important disease of this medical field is diabetes mellitus, which is based on impairement in insulin secretion that affects the blood glucose concentration and so that the body metabolism with grave complications.

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 the plasma glucose oscillations.

The normal pattern of insulin secretion rate displays:

- Very rapid oscillations occurring at 10 second intervals, related to molecular intracellular processes.
- Rapid oscillations occurring from 8 to 15 minutes.
- Slow oscillations occurring at 90 to 120 minutes.
- Circadian oscillations related to cortisol circadian rhythm and growth hormone secretion after sleep.

Rapid and slow oscillations are still a controversial subject of experimental studies, but they are certainly related to the insulin glucose control system. All studies show the oscillatory feature of the long term BG recordings [1], [2], [3]. Also, in the BG control, counter regulatory hormones intercede: glucagon, catecholamine, cortisol and growth hormones which increase the concentration of BG by stimulating the production of hepatic glucose and/or inhibiting tissue glucose uptake.
Experimental Studies have shown "fast" (tens of seconds) and "slow" (4–6 min) insulin oscillations in secretion and their interactions. Bertram and his colab [4] proposed that the fast oscillations result from electrical mechanisms, predominantly feedback of cytosolic free calcium on plasma membrane ion channels, and that the slow oscillations result from metabolic, possibly glycolytic, oscillations.

The ultradian oscillations (period 80-150 min) in insulin secretion rate are tightly coupled to glucose

oscillations of similar period. C. Simon [5] consideres that this oscillations are probably partially the consequences of a negative feedback loop linking glucose and insulin secretion rate. Also, the effects of sleep on insulin secretion are achieved by an enhancement of the oscillation amplitude which could be partly mediated by growth hormon. N. M. O'Meara and colab. [6] have demonstrated through pulse analysis, cross-correlation analysis, and spectral analysis that important dynamic properties of the feedback loop linking insulin secretion and glucose are disrupted not only in established non-insulin dependent diabetes mellitus, but also in conditions where glucose tolerance is only minimally impaired.

J. Sturis and his colab. [7] have shown that the relative amplitudes of both the insulin and glucose oscillations were also similar in diabetic and nondiabetic subjects. The major abnormality in patients with Type 2 diabetes was evidenced by spectral analysis, and confirmed by calculations of the distributions of inter-pulse intervals. It consisted of a slowing of the glucose oscillations, without a similar slowing of the oscillatios in insulin secretion.

C. Simon and G. Brandenberger [8] have proven tha the ultradian oscillations are not related to the ultradian oscillations in sympathoagal balance, as inferred from spectral analysis of cardiac R-R intervals, or the plasma fluctuations of glucagon-like peptide-1.

The complex control system of blood glucose must include many other components and physiological parameters, such as the liver and pancreas and their relationship mediated through the magnitude of insulin pulse mass in regulating the quantity and pattern of systemic insulin delivery. (J. J. Meier) [9].

Research in this area will have in the nearby future a major impact in the medical environment. They belong to the modern tendency to automate and to introduce the informatics in the human medicine.

2 Problem Formulation

Our team's purpose was to develop new, performant algorithms for automatic diagnosis in the diabetic patients monitoring with applications, especially in the intensive care units and telemedicine. Automatic diagnosis in such a medical field requires the introducing of a proper method or a group of mathematical methods capable to achieve moment to moment the following objectives:

- to identify the type of diabetes
- to detect the pathological component in the early stages of the disease
- to quantify the risk level of the metabolic disorders
- to reveal the trend in the pathological state evolution
- to estimate the response to the treatments

In the beginning, we have focused on the spectral analysis methods in order to detect the reliable characteristics, useful in the identification of standard aspects or stable patterns for each type and stage of the complex and long-term evolution of the disease that is diabetes mellitus.

3 Problem Solution

3.1 Experimental lot

For this study we have selected 18 adult subjects (10 female and 8 male), patients with insulin dependent mellitus diabetes and 3 healthy humans. 16 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. Two patients have received a proper dosage of insulin by a new device called "insulin pump". This offers a continuous basal rate of insulin and facilitates the administration of bolus insulin 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 to each patient at five minute intervals, continuously for three days, using the *Real-Time Guardian Continuous Glucose Monitoring System* (CGMS) [10], [11] 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 the blood glucose representation for 24 hours. For exemplification we choose the following individual cases:

- One patient (P1) 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).
- One patient (P2) 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. 2).

- One healthy subject (P3) with normal food administration and activity. The CGMS displays a low variability of the glucose values, expression of an efficienty blood glucose control (Fig. 3).

3.2 Mathematical Methods

The spectral analysis of the time series for the blood glucose reveal a large distribution of spectral components in the frequency range 0 – 1.5 mHz for diabetes patients P1 (injected with insulin), P2 (with insulin pump) and P3 patient (normal subject). The figures 4, 5 (for P1), 8 along with 9 (for P2) and 12 and 13 (for P3) show the spectral power density for the blood glucose time series recorded during two consecutive days (D1 and D2). Despite the present perturbations the reseamblence of the two spectrums is obvious.

The following step has been to eliminate the continuous component (detrend) from each signal and filter it. These signals have been through an order 15, low-pass filter. The difference between the thus obtained signals corresponding to D1 and D2 has been calculated. The results are represented in figures 6, 10 and 14. Note the reduced signal amplitude at the healthy patient.

The spectral analysis of the signal difference reveals the following situations:

- The presence of the spectral components in the very low frequency range (0 – 0.7 mHz), for every investigated patients (P1, P2 and P3).

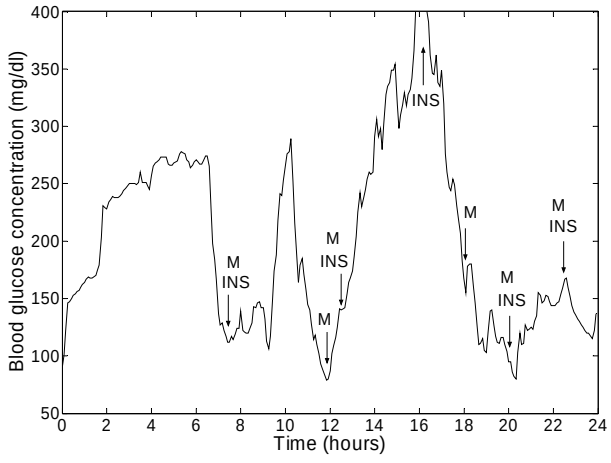

Fig. 1. Time evolution of the glucose concentration for the P1 patient in the day D1.
INS – insulin treatment, M – meal.

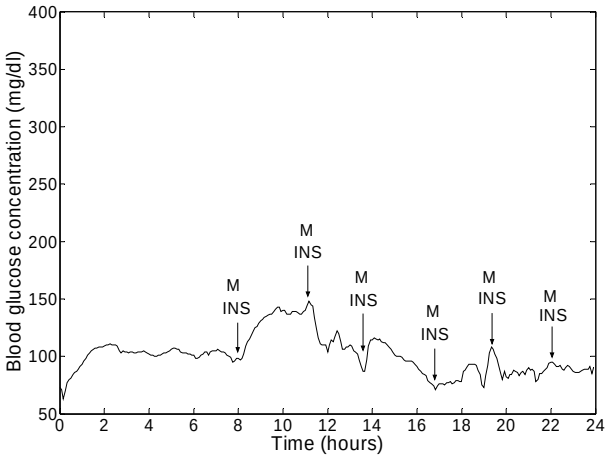

Fig. 2. Time evolution of the glucose concentration for the P2 patient.
INS – insulin treatment, M – meal.

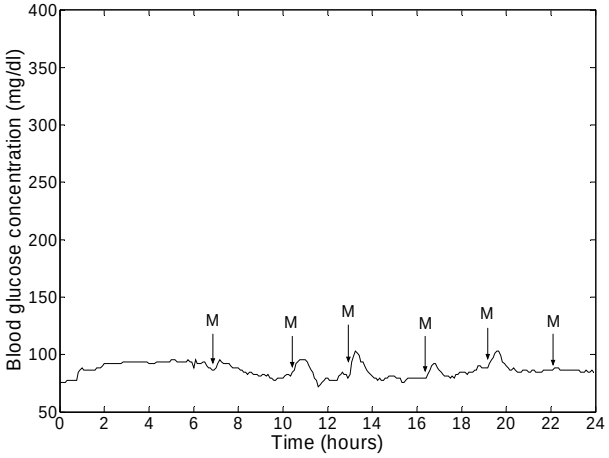

Fig. 3. Time evolution of the glucose concentration for the P3 patient.
M – meal.

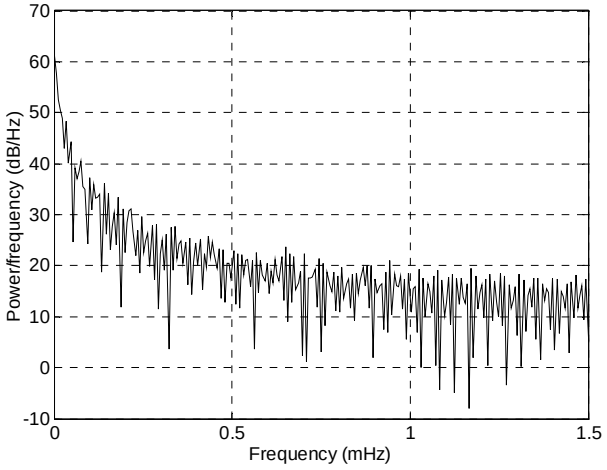

Fig.4. Power spectral density function for the patient P1 in the day D1.

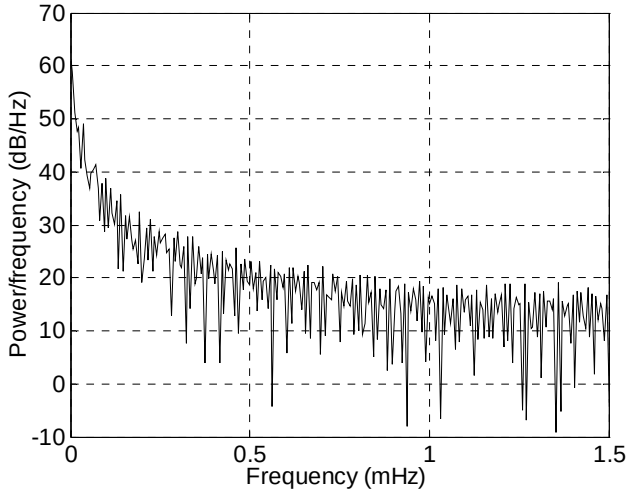

Fig.5. Power spectral density function for the patient P1 in the day D2.

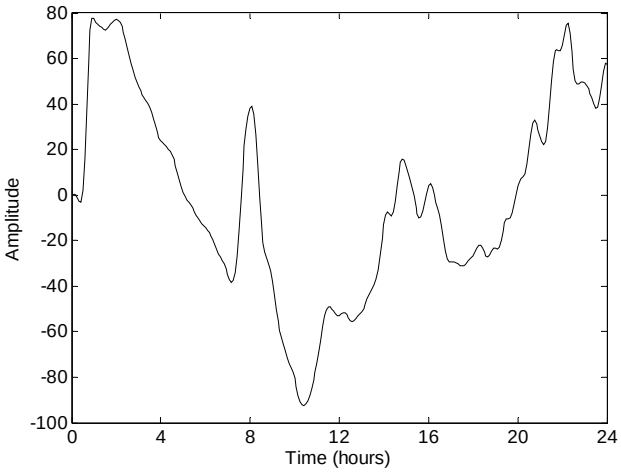

Fig.6. The difference signal (Diff-P1) beetwen the filtered and detrended blood glucose concentrations for patient P1 recorded in the first and second day.

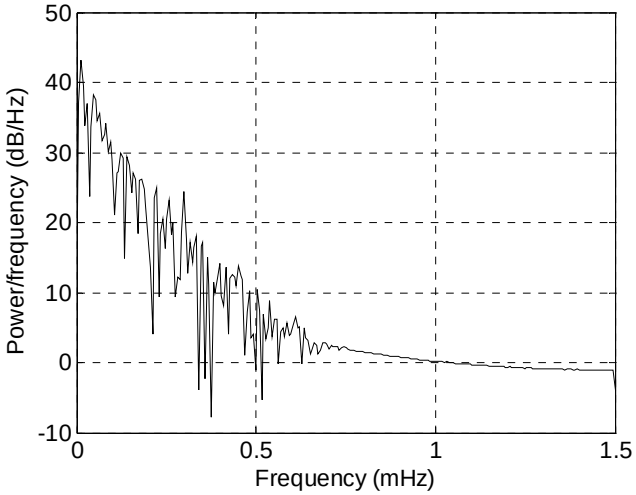

Fig.7. Power spectral density function for the difference signal Diff-P1.

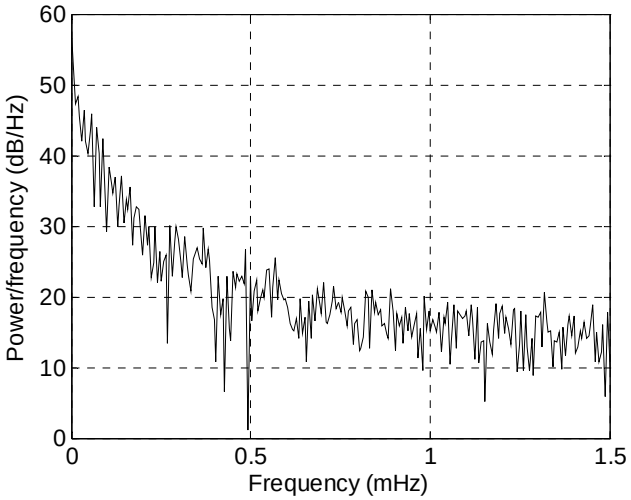

Fig.8. Power spectral density function for the patient P2 in the day D1.

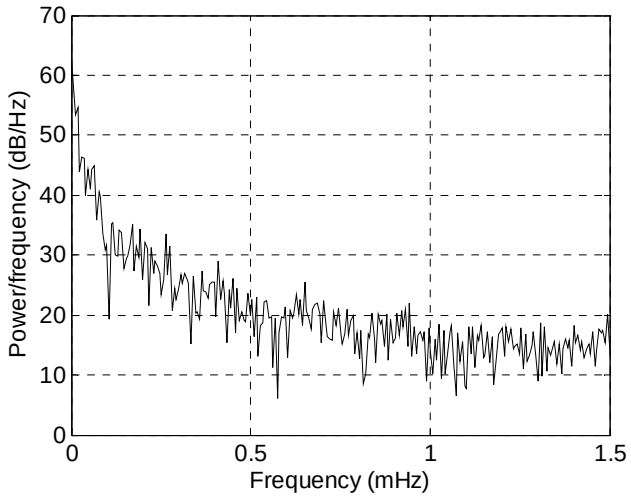

Fig.9. Power spectral density function for the patient P2 in the day D2.

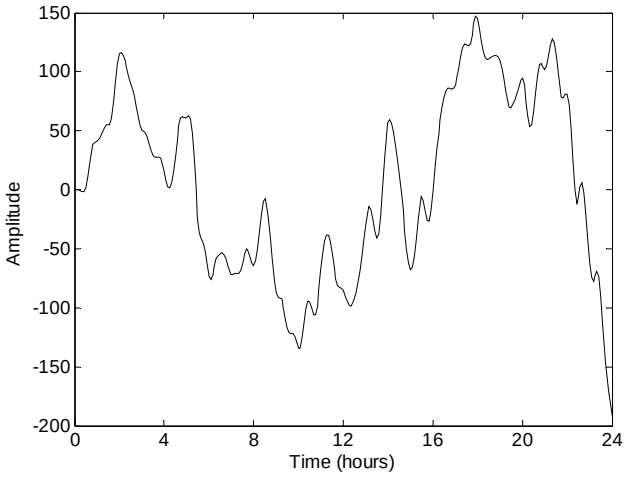

Fig.10. The difference signal (Diff-P2) beetwen the filtered and detrended blood glucose concentrations for patient P2 recorded in the first and second day.

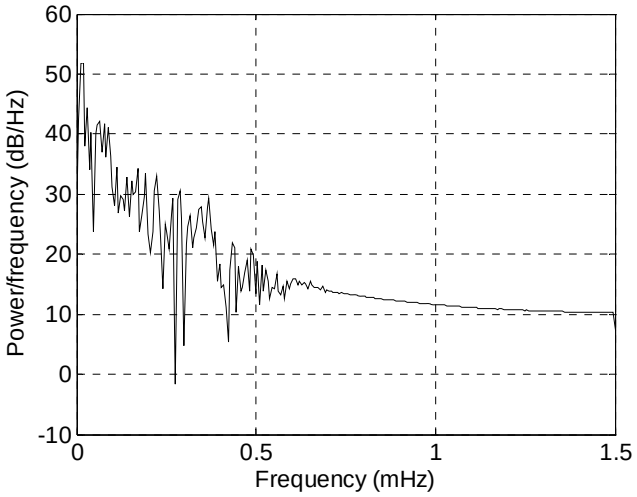

Fig.11. Power spectral density function for the difference signal Diff-P2.

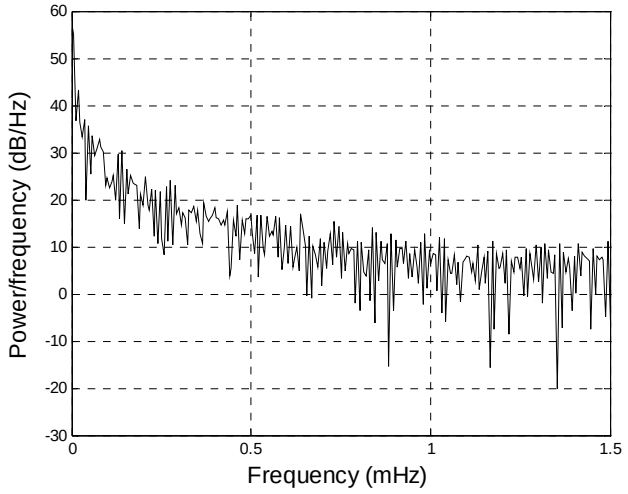

Fig.12. Power spectral density function for the patient P3 in the day D1.

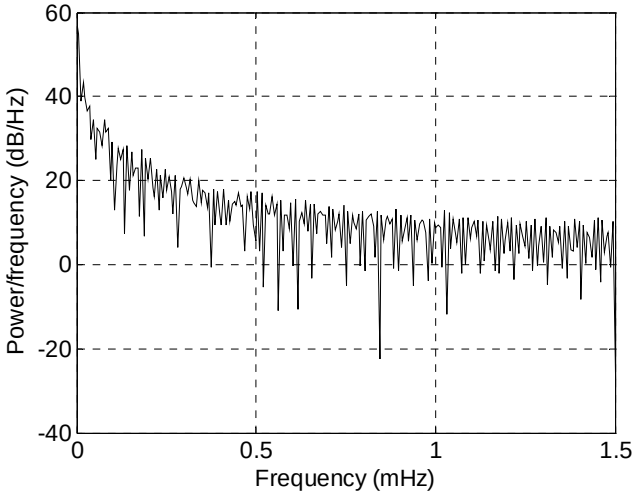

Fig.13. Power spectral density function for the patient P3 in the day D2.

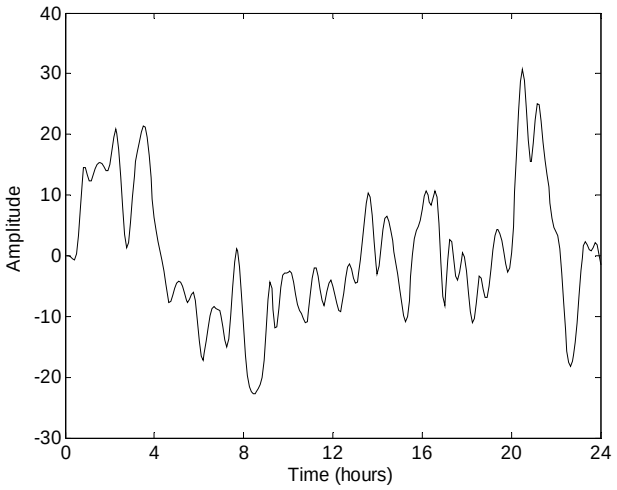

Fig.14. The difference signal (Diff-P3) beetwen the filtered and detrended blood glucose concentrations for patient P3 recorded in the first and second day.

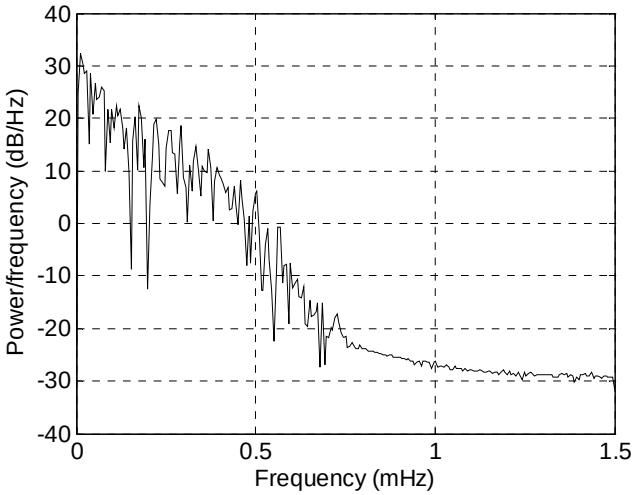

Fig.15. Power spectral density function for the difference signal Diff-P3.

- A decrease in amplitude of the components for the high frequency range (0.7 – 1.5 mHz).
- The decrease is much more noticeable in the case of healthy subjects (Fig. 14) in comparisons to the diabetes patients (Fig. 6 and 10).

4 Conclusion

The physiological interpretation of these phenomenon is very difficult in the absence of the experimental studies in this field of interest.

Our study shows that the blood control system posesses high frequency components that reproduce

daily. The low frequency components are not identical from one day to the other and correspond to the internal oscillations of the control system.
This finding suggests that the control system reacts identically on a short term but takes on different actions on longer term.

Acknowledgments

This paper is part of the projects:
- *The development of automated systems for blood-glucose control at insulin-dependent patients. The implementation of evolved algorithms for computer assisted monitoring and diagnosis*, at the University of Medicine and Pharmacy of Craiova.
- *Algorithms for fault detection and isolation in dynamic systems. Development of analytical methods for diagnose assisted by computer. Applications for the study of the physiological systems,* at the University of Craiova
and was supported by National University Research Council, Romania.

References

[1] Eve Van Cauter, Kenneth S. Polonsky, André J. Scheen, Roles of Circadian Rhythmicity and Sleep in Human Glucose Regulation, *Endocrine Reviews* 18 (5): 716-738, Copyright © 1997 by The Endocrine Society.

[2] Rebecca J. Troisi, Catherine C. Cowie, Maureen I. Harris, Diurnal Variation in Fasting Plasma Glucose, *JAMA* 2000; 284:3157-3159.

[3] David A. Gough, Kenneth Kreutz-Delgado and Troy M. Bremer, Frequency Characterization of Blood Glucose Dynamics, *Journal-Annals of Biomedical Engineering*, Springer Netherlands, ISSN - 0090-6964 (Print) 1573-9686 (Online), Volume 31, Number 1 / January, 2003.

[4] Richard Bertram, Arthur Sherman, and Leslie S. Satin, Metabolic and electrical oscillations: partners in controlling pulsatile insulin secretion *Am J Physiol Endocrinol Metab* 293: E890-E900, 2007

[5] C. Simon, Ultradian Pulsatility of Plasma Glucose and Insulin Secretion Rate: Circadian and Sleep Modulation, *Hormon Research* 1998;49:185-190

[6] N. M. O'Meara, J Sturis, E. Van Cauter, and K. S. Polonsky, Lack of control by glucose of ultradian insulin secretory oscillations in impaired glucose tolerance and in non-insulin-dependent diabetes mellitus. *Clin Invest.* 1993 July; 92(1): 262–271.

[7] Sturis J, Polonsky K.S., Shapiro E.T., Blackman J.D., O'Meara N.M., van Cauter E. Abnormalities in the ultradian oscillations of insulin secretion and glucose levels in type 2 (non-insulin dependent) diabetic patients. *Diabetologia* 1992 Jul; 35 (7): 681-9

[8] C. Simon, Brandenberger G. Ultradian oscillations of insulin secretions in humans, *Diabetes* 2002 Feb; 51 Suppl 1:S258-61

[9] J. J. Meier, Veldhuis J. D., Butler P. C. Pulsatile insulin secretion dictates systemic insulin delivery by regulating hepatic insulin extraction in humans, *Diabetes* 2005 Jun; 54(6): 1649-56.

[10] * * * CLINICIP-Publishable Final Activity Report, www.clinicip.org/fileadmin/clinicip, January 2008.

[11] * * * MiniMed^{R} Manual – *Continous Glucose Monitoring System*, www.minimed.com, U.S.A.