Modeling and Synthesis of Human Insulin Secretion Mechanism Using CAD

Elhassan A.[1], Alzubaidi L.[1], Al Ghazo J.[1]

Abstract. **In this paper, the modeling and synthesis of human Insulin Hormone Secretion Mechanism is accomplished using VHDL and FPGAs technologies. A mathematical model is developed and analyzed using Matlab and Least-Square fitting algorithm. C++ is used to model the behavior of Insulin secretion in humans and converted to VHDL. Results are verified then the mechanism is realized on a Xilinx FPGAs chip. This chip is then tested with simulated input and its behavior is deemed consistent with the mathematical model. The chip is therefore an identical replica of the Human Insulin Secretion Mechanism.**

Keywords: **Computer Aided Design (CAD), FPGAs, Glucagon, Glucose, VHDL, Xilinx.**

1. Introduction

When evaluating new drugs or treatment techniques for common diseases in animals or humans, there are numerous benefits inherent in the availability and use of artificial or synthetic systems that mimic biological mechanisms and functions. These benefits range from costs to ethics and make it much more feasible for new drugs and innovative disease treatment techniques to be assessed risk-free [1] and [3].

Field Programmable Gate Arrays (FPGAs) are a new technology that provides users programmability in the field. They contain arrays of Configurable Logic Blocks (CLBs) that can be programmed to realize different designs. FPGA families differ by their chip-level architecture and by the granularity of the function unit and intra- and inter-chip wiring organizations. Because of the short turnaround time and low cost, there is increased interest in system prototyping using FPGAs [4]. Along with the right programming environment such as VHDL, FPGAs are a very powerful tool for the design and testing of system prototypes.

Manuscript received December 5th 2011; revised January 7th 2012.

[1] Elhassan A., Alzubaidi L., and Al Ghazo J.

The three authors obtained their Ph.D. qualifications from the UK, Austria and USA respectively. Currently, all three are at:

College of Computer Engineering & Science
Prince Muhammad bin Fahd University
Al-Khobar, Saudi Arabia
aelhassan@pmu.edu.sa

VHDL is used to model the secretion mechanism of the Insulin hormone in humans; including the effects of Glucose and Glucagon levels. Xilinx tools are utilized to realize the model onto a FPGA chip. VHDL tools can model the system and realize it onto Integrated Circuit. The model can be simulated and displayed on computer screens to examine the results. Once the results satisfy the users, CAD tools are used to implement the design and produce a bit file to program the FPGAs chip. Once programmed, the FPGAs chip mimics the system.

In this paper, we introduce and demonstrate a technique for the modeling, design and simulation of the behavior of the Insulin hormone in humans. We design a compact integrated circuit chip using various Computer Aided Design (CAD) tools including hardware-descriptive language techniques including Verilog /VHDL); which are hardware description languages to design digital logic using FPGAs. FPGAs provide optimal device utilization through conservation of board space and system power.

The applications for this technology are wide and varying; by offering a platform to simulate the behavior of human Insulin levels in response to varying conditions and drugs, it is hoped that a lot more can be learned about Insulin and new drugs can be produced to help regulate this hormone in humans with diabetes and other medical conditions in an ethical way that preserves the rights and dignity of human subjects.

The chip introduced in this paper can be used in 2 distinct ways:

- By connecting the chip to a human subject, it can receive electrical signals from sensors attached to various regions of the body such as brain, heart, or muscles. These analog signals are converted using an Analog-to-Digital (A/D) converter. The effect of various drugs on the body is thus detected by the sensors and the output signals of the sensors are transmitted to the input pins of the chip. The output pins of the chip display the output of the mechanism for the given input signals. The output signals can be re-converted to analog using Digital-to-Analog (D/A) converters. This is illustrated in Fig.1.

ISBN: 978-988-19251-1-4
ISSN: 2078-0958 (Print); ISSN: 2078-0966 (Online)

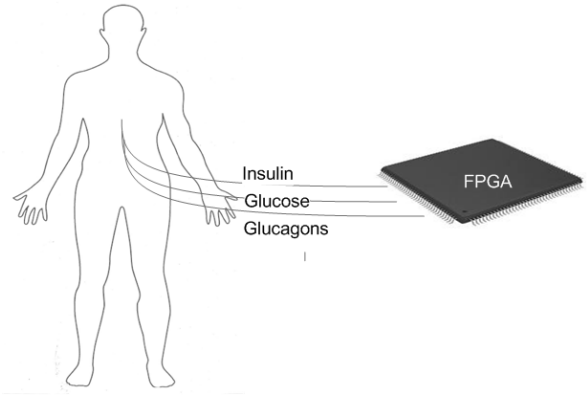

Fig. 1. The FPGAs chip with a human subject

- The other option excludes the human subject from the setup and relies instead on signal/function generators to simulate the human body output sensors, thus allowing the realized mechanism on the chip to be tested extensively and ethically in a lab environment with no human contact. This is illustrated in Fig. 2.

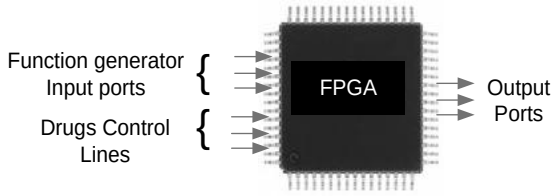

Fig. 2. The FPGAs chip with no human subject

Blood Glucose and Insulin

For their energy needs, the cells in our bodies rely on the breakdown of Glucose which is absorbed from food via the intestines and consequently circulated via the blood stream.

Because food intake, and hence Glucose levels in the blood stream are not constant, it is imperative that this is regulated, hence our bodies store (synthesize) [11, 13] excess Glucose in the muscles and liver as Glycogen, sometimes referred to as animal starch [10]. This can later be called upon (re-synthesized) when there is a shortage of Glucose that is not obtainable from food.

The Glucose -to-Glycogen transformation is essential to prevent Glucose overdose in the cell, for example after meals, the Glycogen-to-Glucose transformation is essential to prevent Glucose shortages in the cell, for example overnight.

To achieve the target of a constant blood-Glucose level, our bodies rely on two hormones produced in the Pancreas that have opposite effects: Insulin and Glucagon.

Insulin, which is a protein hormone that carries 51 amino acids and originates in the Pancreas, is required by almost all of the body's cells to prevent excess Glucose. Insulin plays a particularly significant role in the control of Glucose levels in liver, and muscle cells. For these cells, Insulin is the catalyst in the Glucose -to-Glycogen transformation process (synthesis).

There are other functions that are triggered or regulated by Insulin including the formation of fats from fatty acids within fat cells, the creation of proteins from amino acids and the prevention of the liver and kidneys from making Glucose from intermediate compounds of metabolic pathways (*gluconeogenesis*). These are beyond the scope of this work and shall be disregarded at this; this is in addition to the assumptions in section 2 below.

To sum up, the post-meal Glucose level spikes (*hyperglycemia*) are effectively countered with corresponding Insulin increments [12] while extreme drops in Glucose levels (*hypoglycemia*) due to fasting, starvation, sleep, low-carbohydrate diet or intense exercise are countered with Glucagon, which is another hormone secreted by the Pancreas, that raises blood Glucose levels. Hence, its effect is opposite to that of Insulin [13].

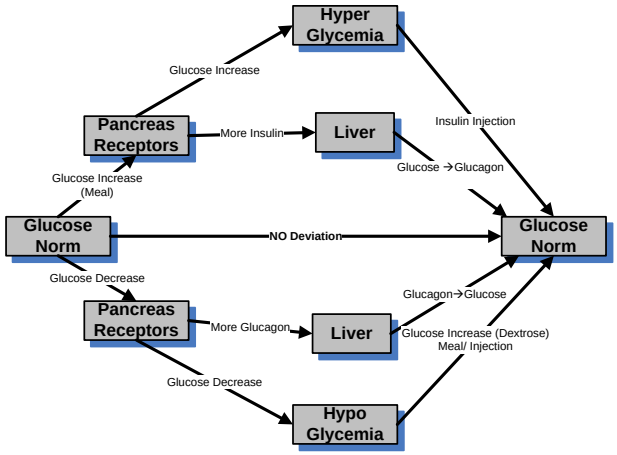

Fig. 3. Insulin & Glucagon as Glucose Controls

2. Background Work & Assumptions

This work is inspired by and builds upon similar work undertaken earlier by [1, 2 & 3] which utilized VHDL, FPGAs and other hardware realization tools to model, build and test an integrated chip that mimics the behavioral patterns of the Human Growth Hormone (HRH) amongst others.

In terms of assumptions, the writers understand, but will sidetrack factors including: Insulin level variations by test region (abdomen vs. extremities vs. brain vs. liver) or the effect of factors (like growth hormone or deficiency thereof) on the levels of Insulin [6]. The effect of other non-biological factors (e.g., alcoholism) are also acknowledged but not covered by this work [7].

The main factor that plays a significant role on the observed behavior pattern of Insulin levels in plasma is the effect of meals and time of day/night on this measurement [8]. The raw data used for this work shows the behavior of Insulin over a time-span of 24 hours, hence this is the time-span

ISBN: 978-988-19251-1-4
ISSN: 2078-0958 (Print); ISSN: 2078-0966 (Online)

with which this work is concerned. For a longer time-span, further work will be required to ascertain the existence of additional patterns of behavior (which will not be covered here) or merely cyclical patterns of behavior (which will implicitly be covered). Other restrictions to the mechanism parameters here exclude the effects of fasting on Insulin release/levels [9].

These restrictions are necessary for the purpose of focusing on the salient point of the research; which is the modeling, design, implementation and simulation of an FPGAs chip that mimics the behavior of Insulin in human plasma. If this work is successful then it will provide impetus for further studies with those additional factors included.

3. Process

The steps that were undertaken in this research are illustrated in Fig. 4 and are explained in this section. The technology of FPGAs provides a programmable interface to enable us to synthesize complex behavior models. FPGAs chips Configurable Logic Blocks (CLBs) can be tailored to represent different models [1].

The three distinguishing features of FPGAs chip: ***architecture, function-unit granularity and intra/inter-chip wiring organization*** can be fine-tuned to represent complex models in a fairly short period of time. Combined with VHDL tools, we have a powerful tool to represent and synthesize our mathematical model.

The input to Matlab is the raw data representing the secretion patterns of Insulin (in response to fluctuations in

Glucose & Glucagon levels). The model in Fig. 5 shows this behavior over a 24-hour time span.

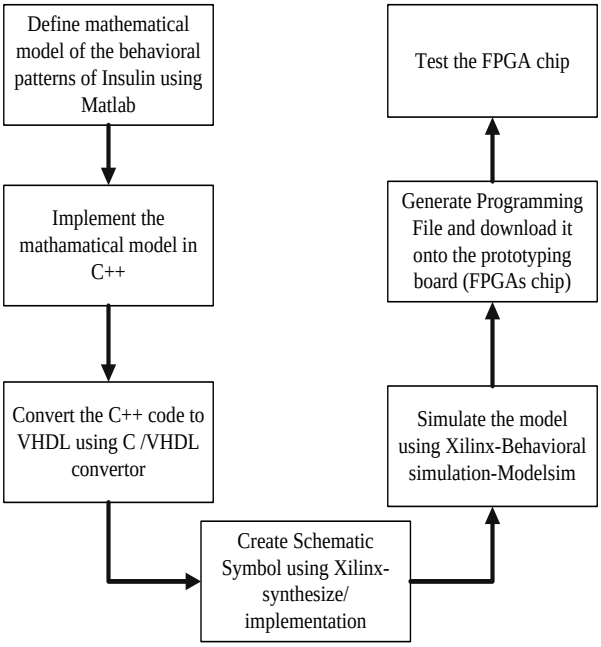

Fig. 4. Mathematical Models to FPGA Chip Model Process

After several trials with the graphics facility using Matlab, the model was fitted using the ***non-linear least-square*** [14,15] algorithm, as shown in the (Eq.'s 1, 2, and 3) below:

$$\boldsymbol{Insulin}\,(\boldsymbol{t}) = \boldsymbol{a1} * \boldsymbol{sin}(\boldsymbol{b1} * \boldsymbol{t} + \boldsymbol{c1}) + \boldsymbol{a2} * \boldsymbol{sin}(\boldsymbol{b2} * \boldsymbol{t} + \boldsymbol{c2}) + \boldsymbol{a3} * \boldsymbol{sin}(\boldsymbol{b3} * \boldsymbol{t} + \boldsymbol{c3}) + \boldsymbol{a4} * \boldsymbol{sin}(\boldsymbol{b4} * \boldsymbol{t} + \boldsymbol{c4}) + \boldsymbol{a5} * \boldsymbol{sin}(\boldsymbol{b5} * \boldsymbol{t} + \boldsymbol{c5}); \quad \text{Eq. 1}$$

$$\boldsymbol{Glucose}\,(\boldsymbol{t}) = \boldsymbol{ga1} * \boldsymbol{sin}(\boldsymbol{gb1} * \boldsymbol{t} + \boldsymbol{gc1}) + \boldsymbol{ga2} * \boldsymbol{sin}(\boldsymbol{gb2} * \boldsymbol{t} + \boldsymbol{gc2}) + \boldsymbol{ga3} * \boldsymbol{sin}(\boldsymbol{gb3} * \boldsymbol{t} + \boldsymbol{gc3}) + \boldsymbol{ga4} * \boldsymbol{sin}(\boldsymbol{gb4} * \boldsymbol{t} + \boldsymbol{gc4}) + \boldsymbol{ga5} * \boldsymbol{sin}(\boldsymbol{gb5} * \boldsymbol{t} + \boldsymbol{gc5}) + \boldsymbol{ga6} * \boldsymbol{sin}(\boldsymbol{gb6} * \boldsymbol{t} + \boldsymbol{gc6}) + \boldsymbol{ga7} * \boldsymbol{sin}(\boldsymbol{gb7} * \boldsymbol{t} + \boldsymbol{gc7}) + \boldsymbol{ga8} * \boldsymbol{sin}(\boldsymbol{gb8} * \boldsymbol{t} + \boldsymbol{gc8}); \quad \text{Eq. 2}$$

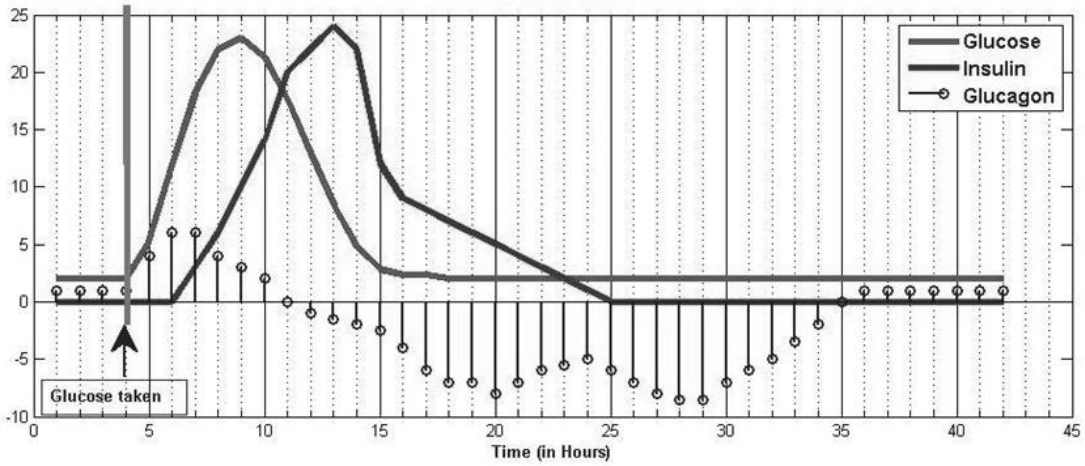

Fig. 5. Insulin, Glucose & Glucagon Production in the blood stream

ISBN: 978-988-19251-1-4
ISSN: 2078-0958 (Print); ISSN: 2078-0966 (Online)

$$\begin{aligned}\boldsymbol{Glucagon}\,(\boldsymbol{t}) = {} & \boldsymbol{gga1} * \boldsymbol{sin}(\boldsymbol{ggb1} * \boldsymbol{t} + \boldsymbol{ggc1}) \\ & + \boldsymbol{gga2} * \boldsymbol{sin}(\boldsymbol{ggb2} * \boldsymbol{t} + \boldsymbol{ggc2}) \\ & + \boldsymbol{gga3} * \boldsymbol{sin}(\boldsymbol{ggb3} * \boldsymbol{t} + \boldsymbol{ggc3}) \\ & + \boldsymbol{gga4} * \boldsymbol{sin}(\boldsymbol{ggb4} * \boldsymbol{t} + \boldsymbol{ggc4}) \\ & + \boldsymbol{gga5} * \boldsymbol{sin}(\boldsymbol{ggb5} * \boldsymbol{t} \\ & + \boldsymbol{ggc5}) + \boldsymbol{gga6} * \boldsymbol{sin}(\boldsymbol{ggb6} * \boldsymbol{t} \\ & + \boldsymbol{ggc6}) + \boldsymbol{gga7} * \boldsymbol{sin}(\boldsymbol{ggb7} * \boldsymbol{t} \\ & + \boldsymbol{ggc7}) + \boldsymbol{gga8} * \boldsymbol{sin}(\boldsymbol{ggb8} * \boldsymbol{t} \\ & + \boldsymbol{ggc8});\end{aligned} \qquad \text{Eq. 3}$$

where:

T	time in hours
a1, a2, a3, a4, a5	fitting parameters for Insulin in mg/dl (milligram /deciliter)
b1, b2, b3, b4, b5	dimensionless fitting parameters for Insulin
c1, c2, c3, c4, c5	fitting parameters for Insulin in hours
ga1, ga2, ga3, ga4, ga5, ga6, ga7, ga8	fitting parameters for Glucose in mg/dl
gb1, gb2, gb3, gb4, gb5, gb6, gb7, gb8	dimensionless fitting parameters for Glucose
gc1, gc2, gc3, gc4, gc5, gc6, gc7, gc8	fitting parameters for Glucose in hours
gga1, gga2, gga3, gga4, gga5, gga6, gga7, gga8	fitting parameters for Glucagon in mg/dl
ggb1, ggb2, ggb3, ggb4, ggb5, ggb6, ggb7, ggb8	dimensionless fitting parameters for Glucagon
ggc1, ggc2, ggc3, ggc4, ggc5, ggc6, ggc7, ggc8	fitting parameters for Glucagon in hours

Eq's 1, 2 & 3 – Fitted Mathematical Model representing the Dynamic Behavior Patterns of Insulin, Glucose & Glucagon Respectively

A C++ program was written in order to **implement the mathematical model** of Insulin secretion including the link to Glucose and Glucagon, the program was executed using the values of the fitting parameters (which were generated by Matlab).

The VHDL code was then generated using **C to VHDL program** (Spark 1.3), wherein 60% of the code was generated by the convertor, the generated code was then edited for correction and further optimization, the VHDL code was subsequently compiled using the Xilinx toolset within Matlab (Fig. 6),

The compiled VHDL code was used to generate the **schematic diagram** using Xilinx which can also be used to realize the implementation of the model into Field programmable gate array (FPGAs). The schematic diagram in Fig. 7 was generated from the VHDL code below which describes the input and output pins of the developed model.

```
ENTITY Insulin_func IS
port(
        clock :          IN      std_logic ;
        Glucose :        OUT     real ;
        Insulin :        OUT     real;
        Glucagon :       OUT     real;
        Time (hours) :   INOUT   real;
        Glucose _taken:  INOUT   std_logic;
        done :           INOUT   std_logic );
END Insulin_func;
```

where:

clock:	input in hours
time_hours:	count the number of pulses
Glucose :	behavior of Glucose
Insulin :	behavior of Insulin
Glucagon :	behavior of Glucagon
Glucose _taken:	a trigger to start the process
done:	indicates the end of the process

Fig. 6. VHDL Code generated by Spark 1.3

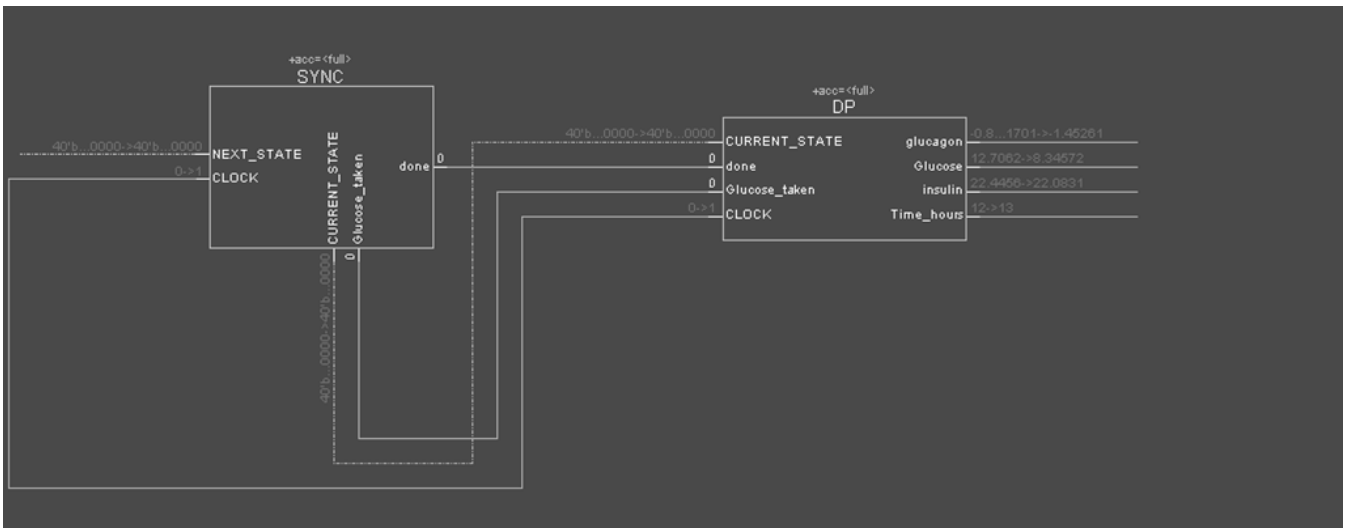

Fig. 7. Schematic Diagram of the developed integrated circuit

ISBN: 978-988-19251-1-4
ISSN: 2078-0958 (Print); ISSN: 2078-0966 (Online)

4. Results - Simulation of the Behavioral Model using Modelsim

The ModelSim toolkit is used for timing simulation which allows us to take the VHDL file of the previous step and use it to simulate the behavioral model.

The following steps describe the simulation process:

i. The process will be started by a trigger corresponding to the Glucose_taken input pin.
ii. The Glucose starts to increase.
iii. This is followed by corresponding increases in Insulin and Glucagon (output pins).
iv. Glucose reaches the MAX value (23 mg/dl) after 5 hours; Insulin reaches the MAX value (24.5 mg/dl) after 14 hours. These values correspond to the data represented in Fig. 5.

The results of the simulation are illustrated in Fig. 8 (a & b) with each pulse corresponding to a single hour. The output of this process is consistent with the simulation results and the model of Fig. 5 above as illustrated in Table 1 which shows the raw data for the this model.

Finally, a bit-file was generated (using Xilinx toolset) and loaded to the FPGAs chip, after testing the chip with this file, the observed results at the output pins of the chip were found to be consistent with the results of the simulation process in Fig's 8a and 8b.

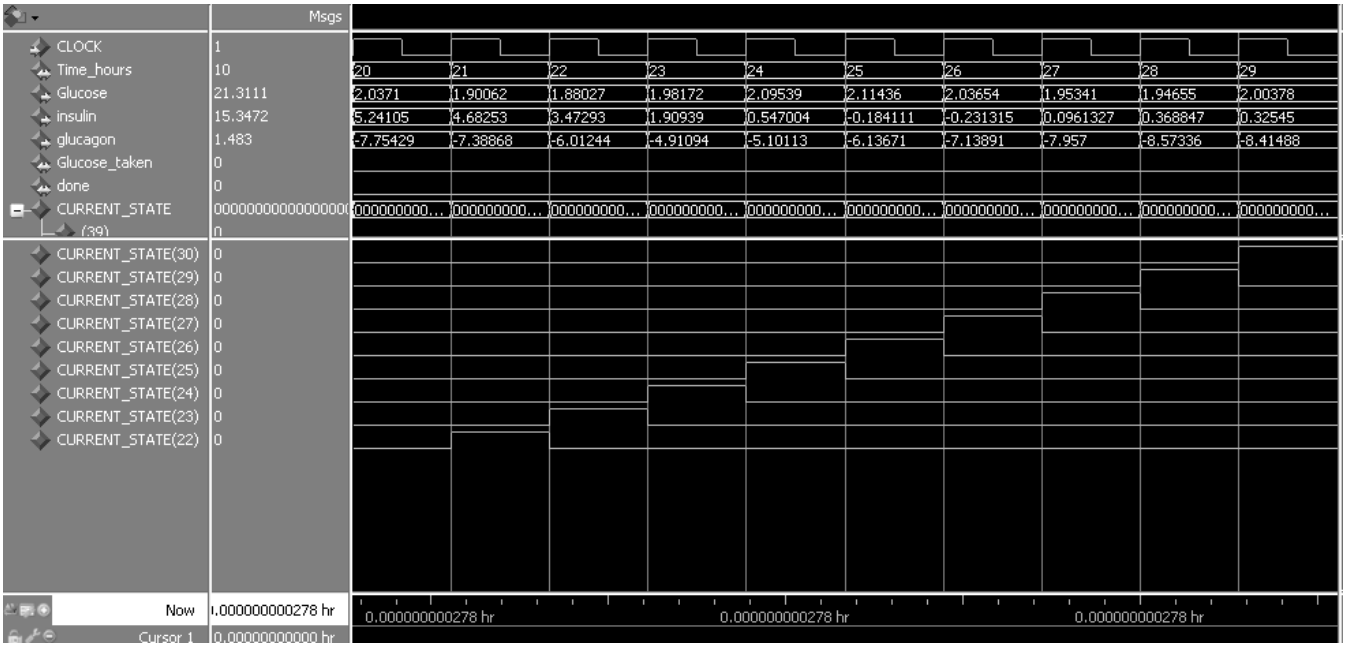

Fig. 8a. The simulation results of ModelSim – 20HRS to 29HRS

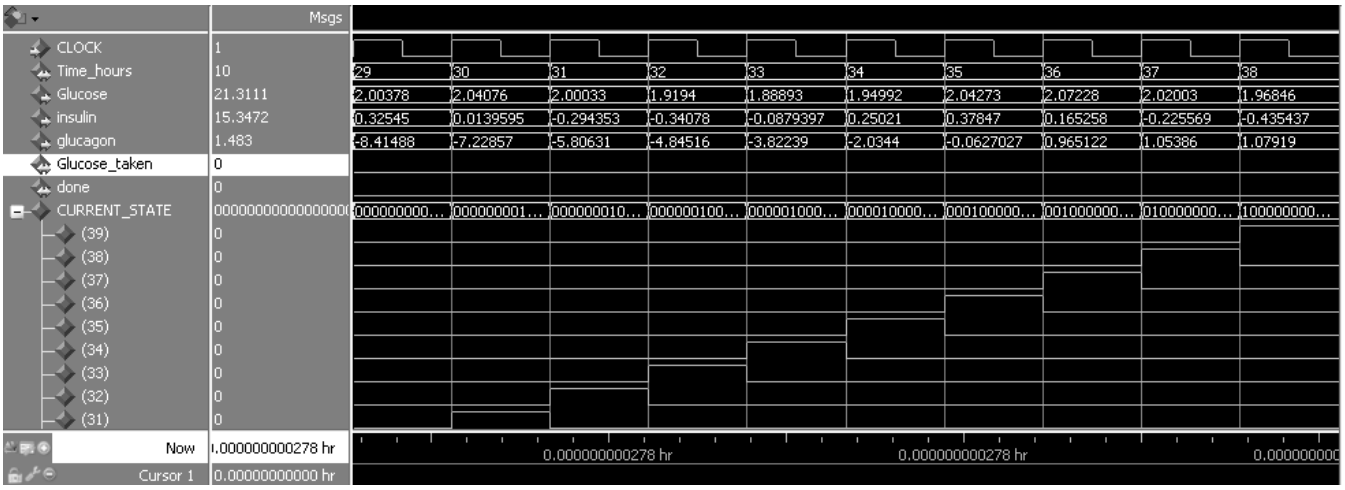

Fig. 8b. The simulation results of ModelSim – 29HRS to 38HRS

ISBN: 978-988-19251-1-4
ISSN: 2078-0958 (Print); ISSN: 2078-0966 (Online)

5. Conclusions & Future Work

We have successfully formulated a mathematical model that describes the Insulin secretion patterns in humans, then used this model to generate a blueprint for a microchip and generated a bit file to the prototyping board and produced some simulated hormone level figures from the chip.

There are a few restrictions with which this work started, some of which can be overcome with similar further work. Some of the areas that could be re-addressed include the mathematical model; the model used in this work represents the behavior of Insulin over a determined period of time as an observed and recorded pattern, further work is needed here to present a more interactive (dynamic) behavior model and hence, chip design which is even truer to form.

Other work limitations have been listed above (section 2) and constitute good opportunities for further investigation which will be addressed in future work.

Table 1 the simulation outputs of the model

Clock #	Glucose	**Insulin**	Glucagon
1	1.94022	0.139586	0.988018
2	2.20565	-0.242261	0.857824
3	1.53008	-0.097909	0.960493
4	2.29797	0.0908576	1.87422
5	5.83729	0.210925	3.8285
6	11.6034	0.667952	5.61706
7	17.6654	2.18048	5.77227
8	21.9154	5.30944	4.40463
9	23.1252	9.98854	2.77541
10	21.3066	15.3459	1.48028
11	17.4043	19.959	0.243453
12	12.7072	22.4435	-0.874752
13	8.34912	22.0807	-1.45498
14	5.04995	19.1528	-1.8151
15	3.05548	14.8044	-2.80759
16	2.19984	10.5044	-4.42101
17	2.05548	7.38829	-5.76012
18	2.14783	5.82138	-6.50887
19	2.16259	5.38369	-7.18259
20	2.03941	5.24438	-7.75458
21	1.89982	4.68526	-7.38991
22	1.87462	3.47557	-6.01495
23	1.9719	1.91258	-4.91322
24	2.08417	0.550801	-5.10151
25	2.10502	-0.180659	-6.13497
26	2.03126	-0.23	-7.13618
27	1.95288	0.0934501	-7.95456
28	1.95068	0.361243	-8.57145
29	2.01251	0.313617	-8.41217
30	2.05398	0.000135618	-7.22304
31	2.01693	-0.307231	-5.79735
32	1.93662	-0.350275	-4.8349
33	1.903	-0.0930237	-3.81382
34	1.9579	0.249009	-2.02803
35	2.04418	0.379735	-0.056115
36	2.06932	0.167725	0.973931
37	2.01552	-0.222227	1.06367

REFERENCES

[1] Alghazo, J., Akaaboune, A. , Botros, N., "Modelling, Synthesis and Realization of Hgh Mechanism UsingVHDL and FPGAs," International Journal of Modeling and Simulation , 2005.

[2] Alghazo J., Aboueida W. and Rabadi W. "Modeling and Synthesis of Thyroid Hormones Secretion Mechanism Using CAD tools" IMIBE594

[3] Botros, N., Akaaboune, M., Alghazo, J., and Alhreish, M., "Hardware Realization of Biological Mechanisms Using VHDL and FPGAs," Proceedings of the Third International Conference on Modeling and Simulation of Microsystems, San Diego, CA, USA, March 27-30, pp. 233-236, 2000.

[4] Botros, N., Akaaboune, A., Alghazo, J., " Modeling and Synthesis of Human Growth Hormone Secretion Mechanism Using CAD Tools," Proceedings of the 29th annual Conference of the IEEE Industrial Electronics Society, Roanoke, Virginia, USA, November 2-6, pp. 2429-2434, 2003.

[5] William F. Ganong, *Review of Medical Physiology, 15th edition.* Univ of California, San Francisco: Prentice Hall International Inc, 1991.

[6] Groop L., Segerlantz M. and Bramnert M. "Insulin Sensitivity in Adults with Growth Hormone Deficiency and Effect of Growth Hormone Treatment". Horm Res 2005;64(suppl 3):45–50. On-line January 2006

[7] Addolorato G., Leggio L., Hilemacher T., Kraus T., Jerlhag E., Bleich S. "Hormones and drinking behavior: New findings on ghrelin, Insulin, leptin and volume-regulating hormones.
An ESBRA Symposium report". Drug and Alcohol Review (March 2009), 28, 160–165. DOI: 10.1111/j.1465-3362.2008.00023.x

[8] Malherbe C., de Gasparo M. , de Hertogh R. and Hoem J. J. "Circadian variations of blood sugar and plasma Insulin levels in man". Presented at the Fourth Annual Meeting of the European Association for the Study of Diabetes, Louvain, July 23, 1968.
Online in DIABETOLOGIA Volume 5, Number 6, 397-404, DOI: 10.1007/BF00427978

[9] Juhl C., Grofte T., Butler P., Veldhuis J., Schmitz O. and Pørksen N. "Effects of Fasting on Physiologically Pulsatile Insulin Release in Healthy Humans".
Diabetes. February 2002 vol. 51 no. suppl 1 S255-S25, http://diabetes.diabetesjournals.org/content/51/suppl_1/S255.full

[10] Saladin, Kenneth S. "Anatomy and Physiology".
McGraw-Hill, 2007.

[11] Pedersen DJ, Lessard SJ, Coffey VG, et al. (July 2008). "High rates of muscle Glycogen resynthesis after exhaustive exercise when carbohydrate is coingested with caffeine".
Journal of Applied Physiology 105 (1): 7–13

[12] Freudenrich C., Ph.D. "Diabetes Overview" 22 June 2001. HowStuffWorks.com.
http://health.howstuffworks.com/diseasesconditions/diabetes/diabetes.htm 23 October 2011

[13] Reece J, Campbell N. (2002) "Biology". San Francisco: Benjamin Cummings. ISBN 0-8053-6624-5.

[14] Kelley C. T. "Iterative Methods for Optimization", SIAM Frontiers in Applied Mathematics, no 18, 1999

[15] Strutz T. "Data Fitting and Uncertainty (A practical introduction to weighted least squares and beyond)". Vieweg+Teubner, ISBN 978-3-8348-1022-9

ISBN: 978-988-19251-1-4
ISSN: 2078-0958 (Print); ISSN: 2078-0966 (Online)