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Mechanism of Glucose Insulin Control in Type 1 Diabetes Using Harr Wavelet Method

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Abstract: The main aim of this study is to inject insulin for type 1 diabetes using pumping of insulin. The blood glucose level has to be monitored with the help of glucose tolerance test. For efficient method to control type 1 diabetes researcher will use embedded linear parameter varying methodology controller. In this study, there are three things researchers need to focus. The first is the sensor values read from the sensors has to be monitored and the second is the lab information (patient's basic level of tests). Depending on the patients test details, the insulin has to be injected. For example, if the person sensor value is greater than the reference limit then he has to be provided with insulin for a longer period. So, the comparison of lab details with the patients current sensor values play a vital role in determining the insulin level for a patient. Finally, the feedback has to be obtained with the help of those comparisons and it has to be sent once again as a loop to the controller for later comparison and also for database information. Here, the controller is the key element for updating all the information about the patient and it will control all the parameters of the board. Here, researchers will use EEPROM for saving all the data on a location basis. It is capable of holding 256 bytes at a time and each location can store one byte information at a time.

Key words: Blood glucose, insulin, glucose tolerance test, pre-diabetes, controller section, pumping method, Haar wavelet

INTRODUCTION

The diabetes is the most common disease in India. The Indian population, nearly 60% of them are suffering from this disease. Insulin is an enzyme made by the pancreas. The pancreas releases insulin into the blood. If the body does not make insulin or if the insulin does not work the way it should, glucose stays in the blood instead and blood glucose level gets too high, carrying pre-diabetes or diabetes. Diabetes mellitus is a group of metabolic diseases characterized by high blood sugar levels that result from defects in insulin secretion or action or both. Elevated levels of blood glucose lead to spillage of glucose into the urine. Normally, blood glucose levels are tightly controlled by insulin. When the blood glucose elevates, insulin is released from the pancreas to normalize the glucose level. Diabetes is a chronic medical condition, meaning that although it can be controlled, it lasts a lifetime. Over time, diabetes can lead to blindness, kidney failure and nerve damage. These types of damage are the result of damage to small vessels, referred to as micro vascular disease. Diabetes is also an important factor in accelerating the hardening and narrowing of the arteries leading to strokes, disease and other large blood vessel diseases. This is referred to as macro vascular disease. In this study, the condition researchers are going to consider is type 1 (Juvenile) which is usually diagnosed in children, teenagers and young adults. Here, the beta cells of the pancreas no longer make insulin because the body's immune system has destroyed them. Treatment for type 1 diabetes includes taking insulin and possibly another injectable medicine, making wise food choices, being physically active, taking aspirin daily for some and controlling blood pressure and cholesterol.

Blood glucose regulation: Automatic regulation of blood glucose level in a patient requires a minimum of three components, blood glucose sensor, a controller that matches blood glucose level with an appropriate insulin delivery rate and an infusion pump to deliver the insulin

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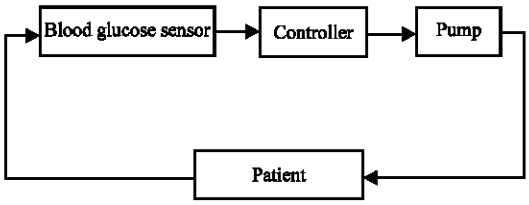

Fig. 1: Block diagram of blood glucose regulation

to the patient. The block diagram of the blood glucose regulation is shown in Fig. 1. The blood glucose of the patient is measured by the glucose sensor and is given as the input to the control system. Various blood glucose measurement techniques exist and each has its unique characteristics. The various blood glucose measurement techniques in existence are invasive, minimally invasive and non-invasive techniques. According to the requirement and the cost the measuring technique can be chosen (Man *et al*., 2007; Del Favero *et al*., 2011).

The role of controller in insulin delivery system is to regulate the patient's blood glucose level, replacing the intrinsic glucose regulatory function. The control algorithms proposed are categorized based on the two different approaches namely model-less approach and model based approach where the model is linear or non-linear. This study deals with the model less approach (Cobelli and Mari, 1983; Cobelli and Ruggeri, 1983; Salzsieder *et al*., 1985; Sorensen, 1985; Lehmann and Deutsch, 1992; Andreassen *et al*., 1994; Vicini *et al*., 1999).

In Fig. 1, the insulin infusion pump will deliver the insulin according to the controller output. For simulation analysis the compartmental model of the patient is taken. The glucose insulin system is expressed as non-linear One Dimensional Equation (ODE), comprising of 19 equations and is divided into 3 subsystems: Glucose, insulin and glucagon. The first 2 subsystems are modeled for brain, heart, lungs, liver, gut, kidney and periphery compartments; the glucagon is modeled as a single blood pool compartment (Hovorka *et al*., 2004; Basu *et al*., 2003, 2006; Taylor *et al*., 1996; Man *et al*, 2006; Pillonetto *et al*., 2001).

The diabetic patient model was constructed using MATLAB software to represent a sedentary 70 kg male patient, it has two inputs, insulin delivery with nominal value of 22.3 mU min^{-1} and meal disturbance with nominal value 0 mg min^{-1} and one measured output, blood glucose concentration with nominal value of 81.1 mg dL^{-1} (Vicini *et al*., 1997; Lepik, 2008a-c, 2011).

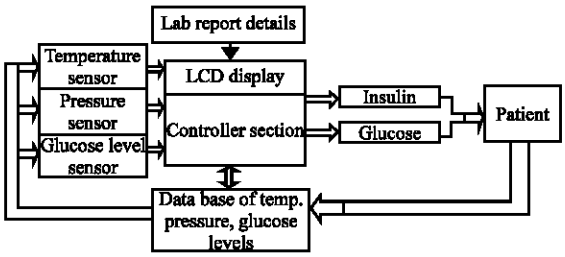

Fig. 2: Embedded model system

Embedded model system: Figiure 2, glucose level sensor, pressure sensor, temperature sensor are the sensors used in this study. The sensors will be of analog format so, researchers will use analog to digital converter to convert analog to digital values. Whenever the patient enters the lab they need to be monitored and provided with exact solution with the help of database.

Whenever the patient glucose level goes beyond the normal level, automatically insulin will be injected with the help of controller section. In this study, researchers will first look for the entry of the person. If the person enters the hospital, then the lab test has to be conducted for them. Researchers will conduct only one test based on glucose level. This researchers need to call as lab report. Next researchers will check the glucose, temperature, pressure of the person and maintain a database with all the details based on time. Next from the details, researchers will compare the test result with the original values. In this, there are three conditions to be compared and monitored. The first one is normal level of glucose and the next is below level of glucose and the final one is higher level of glucose. From this comparison, researchers will come to know how much of insulin researchers need to inject to the person and this will be send as a feedback to the controller again for maintaining the glucose level in the blood the data is shown in Table 1. The process will be repeated for a certain period of time to maintain a database because whenever we need researchers will check the database with the help of time calculations and it will be easy for maintaining a patient detail in a database manner.

The entry of the person is based on sensors and whenever the person enters, then lab test has to be conducted for the patient and the details will be stored in EEPROM and as well as display's in LCD. Then with the help of sensors, researcher will measure the information's and should displays in LCD. At the same time, the measured values will be saved in EEPROM for comparison and as well as for getting the details of the

Table 1: Blood glucose levels

	Blood glucose levels			
Treatements	1	2	3	4
Altering in infusion rate	BGL ≥180 mg dL^{-1}	BGL 120-179 mg dL^{-1}	BGL 90-119 mg dL^{-1}	BGL 70-89 mg dL^{-1}
↑Infusion by 2Δ	BGL↑	BGL↑ by >40 mg/dL/h	-	-
↑Infusion by Δ	BGL↓by 1-40 mg/dL/h	BGL↑by 1-40 mg/dL/h	BGL↑by >20 mg/dL/h	-
No infusion change	BGL↓by 41-80 mg/dL/h	BGL↓by 1-40 mg/dL/h	BGL↑by 1-20 mg/dL/h	BGL↑
↓Infusion by Δ	BGL↓by 81-120 mg/dL/h	BGL↓by 41-80 mg/dL/h	BGL↓by 21-40 mg/dL/h	BGL↓by 1-20 mg/dL/h
↓Infusion by 2Δ	BGL↓by >120 mg/dL/h	BGL↓by >80 mg/dL/h	BGL↓by >40 mg/dL/h	BGL↓by >20 mg/dL/h

patient at any time. Compare the stored information's of the sensors and lab test value with the help of EEPROM. With the comparison, researchers will provide suitable level of insulin to the patient. Repeat the process with the help of controller.

Algorithm: The algorithmic process is given as:

$$h_i(x)=\begin{Bmatrix}1 \text{for} x\varepsilon\left[\varepsilon_1(i),\varepsilon_2(i)\right]\\ -1 \text{for} x\varepsilon\left[\varepsilon_2(i),\varepsilon_3(i)\right]\\ 0 \text{elsewhere}\end{Bmatrix} \quad (1)$$

$$i=2^j+k+1, j\geq 0, 0\leq k\leq 2^j-1$$

Here,

$$\varepsilon_1=\frac{k}{m},\ \varepsilon_2=\frac{k+0.5}{m},\ \varepsilon_3=\frac{k+1}{m},$$

And m = 2^j, j = 0, 1, 2, ..., J. J is the maximum level of resolution. k = 0, 1, 2, ..., m-1, the translation parameter. The index i = m+k+1. Maximum of I is M = 2 m = 2^{j+1}.

The collocation points x_ι = l-0.5/2m, l = 0, 1, 2, ..., 2 m are obtained by discretizing Haar function h_i (x) by dividing the interval [0, 1] into 2 m parts of equal length Δt = ½ m to get coefficient matrix H or order 2×2 m.

$$H=\begin{bmatrix}1 & 1 & 1 & 1\\ 1 & 1 & -1 & -1\\ 1 & -1 & 0 & 0\\ 0 & 0 & 1 & -1\end{bmatrix}$$

Notice that Haar wavelets are orthogonal, i.e:

$$\int_0^1 h_i(x)h_\iota(x)dx=\begin{Bmatrix}\frac{1}{m} \text{for} i=1\\ 0 \text{for} i\neq 1\end{Bmatrix}$$

The operational matrix P which is a 2 m. Square matrix is defined by:

$$p_{1,i}(x)=\int_0^x h_i(t)dt$$

Then:

$$p(x)=\int_A^x\int_A^x.....\int_A^x h_i(t)dt=\frac{1}{(\propto-1)!}\int_A^x(x-t)^{\propto-1}h_i(t)dt... \quad (2)$$

∝ = 2, 3, ..., n and i = 1, 2, ..., 2 m

Function approximation: As Haar wavelets are orthogonal; this means that any square integral Lebesgue function over [0, 1] can be expressed into Haar wavelets series as (Hariharan *et al*., 2009a, b; Hariharan and Kannan, 2009, 2010a-c):

$$y(x)=\sum_{i=1}^{\propto}a_i h_i(x) \quad (3)$$

Here, a_i's are Haar wavelet coefficients. If y (x) be piecewise constant, then sum can be terminated to finite term that is:

$$y(x_\iota)=\sum_{i=1}^{2M}a_i h_i(x_\iota)=a^T H,\ a^T=\{a_1,a_2,...,a_{2M}\},$$
$$H=\{h_1(x),h_2(x),...,h_{2M}(x)\}_T$$

Norm of error function; v (ι) = y_{app} (x_ι)−y_{ex} (xι) is defined by:

$$\|v\|_p=\left(\sum_{i=1}^{2M}|v(1)|^p\right)^{1/p} \quad (4)$$

Local estimates:

$$\delta_j=\left\|\frac{v}{y_{ex}}\right\|_\infty=\text{Max} 1\leq l\leq 2M\left|\frac{y(xl)}{y_{ex}(xl)}-1\right| \quad (5)$$

Global estimate:

$$\sigma_j=\frac{\|v\|_2}{2M} \quad (6)$$

Absolute error is given by:

$$e_j=\text{Max} 1\leq l\leq 2M\left|y_{app}(x_l)-y_{ex}(x_l)\right| \quad (7)$$

Application in solving linear ODE: Consider n^{th} order linear ODE Ly (x) = f (x), A≤x≤B, L-differential operator.

Step 1:

$$y^{n}(x)=\sum_{i=1}^{2M}a_{i}h_{i}(x) \quad (8)$$

Step 2: For ∝<n:

$$y^{n}(x)=\sum_{i=1}^{2M}a_{i}p_{n-\alpha,i}(x)+\sum_{\sigma=1}^{n-\alpha-1}\frac{1}{\sigma!}(x-A)^{\sigma}y_{0}^{(\alpha+\sigma)} \quad (9)$$

Step 3: Substitute various derivatives as obtained in step 1 and 2 in Eq. 9, researchers calculate a_i's to get the numerical solution:

$$x'=\sum_{i=1}^{2M}a_{i}h_{i}(x) \quad (10)$$

$$x=\sum_{i=1}^{2M}a_{i}p_{1,i}(x)+x(0) \quad (11)$$

Where, $p_{1,i}(t)=\int_{0}^{x}h_{i}(t)\,dt$.

Method of solution: Consider the Equations:

$$C_{G}\frac{dx}{dt}=U(t)+QL-\lambda x-vxy \quad (12)$$

$$x'=\sum_{i=1}^{2M}a_{i}h_{i}(x) \quad (13)$$

$$x=\sum_{i=1}^{2M}a_{i}p_{1,i}(x)+x(0) \quad (14)$$

Sub Eq. 13 and 14 in Eq. 12:

$$C_{G}\left[\sum_{i=1}^{2M}a_{i}h_{i}(x)\right]=U(t)+QL-\lambda\left[\sum_{i=1}^{2M}a_{i}p_{1,i}(x)+x(0)\right]-v\left[\sum_{i=1}^{2M}a_{i}p_{1,i}(x)+x(0)\right]y \quad (15)$$

RESULTS AND DISCUSSION

The model also allows us to predict the effect of the various control signals on glucose production, as well as the insulin-independent and dependent components of glucose utilization in addition; hepatic insulin extraction can also be predicted. The model consists of a glucose and insulin subsystem. The glucose system is described by a two compartment model, the first representing glucose mass in plasma and rapidly equilibrating tissues and the second the slowly equilibrating tissues.

Glucose utilization has both an insulin independent component occurring in plasma and an insulin dependent component in the second compartment as shown in Fig. 3.

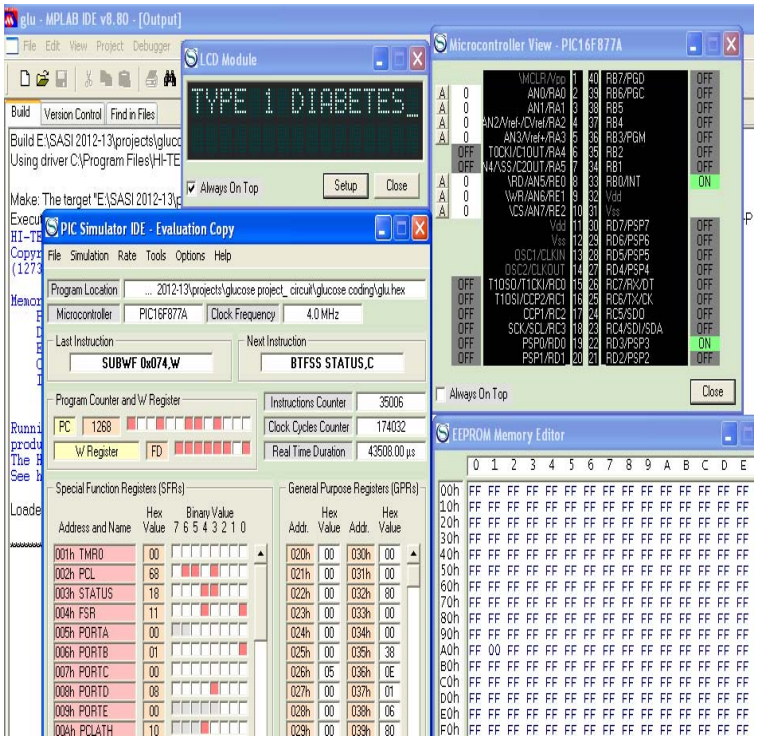

Fig. 3: Type 1 diabetes

The insulin independent utilization is constant and represents glucose uptake by Central Nerves System (CNS) and erythrocytes while the insulin dependent utilization is controlled nonlinearly by glucose in the tissue compartment and insulin in the interstitial fluid. Endogenous glucose production control by glucose and insulin implements recent knowledge in particular it assumes that fast suppression occurs through a portal insulin signal while slower inhibition by a delayed insulin signal, possibly a surrogate of interstitial fluid free fatty acids signaling. A new model of glucose transit through the gastro-intestinal tract is used to describe glucose ingestion and absorption. This feature is important because previous simulation models either allowed only intravenous glucose administration.

PIC simulator IDE is used as a simulator for this study. Modules used in this simulation are LCD, Microcontroller view and EEPROM for seeing the desired sensor values and outputs.

The insulin system is described by a two compartment model. Degradation is assumed to occur linearly in the periphery while liver degradation is assumed to be time-varying in agreement with current knowledge. Insulin secretion is assumed to be dependent on both plasma glucose concentration and its rate of change as with all models, there are some limitations.

The most important is that count regulatory hormones, such as glucagon, epinephrine and growth hormone have not been considered. This will be considered in future model developments. This will be also important for extending the model to type 1 diabetes blood glucose level in Fig. 4. Another limitation concerns the glossocentric nature of the model, i.e., the role of other fuel substrates like free fatty acids and their interaction with glucose and insulin is not considered. Finally when modeling daily life, it would be important to include diurnal variation of parameters A new in silico model of the glucose-insulin regulatory system has been presented. Focusing on quantitating physiological events after a meal is of obvious importance because this route is used in everyday life.

This view is mainly for entry of the patient. This is actually the lab test report done earlier as in laboratory test in Fig. 5.

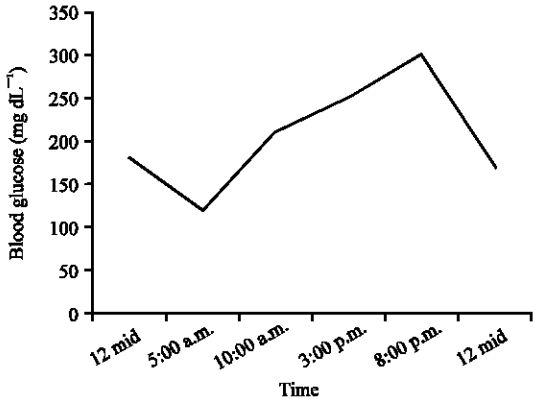

Fig. 4: Blood glucose level on 5 h period with time

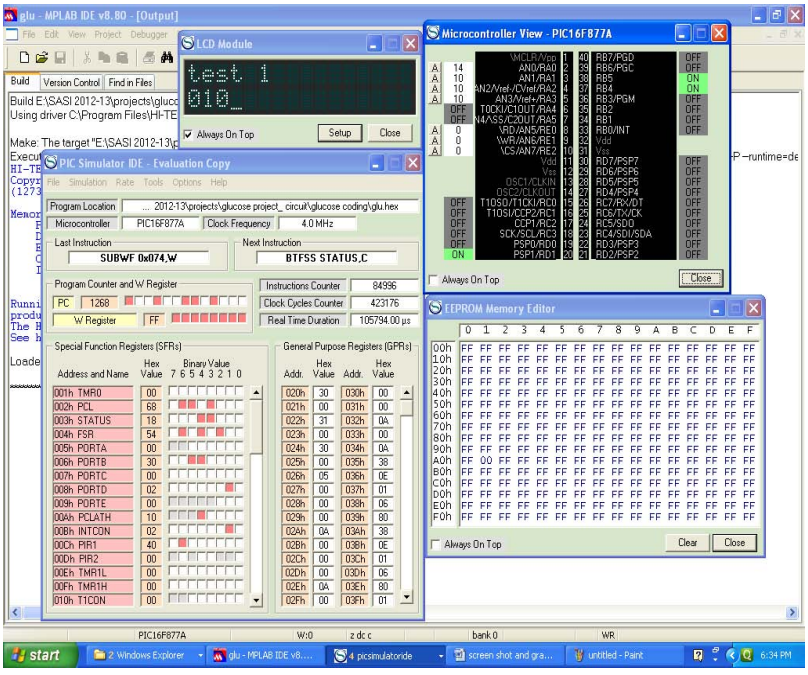

Fig. 5: Laboratory test 1

The postprandial state has also been intensively investigated in recent years, thus one can take advantage of all new quantitative knowledge that has became available. The model is made by a number of parsimonious sub models describing the various unit processes that have been identified using a forcing function strategy.

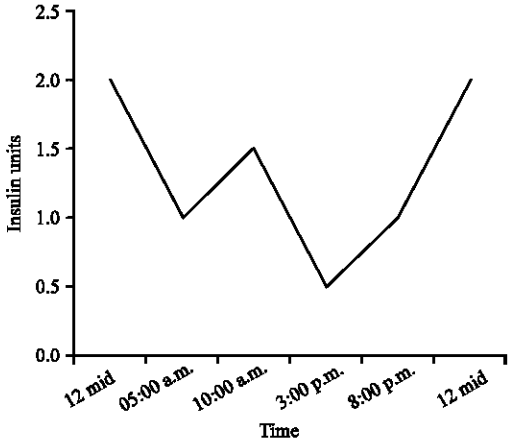

Fig. 6: Insulin level on 5 h period with time

This falls into three basic components of the insulin regimen: A correction dose based on the difference between actual BG level and a target BG level divided by a correction factor of insulin sensitivity (in BG counts per unit of insulin or more correctly mg/dL/unit).

A meal bolus or a single large dose of insulin to cover a meal about to be eaten based on a count of carbohydrate grams of the food multiplied by the insulin-to-carb-ratio (I/c) in units per gram.

A basal insulin or a slow release (background) insulin that a person needs all the time. New insulin analogs, such as Lantus and Levimur last for 12-24 h and give a low slow dose of background insulin the insulin level on 5 h period as shown in Fig. 6. Therefore, the algorithm for interfacing with the insulin pump is the same as with intensive insulin therapy but utilizes a basal rate of fact-acting insulin.

The key parameters, as shown in the data store boxes in Fig. 7 are all needed to control the insulin pump and can be learned by the insulin pump with the use of adaptive variables as shown in Fig. 8-12.

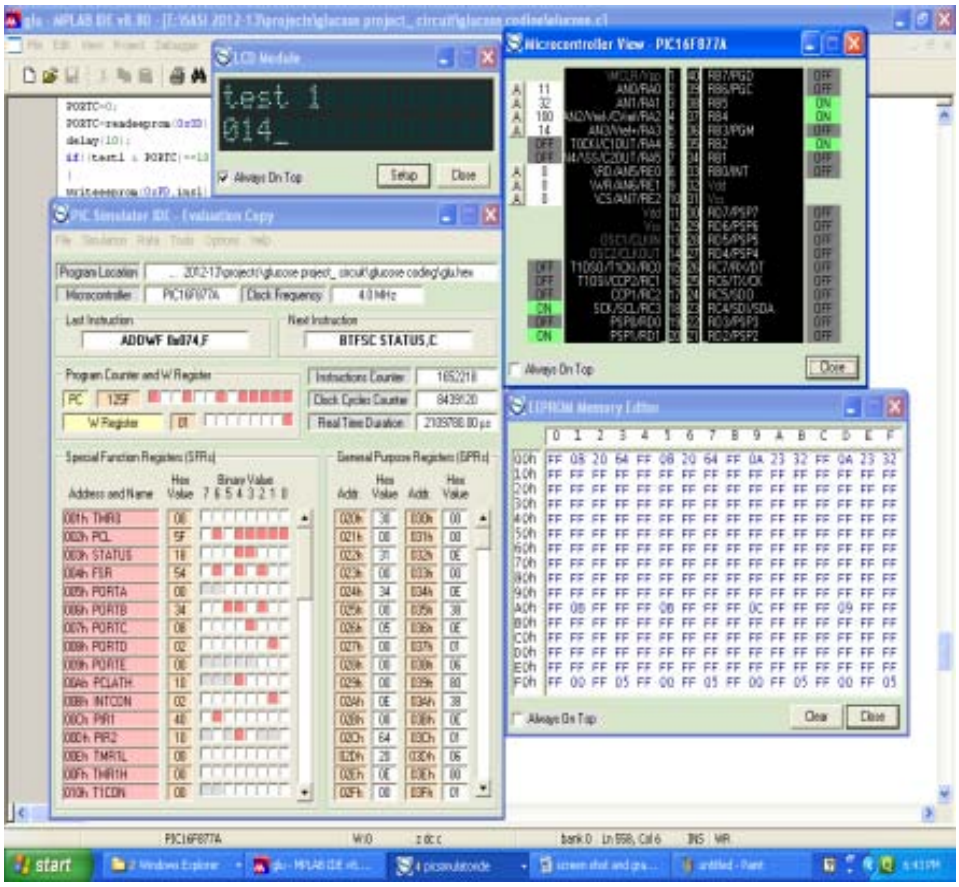

Fig. 7: Laboratory test 2

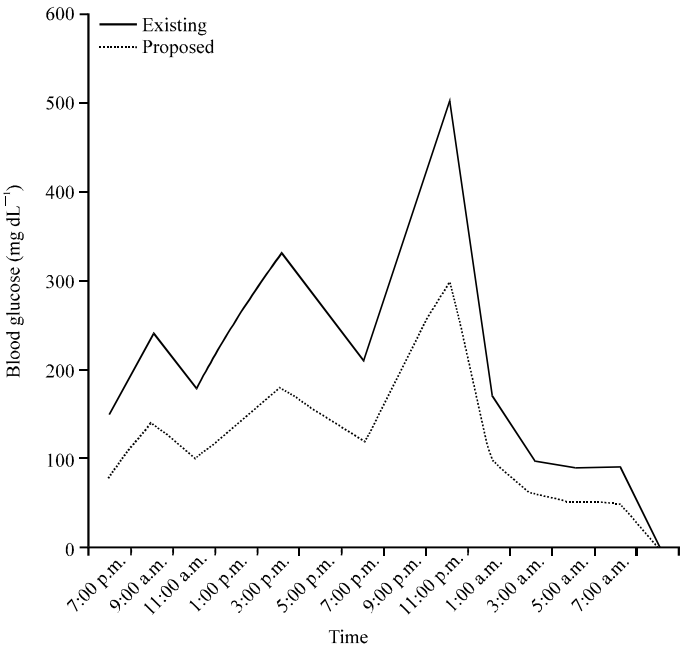

Fig. 8: Existing and proposed blood glucose level on 6 h period with time

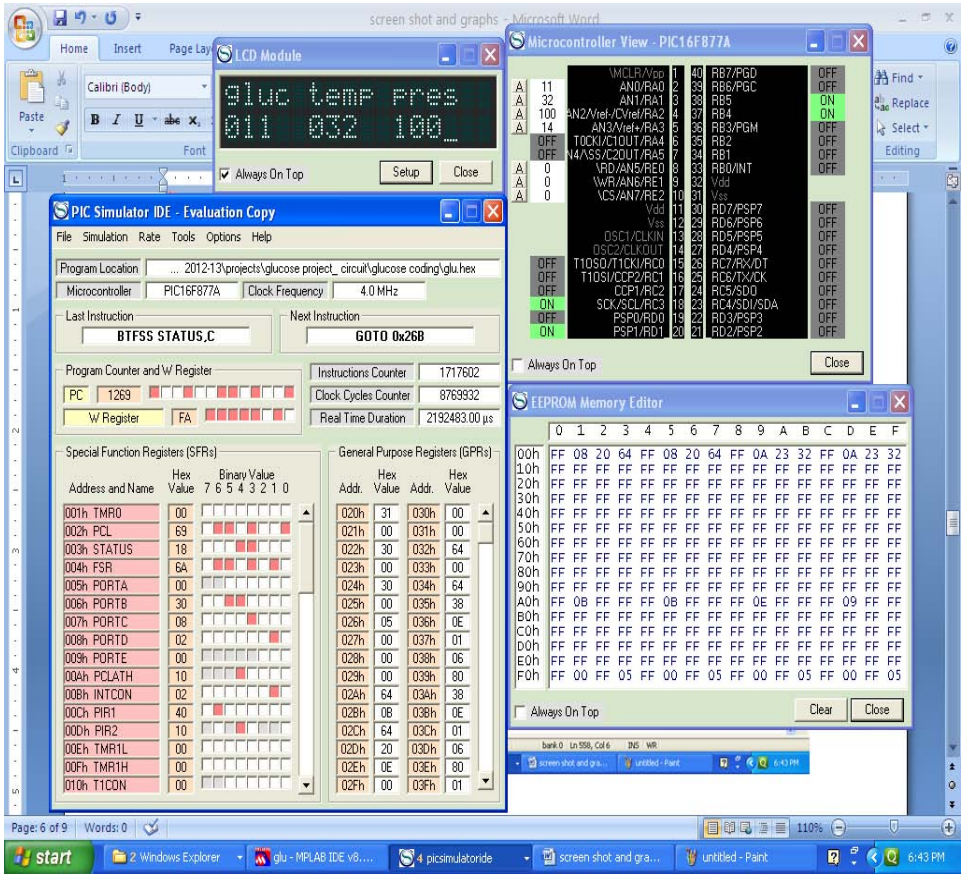

Fig. 9: Glucose temperature pressure output

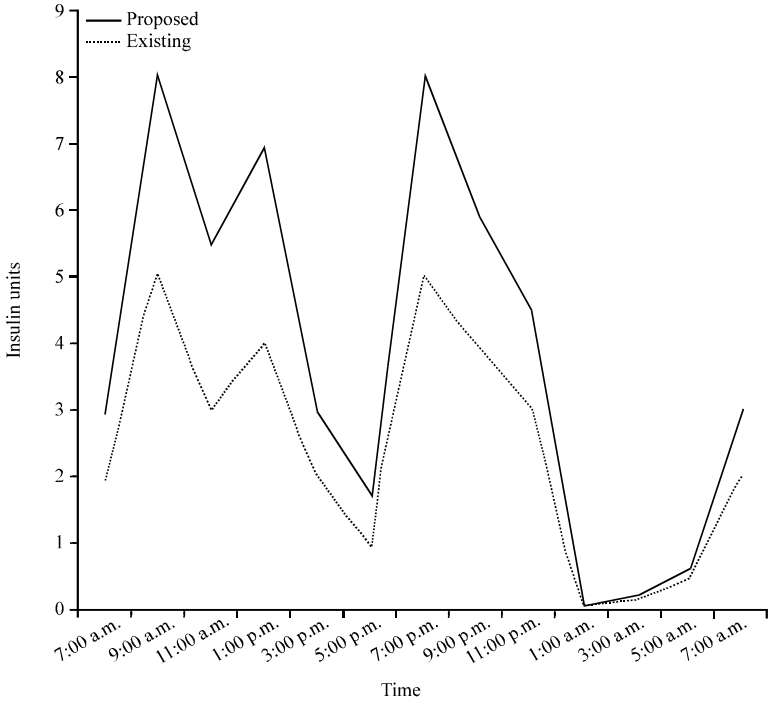

Fig. 10: Existing and proposed glucose levels; insuline level on 6 h period with time

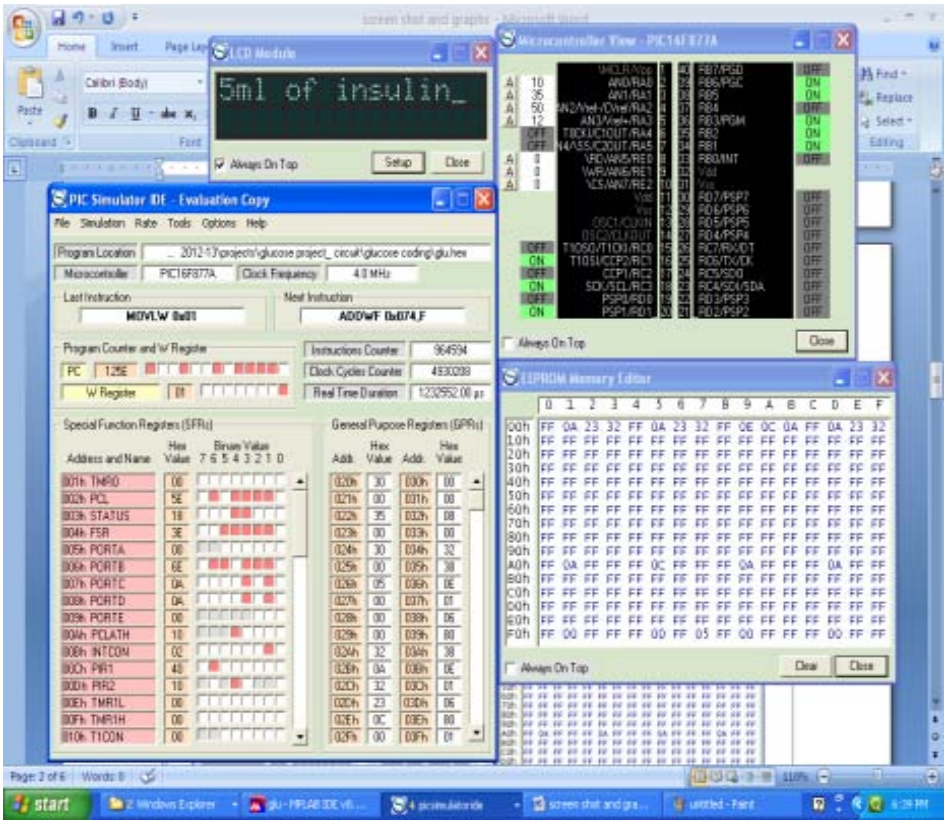

Fig. 11: Insulin to be injected

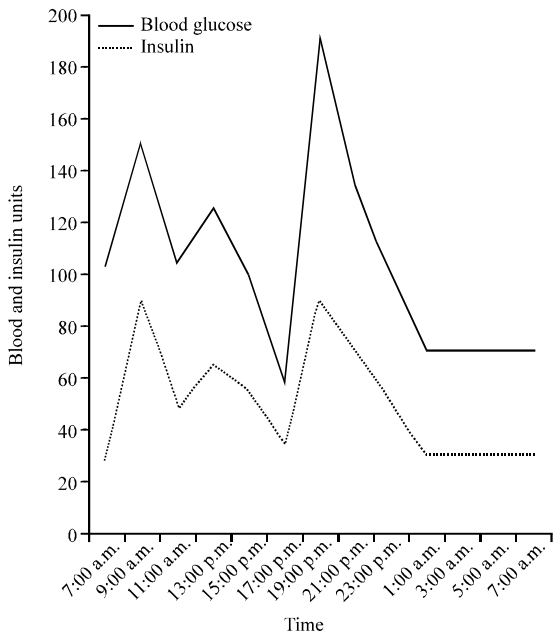

Fig. 12: Blood and insulin levels on 6 h period with time

CONCLUSION

The proposed a physiologically based model of the glucose-insulin system. The modeling strategy is novel and has taken advantage of a unique meal data set both in normal and type 1 diabetes in which not only plasma concentrations but also relevant glucose and insulin fluxes during a meal were available. The main advantages of Haar Wavelet Method (HWM)s method are its simplicity and minimal computation costs. It is due to the scarcity of the transform matrices and to the small number of significant wavelet coefficients. In comparison with existing numerical schemes used to solve the differential equations, the Haar wavelet method is an improvement over other methods in terms of accuracy. It is worth mentioning that Haar solution provides excellent results even for small values of m (m = 16).

For larger values of m (m = 32, 64, 128), researchers can obtain the results closer to the real values. The reasons of use of Haar Wavelet Method (HWM) are sparse matrix representation, fast transformation and possibility of implementation of fast and efficient algorithms. The method with far less degrees of freedom and with smaller CPU time provides better solutions than classical ones. The method is also very convenient for solving the boundary value problems, since the boundary conditions are taken care of automatically. The model should prove valuable as simulator in several situations dealing with the patho physiology of diabetes. The availability of a simulation model of the glucose insulin control system during meals and normal daily life is highly desirable for studying the patho physiology of diabetes and in particular for the design and evaluation of glucose sensors, insulin infusion algorithms and decision support systems for treating diabetes in particular type 1 (insulin dependent). In this insulin experiments, researchers simulated hypoglycemia by injecting an overabundance of insulin into the blood. However, the experiments only simulated a temporary hypoglycemia in an otherwise normal system for a healthy or diabetic individual, i.e., normal concentration levels, rates and parameters for their particular system. Contrary to insulin shock, hyperinsulinism is a chronic disorder which results in an overproduction of insulin which drives down the plasma glucose (concentration), cally based model of the glucose-insulin system. The modeling strategy is novel and has taken advantage of a unique meal data set both in normal and type 1 diabetes in which not only plasma concentrations but also relevant glucose and insulin fluxes during a meal were available. The model should prove valuable as simulator in several situations dealing with the patho physiology of diabetes. The availability of a simulation model of the glucose-insulin control system during meals and normal daily life is highly desirable for studying the patho physiology of diabetes and in particular for the design and evaluation of glucose sensors, insulin infusion algorithms and decision support systems for treating type 1 diabetes.

REFERENCES

Andreassen, S., J.J. Benn, R. Hovorka, K.G. Olesen and E.R. Carson, 1994. A probabilistic approach to glucose prediction and insulin dose adjustment: Description of metabolic model and pilot evaluation study. Comput. Methods Programs Biomed., 41: 153-163.

Basu, R., B. di Camillo, G. Toffolo, A. Basu and P. Shah *et al*., 2003. Use of a novel triple-tracer approach to assess postprandial glucose metabolism. Am. J. Physiol. Endocrinol. Metab., 284: E55-E69.

Basu, R., C.D. Man, M. Campioni, A. Basu and G. Klee *et al*., 2006. Mechanisms of postprandial hyperglycemia in elderly men and women: Gender specific differences in insulin secretion and action. Diabetes, 55: 2001-2014.

Cobelli, C. and A. Ruggeri, 1983. Evaluation of portal/peripheral route and of algorithms for insulin delivery in the closed-loop control of glucose in diabetes-A modeling study. IEEE Trans. Biomed. Eng., BME-30: 93-103.

Cobelli, P.C. and A. Mari, 1983. Validation of mathematical models of complex endocrine-metabolic systems. A case study on a model of glucose regulation. Med. Biol. Eng. Comput., 21: 390-399.

Del Favero, S., G. Pillonetto, C. Cobelli and G. de Nicolao, 2011. A novel nonparametric approach for the identification of the glucose-insulin system in Type 1 diabetic patients. Proceedings of the 18th IFAC World Congress, August 28-September 2, 2011, Milano, Italy, pp: 8340-8346.

Hariharan, G. and K. Kannan, 2009. Haar wavelet method for solving cahn-allen equation. Applied Math. Sci., 3: 2523-2533.

Hariharan, G., K. Kannan and K.R. Sharma, 2009a. Haar wavelet in estimating depth profile of soil temperature. Appllied Math. Comput., 210: 119-125.

Hariharan, G., K. Kannan and K.R. Sharma, 2009b. Haar wavelet method for solving Fisher's equation. Applied Math. Comput., 211: 284-292.

Hariharan, G. and K. Kannan, 2010a. A comparison of Haar wavelet and adomain decomposition method for solving one-dimensional reaction-diffusion equations. Int. J. Applied Math. Comput., 2: 50-61.

Hariharan, G. and K. Kannan, 2010b. A comparative study of a haar wavelet method and a restrictive taylor's series method for solving convection-diffusion equations. Int. J. Comput. Methods Eng. Sci. Mech., 11: 173-184.

Hariharan, G. and K. Kannan, 2010c. Haar wavelet method for solving FitzHugh-Nagumo equation. World Acad. Sci. Eng. Technol., 43: 560-564.

Hovorka, R., V. Canonico, L.J. Chassin, U. Haueter and M. Massi-Benedetti *et al*., 2004. Nonlinear model predictive control of glucose concentration in subjects with type 1 diabetes. Physiol. Meas., 25: 905-920.

Lehmann, E.D. and T. Deutsch, 1992. A physiological model of glucose-insulin interaction in type 1 diabetes mellitus. J. Biomed. Eng., 14: 235-242.

Lepik, U., 2008a. Solving differential and integral equations by the Haar wavelet method: Revisited. Int. J. Math. Comput., 1: 43-52.

Lepik, U., 2008b. Haar wavelet method for solving higher order differential equations. Int. J. Math. Comput., 1: 84-94.

Lepik, U., 2008c. Solving integral and differential equations by the aid of non-uniform Haar wavelets. Applied Math. Comput., 198: 326-332.

Lepik, U., 2011. Solving PDEs with the aid of two-dimensional Haar wavelets. Comput. Math. Appl., 61: 1873-1879.

Man, C.D., M. Camilleri and C. Cobelli, 2006. A system model of oral glucose absorption: Validation on gold standard data. IEEE Trans. Biomed. Eng., 53: 2472-2478.

Man, C.D., R.A. Rizza and C. Cobelli, 2007. Meal simulation model of the glucose-insulin system. IEEE Trans. Biomed. Eng., 54: 1740-1749.

Pillonetto, G., G. Sparacino and C. Cobelli, 2001. Reconstructing insulin secretion rate after a glucose stimulus by an improved stochastic deconvolution method. IEEE Trans. Biomed. Eng., 48: 1352-1354.

Salzsieder, E., G. Albrecht, U. Fischer and E.J. Freyse, 1985. Kinetic modeling of the glucoregulatory system to improve insulin therapy. IEEE Trans. Biomed. Eng., BME-32: 846-855.

Sorensen, J.T., 1985. A physiologic model of glucose metabolism in man and its use to design and assess improved insulin therapies for diabetes. Ph.D. Thesis, Chemical Engineering Department, Massachusetts Institute of Technology, Cambridge, UK.

Taylor, R., I. Magnusson, D.L. Rothman, G.W. Cline, A. Caumo, C. Cobelli and G.I. Shulman, 1996. Direct assessment of liver glycogen storage by 13C nuclear magnetic resonance spectroscopy and regulation of glucose homeostasis after a mixed meal in normal subjects. J. Clin. Invest., 97: 126-132.

Vicini, P., A. Caumo and C. Cobelli, 1997. The hot IVGTT two-compartment minimal model: Indexes of glucose effectiveness and insulin sensitivity. Am. J. Physiol., 273: E1024-E1032.

Vicini, P., A. Caumo and C. Cobelli, 1999. Glucose effectiveness and insulin sensitivity from the minimal models: Consequences of undermodeling assessed by Monte Carlo simulation. IEEE Trans. Biomed. Eng., 46: 130-137.