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# VHDL implementation of glucose control and monitor algorithm for Diabetes

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***ABSTRACT***

***Neural Networks ability in generalization and reconfigurable utilizing support a solid base to prospering critical embedded scheme, capable of efficiently adapt itself as requirements alteration. Different level adaptation, from physical level up to system level, can be combined to support efficient solutions utilizing FPGA. In this paper, FPGA exercise of a discrete-time inverse (DTI) neural network optimal mastery for trajectory following is suggested to regulate glucose level for type 1 diabetes mellitus (T1DM) patients. This study presents an adaptive, patient-specific control strategy for glucose regulation based on reinforcement learning and more specifically on the Actor-Critic (AC) learning approach. The control algorithm provides daily updates of the basal rate and insulin-to-carbohydrate (IC) ratio in order to optimize glucose regulation. A method for the automatic and personalized initialization of the control algorithm is designed based on the estimation of the transfer entropy (TE) between insulin and glucose signals. We present a VHDL implementation of the Biostator II control algorithm.A virtual patient is implemented on a PC host computer, which is interdependent with the FPGA masteries. This mastery constitutes a step forward to prosper an autonomous artificial pancreas.***

**Keywords**

**Glucose level, T1DM, recurrent high-order neural network (RHONN).**

## 1.INTRODUCTION

Diabetes mellitus (DM) is one of the main threats to human health in the 21st century. In 2013 more than 382 million people worldwide were affected by DM and the estimated global expenditures on healthcare for diabetes were US$548 billion, according to the International Diabetes Federation. TIDM is a chronic illness characterized by the body inability to produce insulin due to the autoimmune destruction of the beta cells on the pancreas.

Onset most often occurs in childhood, but the disease can also prosper in adults in their late 30s and early 40s. Considering all the problems related to DM, the prosper of an artificial pancreas is a challenging task. Progress has been important, related to insulin pumps (actuators) and glucose sensors, improving the quality life of patients; the Medtronic MiniMed Paradigm Revel Insulin Pump (Fridley, MN, USA) improves the quality life of patients with DM.

The simultaneous use of Continuous Glucose Monitors (CGMs) for measurement of glucose levels and pumps for the subcutaneous infusion of insulin is one of the fundamental

therapeutic schemes for individuals suffering from Type 1 Diabetes (T1D) mellitus. A control algorithm able to estimate the appropriate per patient insulin dose to be infused by the pump based on glucose data provided by the CGM could lead to the development of an Artificial Pancreas (AP). Various approaches for such control algorithms have been proposed including Proportional-Integral-Derivative (PID) control [1]-[4], Model Predictive Control (MPC) [4]-[10], run-to-run algorithms [11]-[14] and MD-Logic (MDL) control [15]-[16].

This device has a tool to calculate the amount of insulin required; however, the patient still has to take decisions, because the pump does not do everything by itself. This paper centres on the FPGA exercise of a neural identifier for insulin-glucose dynamics on TIDM patients. There already exist publications about modelling of insulin glucose dynamics as mentioned in (references there in).

However, it is difficult to apply deterministic methods to estimate the insulin release based on these models, because of parameter uncertainties and due to the complexity and the cost associated with the measurements in order to determine the related parameters. In, a model based on neural networks (NN), specifically, on the recurrent multilayer perception (RMLP) is suggested.

We present a VHDL implementation of the Biostator II control algorithm [2] for intensive glucose control in the hospital, optimized. glucose sensing and insulin delivery. Selection of the Biostator II was motivated by the fact that it has been the most clinically validated algorithm in the past for this type of application. This implementation is aimed to be the core element of a CMOS ASIC (Application Specific Integrated Circuit) integrating glucose sensor instrumentation and communication protocol for control.

The ASIC implementation is to be used to create a portable, reliable and affordable system for safe and effective control of blood glucose in of the hospitalized patient using commercially available subcutaneous continuous glucose sensors and intravenous insulin pumps. The VHDL algorithm has been successfully implemented and evaluated using a hardware-in-the loop platform whereby the commercially available simulator of a Type 1 Diabetes Mellitus (T1DM) subject (University of Virginia, VA, USA) [5] serves as the patient model and a National Instruments DAC is calibrated to perform as a glucose sensor with an FPGA (Field Programmable Gate Array) board (Altera DE2) used to test the algorithm in real time.

## II.Literature survey

Extracorporeal and implantable insulin pumps have been in service for over 15 yr [1], [2]. Initially these devices had a single delivery rate, but technological advances have allowed a wide variety of programmable and variable-rate infusion pumps to be available currently [3]. Research shows [4], [5] continuous infusion and programmable pumps are effective for insulin therapy. By utilizing a variable rate pump in a closed-loop framework, further improvements in glucose control and normalization of the glucose distribution in the body are possible.

Current blood glucose monitoring is accomplished through invasive methods, such as a finger prick, but use of a noninvasive monitor would increase patient comfort and therefore, compliance to the insulin therapy. An implantable glucose concentration sensor would measure diabetic patient blood glucose levels online and eliminate the patient from the feedback loop.

Significant work has been performed on the development of an implantable glucose sensor [6]–[8], and the duration of *in vivo* sensor reliability continues to increase. A significant effort has been put forth toward the development of a closed-loop algorithm for blood glucose control [9]–[12]. These approaches have utilized almost exclusively feedback control to maintain normoglycemia, even for the purpose of disturbance rejection. This paper takes a different approach, specifically the use of model-based predictive control (MPC).

The unconstrained controller guarantees optimal drug delivery through solution of an optimization problem at each time step. A motivating factor for utilizing this strategy is the success of MPC when applied to other biomedical control problems,

including blood pressure control [13], [14] and anesthesia delivery [15], [16]. This controller architecture is particularly well suited to the multivariable nature of these systems, as well as the inherent constraints involved in the respective control problems. To date, successful controller implementation has been bedside in nature, due to the significant computing power required for the calculations.

Computational power and speed aside, one benefit of using predictive control in place of a classical control algorithm is the estimation of future glucose behavior based on the past insulin inputs, with measurement of the patient's actual glucose levels used as a feedback signal to correct the glucose concentration predictions. As a result, the MPC controller takes action for a predicted hypo- or hyperglycemic excursion well before it occurs, while a feedback-only controller responds after the effect of the disturbance is manifested.

Similar to the other biomedical applications, the human glucose-insulin control problem has inherent input rate and magnitude constraints as well as an output magnitude constraint which MPC can easily handle. The aforementioned feedback controllers require special formulations to compensate for these same types of constraints, and performance degradation can result. Hence, the MPC controller algorithm exhibits a range of appropriate characteristics for the blood glucose control problem.

## III.PROPOSED SYSTEM

One of the major challenges in diabetes regulation is the high inter- and intra-population variability. For this purpose, personalized insulin treatment has been recently highlighted as a crucial goal towards efficient glucose control. This study discusses the use of a novel and online adaptive approach for glucose regulation based on the principles of reinforcement learning and optimal control for personalized diabetes treatment.

In previous work of the Diabetes Technology Research Group [17], an algorithm based on the Actor-Critic (AC) learning has been designed and developed. The algorithm provides daily updates of the average basal rate (BR) and the insulin-to-carbohydrate (IC) ratio towards minimization of hyper-/hypoglycemia. As an extension to this study, a method for the automatic and personalized tuning of the AC based algorithm is proposed based on the estimation of information transfer (IT) between insulin and glucose signals.

### A. The AC algorithm

AC belongs to the class of reinforcement learning (RL) algorithms. RL involves adaptive agents able to optimize their performance over time through interaction with the environment, which may include partially known or unknown dynamics [18]. AC consists of two complementary adaptive agents: the Critic and the Actor, with the former being responsible for the control policy evaluation and the latter for the control policy optimization. AC implementations may vary in the design of both the Actor and the Critic part. An extensive review can be found in [19]. A schematic view of a system controlled by an AC algorithm is shown in Figure 1.

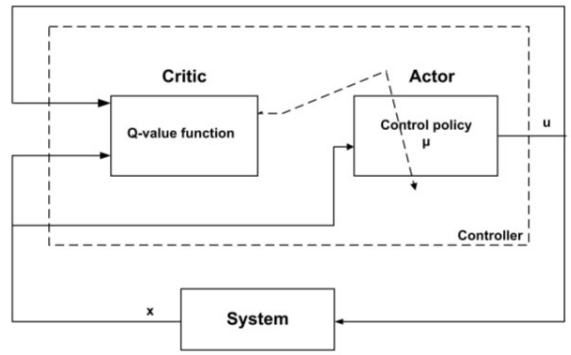


Figure 1: System controlled by an Actor-Critic algorithm

It required a glucose sampling period of 1 minute which has been employed in this work. The amount of insulin required by the subject is given by:

$$IR_{calc} = \begin{cases} IR_1 & \text{if } G_Y - B < 0 \\ IR_1 + IR_2 & \text{if } G_Y - B \geqslant 0 \\ IR_{max} & \text{if } IR_{calc} > IR_{max} \end{cases}$$

where *IRcalc* (mU/min)is the insulin dosing rate, which is equal to *IR*1 when the glucose estimate *GY* (mg/dL) is below the glucose set-point *B* (mg/dL) or equal to *IR*1+*IR*2 when the glucose estimate is above the glucose set-point. The glucose estimate is calculated as:

$$G_Y = 2 \cdot m + (G_4 + G_3 + G_2 + G_1 + G_0)/5$$

Where *G*1 to *G*5 are the last five glucose measurements and *m* is an approximation of the glucose derivative calculated as:

$$m = (2 \cdot G_5 + G_4 - G_2 - 2 \cdot G_1)/10$$

It is important to note that *IRcalc* can only take on values below a predefined maximum insulin infusion rate *IRmax* (mU/min). The insulin dosing rates, *IR*1 and *IR*2, are defined as:

$$IR_1 = \begin{cases} R \cdot \left[\frac{G_Y - B}{Q} + 1\right]^2 & \text{if } \left[\frac{G_Y - B}{Q} + 1\right] \geqslant 0 \\ 0 & \text{if } \left[\frac{G_Y - B}{Q} + 1\right] < 0 \end{cases}$$

$$IR_2 = \begin{cases} R \cdot KR \cdot \frac{m}{1000}(G_Y - B) & \text{if } m \geqslant 0 \\ R \cdot KF \cdot \frac{m}{1000}(G_Y - B) & \text{if } m < 0 \end{cases}$$

Whereby *IR*1 is a nonlinear proportional action and *IR*2 is derivative action. The choice of proportional or derivative control actions is based on the error trend (*GY* −*B*). *Q* is used as a gain for the controller function; *R* is the basal infusion rate (mU/min); *KR* is the constant for rising glycaemia and *KF* is the constant for decreasing glycaemia.

**B.Adaptation for s.c. glucose sensing**

Although continuous glucose sensors have superior accuracy than current available s.c. continuous glucose sensors, they present some important disadvantages that have prevented them from their mainstream utilisation in critical care. These disadvantages include a higher risk of infection and thrombosis; risk of catheter occlusion; a complex and expensive instrumentation and high maintenance needs. On the other hand, s.c. continuous glucose sensors overcome most of these drawbacks and their accuracy and reliability is getting better every year.

They do however contain a delayed response reported to be greater than 10 minutes [6] as the glucose is measured from the interstitial fluid rather than blood. In order to minimise hypoglycemia associated with the delay introduced by s.c. glucose sensing, a safety mechanism was used on top of the controller that suppresses, or reduce, insulin delivery when low glucose values are predicted [7]. This mechanism consists of forecasting the glucose concentration 30 minutes ahead and stopping or reducing the insulin delivery if the glucose levels fall below a predefined threshold. The safety mechanism is defined as:

$$IR_{calc} = \begin{cases} 0 & \text{if } G_{30} < 70 \\ \frac{IR_{calc}}{2} & \text{if } G_{30} < 90 \end{cases}$$

where *G*30 is the glucose value forecasted 30 minutes using the glucose derivative m, and calculated as

$$G_{30} = G_Y + m \cdot 30$$

The parameters of the Biostator II were optimized to achieve good control and whilst minimizing hypoglycemia, for a large patient population using the T1DM simulator. This simulator is a virtual platform used to support the development of the artificial pancreas, which has been proven capable of simulating the glucose-insulin dynamics of a wide cohort of diabetic subjects and is thus suitable for this application. It contains models for commercially available s.c. glucose sensors in addition to subjects with glucose fluctuations similar to what you would observe in a patient in critical care which is sufficient to test the system.

Through this optimisation the only parameter which was required to be changed with respect to the original paper to work subcutaneously [2] was *R* which controls how fast Biostator will brings the glucose to normal levels. *R* was manually tuned to achieve good control through maximizing

the time spent in target and minimising the episodes of hypoglyceamia, not requiring prior data from the subject as would be the case in a critical care scenario.

## IV.PARAMETER VALUES FOR VHDL IMPLEMENTATION

| | B | Q | R | KR | KF | $IR_{max}$ |
|---|---|---|---|---|---|---|
| Adults | 80 | 75 | 7.9 | 165 | 45 | 400 |
| Adolescents | 80 | 75 | 4.5 | 165 | 45 | 400 |
| Precision | Q3 | Q3 | Q3 | Q0 | Q0 | Q3 |

### A.VHDL Implementation of the Biostator II

The Biostator II algorithm was implemented in VHDL to allow direct synthesis for implementation in an ASIC incorporating the glucose sensor front end, and communication stack for the i.v pump.The design and simulation in VHDL we used the Quatrus 2 software package to allow implementation on an FPGA testing. Fixed point numbers were used for the algorithm to reduce the computational complexity and memory requirements. The algorithm uses a 11 bit binary fractional to represent the glucose input, *G*1 in the physiological range of 0 - 511 mg/dl, bits 10-2, with bits 0-1 used for the fractional part, and a 12 bit binary fractional to represent the inulin output rate, *IRcalc*, in the range of 0-511 mU/min, bits 11-3, with bits 0-2 used to increase the accuracy of the fractional part. A 3 bit RAM file component was used to store the required five last glucose measurements. Two std logic parameters were also assigned,one for the Clock and one for the VA, which is a signal responsible for indicating when a new glucose measurement is available.

The rising edge of VA triggers the RAM to store the latest glucose value, from which the last five glucose values are read and used by the algorithm. After *IRcalc* is calculated, these values are shifted to allow the next glucose value to be stored on the next rising edge of VA. The synthesised VHDL implementation of the Biostator II consists of 43 states, requiring 43 clock cycles to compute the result. The complete system uses 2352 logic elements with 176 registers and 36 embedded multipliers.

### B.Automatic tuning of the AC-based algorithm

Assessing causality and IT between signals has been extensively studied and various measures have been proposed. A comprehensive review can be found in [21]. Transfer entropy (TE) is a powerful measure of IT, mainly due to its nonlinear and directional structure, and has found promising application in biomedical signal analysis [22]-[24].
TE measures the information flow from a signal (source) to a signal (target) while it excludes redundant effects coming from other signals. Let $X=\{x_i,\ i=1:n\}$, $Y=\{y_i,\ i=1:n\}$, $Z=\{z_i,\ i=1:n\}$ Be three observed random processes of length. TE estimates the IT from process to , which can be also translated as the amount of knowledge we gain about when we already know , based on the following formula:

$$T_{Y\to X}=\sum_i p(x_i,y_i,z_i)\log\frac{p(x_i|y_i,z_i)}{p(x_i|z_i)}$$

where denotes probability density function (pdf) and is the basis two logarithm. Division with the conditional probability of to excludes the redundant information coming from both and without excluding, though, the possible synergistic contribution of the two signals on [23]. Main challenge in computing (8) is the estimation of the involved pdfs. Several approaches have been proposed for this purpose [21]. One of the most commonly used methods is the fixed data partitioning in which the time-series are partitioned into equi sized bins and the pdfs are approximated as histograms [25]. Expecting that high TE is related to smaller rates of change in the insulin scheme, the initial values of the policy parameter vectors are set to be inversely proportional to the estimated TE per patient as:

$$\theta_0^S(p)=W/TE(p)$$

'P' denotes a specific patient and is a constant.It is manually set as 1 with 1 for the elements related to hyperglycemia and -1 for the elements related to hypoglycemia.

**V. Result and Analysis**

The algorithm was tested on a cohort of 20 subjects, 10 adults and 10 adolescents, each with different glucose-insulin dynamics. The test bench comprised of a scenario whereby three meals (breakfast, lunch and dinner)were given of the course of 24 hours. The employed meal protocol consisted of three meals of 40, 60 and 50 grams of CHO at times 3, 10 and 17 hours from the beginning of the simulation. To achieve more optimal control, a different set of parameters was employed for each population . Target glyceamia is defined to be in the range of 70-180 mg/dL.

The results of the tests on the 20 subjects. What we can see is that the algorithm achieves good control in both cases presenting low risk index with the adults being 98.7% in target with a mean blood glucose of 134.67 mg/dl and the adolescents being 93.56% in target with a mean blood glucose of 126.01 mg/dl. The adolescents achieve slightly lower percentage due to their greater variability in glucose-insulin dynamics, making them harder to control . both populations achieved less 1% time in hypoglyceamia and only being 7% in hyperglyceamia. The example of glucose control and insulin release corresponding to adult subject number 2. show the average results for the adult and adolescent population respectively together with one standard deviation and the extreme values showing that good control is achieved.

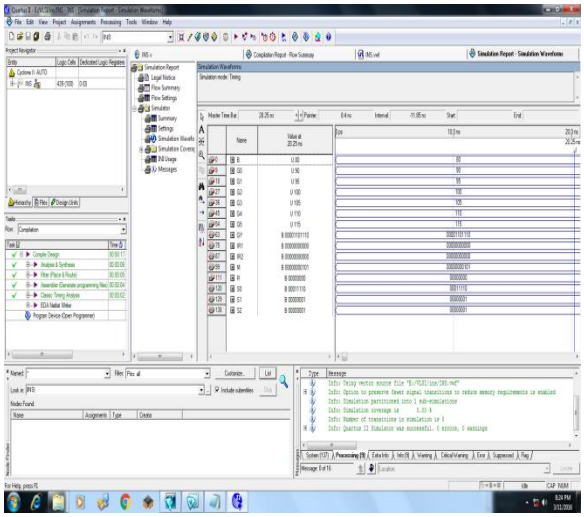

Figure 2:Simulation

**VI.CONCLUSIONS**

An AC-based control algorithm for glucose regulation in T1D has been designed and developed. In order to achieve faster and safer learning process, a novel approach for the automatic and patient-specific initialization of the algorithm, based on the estimation of the TE from insulin to glucose, has been proposed. Significant contribution of this method has been found compared to zero or random initialization especially in the case of children where the initial BR and IC ratio were far from their optimal values. Future work will include investigation of alternative ways for TE estimation and extensive evaluation of the AC control algorithm both in silicon and in clinical practice.

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