International Journal of Artificial Intelligence and Neural Networks – IJAINN
Volume 4 : Issue 3 [ISSN 2250 – 3749]
Publication Date : 30 September, 2014

Glucose-Insulin regulator for Type 1 Diabetes using high order neural networks

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***Abstract*—In this paper a Glucose-Insulin regulator for Type 1 Diabetes using artificial neural networks (ANN) is proposed. This is done using a discrete recurrent high order neural network in order to identify and control a nonlinear dynamical system which represents the pancreas' beta-cells behavior of a virtual patient. The ANN which reproduces and identifies the dynamical behavior system, is configured as series parallel and trained on line using the extended Kalman filter algorithm to achieve a quickly convergence identification *in silico*. The control objective is to regulate the glucose-insulin level under different glucose inputs and is based on a nonlinear neural block control law. A safety block is included between the control output signal and the virtual patient with type 1 diabetes mellitus. Simulations include a period of three days. Simulation results are compared during the overnight fasting period in Open-Loop (OL) versus Closed-Loop (CL). Tests in Semi-Closed-Loop (SCL) are made feed-forward in order to give information to the control algorithm. We conclude the controller is able to drive the glucose to target in overnight periods and the feedforward is necessary to control the postprandial period.**

***Keywords*—Identification, Recurrent Neural Networks, Extended Kalman, Diabetes, Artificial Pancreas, insulin, glucose**

I. Introduction

Diabetes is a chronic disease, which occurs when the pancreas does not produce enough insulin or when the body cannot effectively use the insulin it produces. Hyperglycemia, or raised blood sugar, is a common effect of uncontrolled diabetes and over time leads to serious damage to many of the body's systems, especially the nerves and blood vessels. Diabetes can be classified in type 1 diabetes (T1DM) characterized by a whole lack of insulin production so the beta-cells are destroyed. Type 2 and gestational diabetes are caused by the body's ineffective use of insulin. T1DM can be controlled by exogenous insulin, a serious complication is Hypoglycemia which appears when the glucose level is lower than 70 mg/dl. Currently, 347 million people worldwide have diabetes, more than 80% of diabetes deaths occur in low and middle income countries. World Health Organization (WHO) estimates that deaths caused by diabetes will double between 2005 and 2030 and will be the 7th leading cause of death in 2030.

At present it is impossible to regenerate the beta cells and cure this disease. The therapy in patients with T1DM requires exogenous insulin injected subcutaneously 3 or 4 times per day with same number or more of glucose test with glucometers [7]. Each glucose measurement consists of finger pricks to get a drop of blood. This treatment is very invasive and painful. Continuous subcutaneous insulin infusion systems, also known as insulin pumps can be used to optimize the patient's insulin therapy and to improve lifestyle flexibility.

A glucose compartmental model is a set of nonlinear equations that represents the glucose and insulin masses. The set of equations emulates the glucoregulatory system trying to explain the blood or subcutaneous glucose dynamics through the insulin and meals. The availability of a glucose model to simulate the behavior in particular of T1DM patients gives the possibility of designing and evaluating insulin infusion algorithms. Sometimes the real experiments cannot be done at all, because they are dangerous in vivo, difficult or not ethical. There are several compartmental models to evaluate the glucose on people with T1DM. In the last ten years, two have been the compartimentals models widely used: Hovorka's model in which the insulin had 3 different sensibilities on glucose distribution/transport, disposal, and endogenous production [12], [13]. Cobelli's model in which patients daily events and a submodel of the digestive track was used to determinate the glucose [6].

T1DM patients have a lot of problems to fit the insulin therapy to their life habits. The main problem is not to use too much insulin in order to avoid hypoglycemia events. The goal of all alternatives of treatment in T1DM is to keep the glucose concentration in normal ranges using as much doses of exogenous insulin as necessary. Continuous glucose measurement and pump insulin administration require the subcutaneous route, which complicates control because of delays in both measurement and insulin action.

The artificial pancreas should keep the blood glucose levels to close normal levels, avoiding hypoglycemia. According to Klonoff [16] an artificial endocrine pancreas device is built of synthetic materials and replaces the endocrine function of the pancreas. An artificial pancreas is composed by a control algorithm that determines the amount of insulin needed, using measurements of subcutaneous glucose as primary source. A lot of work has been proposed trying to achieve the artificial endocrine pancreas. Some of the

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CL techniques applied in diabetes to design the control algorithm include PID approximations, model predictive control, fuzzy control, and robust control. SCL control has been also evaluated as a means to reduce the peak postprandial glucose levels [3].

In control design, it is difficult to infer the behavior of the nonlinear systems which have internal or external disturbances, unknown parameters or unmodeled dynamics and delays. The ANNs have become an attractive tool in different applications such as to construct, identify, and control complex nonlinear systems [5]. A neural network is a massively parallel distributed processor made up of simple processing units, which has a natural propensity for storing experimental knowledge and making it available for use [21]. It resembles the brain in two aspects: Knowledge is acquired by the network from its environment through a learning process. Interneuron connections strengths, known as synaptic weights, are used to store the acquired knowledge.

Recurrent High Order Neural Network (RHONN) have become a well-established methodology as exemplified by their applications to identification and control of nonlinear and complex systems. The ANN control problem can be approached in two ways: direct NN control and indirect one. In the first approach, first, a control law is designed based on the plant physical model, and then, a RHONN is adopted to approximate the designed control algorithm or its parameters [10], [17]. In the second approach, first, the plant identification problem is solved. This problem consists in the selection of an appropriate RHONN identification model with parameters, which are adjusted according to an adaptive law, such that the response of the model to an input signal (or a class of input signals) approximates the response of the real system for the same input. Then, based on the designed RHONN identifier, a stabilizing or reference tracking controller is proposed [19], [9].The indirect design is very flexible, only the plant model structure (for example, relative degree) is used.

In this paper we propose a discrete-time recurrent neural network in order to identify a complete model [12], [13] and T1DM dynamics. To achieve fast learning convergence, extended Kalman filter (EKF)-based algorithms are used to train the proposed RHONN. Moreover, an identification error is considered in the design controller procedure. The proposed neural identifier fits the nonlinear block-controllable form (NBC). The block-control technique is used to ensure stability and robustness of the CL system in the presence of internal and external perturbations. In general perturbations are meal intakes, exercise, stress and alcohol intake between others, but the most important considered in this work is the carbohydrates (CHO's) intakes. A meal, composed mainly of carbohydrates, is used to stimulate the dynamic system simulating a T1DM patient. We propose an algorithm with disturbances only defined by CHO's intakes in three meals per day.

II. Glucose-Insulin Model

In this work, we consider the continuous Hovorka's model that is presented in [12] because it is one of the most used and widely accepted models of the glucose-insulin metabolism. This model is discretized using the Euler method [15] and represented in states space as follows

$$Q_1(k+1) = Q_1(k) + T\left\{\begin{array}{l}-\left[\frac{f_{01}^c}{V_G G(k)} + X_1(k)\right] Q_1(k) + k_{12} Q_2(k) \\ -f_R + U_G(k) + EGP_0\left[1 - X_3(k)\right]\end{array}\right\}$$

$$Q_2(k+1) = Q_2(k) + T\left\{X_1(k) Q_1(k) - \left[k_{12} + X_2(k)\right] Q_2(k)\right\}$$

$$X_i(k+1) = X_i(k) + T\left[-k_{ai} X_i(k) + k_{bi} I(k)\right],\ i = 1,\ldots,3$$

$$I(k+1) = I(k) + T\left[\frac{U_I(k)}{V_I} - k_e I(k)\right]$$

$$S_2(k+1) = S_2(k) + T\left[\frac{S_I(k)}{T_{\max,I}} - \frac{S_2(k)}{T_{\max,I}}\right];\ S_1(k+1) = S_1(k) + T\left[u(k) - \frac{S_I(k)}{T_{\max,I}}\right]$$

with $y(k) = Gsc = \frac{g}{\tau} Gsc + \frac{1}{\tau} G(k)$

$$f_R = \begin{cases} 0.003(G(k) - 9) V_G & \text{if } G(k) \geq 9 mmol L^{-1} \\ 0 & \text{otherwise} \end{cases},\quad U_G(k) = \frac{D_G A_G t e^{\frac{-t}{t_{\max,G}}}}{t_{\max,G}},$$

$$f_{01}^c = \begin{cases} f_{01} & \text{if } G(k) \geq 4.5 mmol L^{-1} \\ f_{01} \frac{G(k)}{4.5} & \text{otherwise} \end{cases},\quad U_I(k) = \frac{S_2(k)}{t_{\max,I}},\quad G(k) = \frac{Q_1(k)}{V_G}$$ where

$Q_1(k)$ and $Q_2(k)$ represent the masses of glucose in the accessible (where measurements are made) and non-accessible compartments, respectively; $X_1(k)$, $X_2(k)$ and $X_3(k)$ denote the remote effects of insulin on glucose distribution/transport, glucose disposal and endogenous glucose production, respectively; $I(k)$ describes the plasma insulin concentration; $S_1(k)$ and $S_2(k)$ are a two-compartment chain representing absorption of subcutaneously administered short-acting insulin; u is the insulin pump infusion; T is the sampling time. In this paper we only describe the states space variables because only these matter for this work. The definition and values of these parameters can be found in [12] and [13].

In patient's continuous subcutaneous insulin infusion therapy (OL therapy) two insulin concepts exist: Basal insulin involves the insulin supply in fasting periods to keep the normal levels of glucose, usually is defined by the ratio basal in IU/h units and "Bolus priming" is the prandial insulin usually administered before each meal intake. Both concepts are calculated particularly for each T1DM patient depending of his Daily Insulin Requirements (DIR) and Insulin to Carbohydrates ratio (ICR) respectively. The OL control signal $u(k)$ is formed as defined in equation (2):

$$u(k) = u_b(k) + u_p(k)$$

where $u(k)$ is the total insulin bolus infusioned; $u_b(k)$ is the basal bolus; and $u_p(k)$ is the prandial bolus.

III. Training Algorithm and NBC design

In this section high order neural networks are explained as well as their training algorithm based on extended Kalman filter. Also the block control technique is shown.

A. Discrete-time recurrent high order neural network

A high order neural network is a NN in which not only a linear combination of the components, but also of their products are considered, as it is explained in [8]. A RHONN model is flexible and allows incorporating to the neural model of a priory information about the system structure with less units. Additionally, with the RHONN it is possible to reduce the identification error by increasing the number of adjustable weights as well as the high order terms [11].

In this work we propose a RHONN represented by

$$x^1(k+1) = W_1(k) z_1(\chi^1(k)) + \bar{W}_1 \chi^2(k)$$

$$x^i(k+1) = W_i(k) z_i(\chi^1(k),...,\chi^i(k)) + \bar{W}_i \chi^{i+1}(k)$$

$$x^r(k+1) = W_r(k) z_r(\chi(k)) + \bar{W}_r u(k)$$

$$\tilde{y}(k) = x^1(k), \quad i = 2, ..., r-1$$

where $x=(x^1,\ldots,x^i)^T$ represent the neural network states, $x^i \in R^{ni}$ and the numbers; $z^i(\bar{\chi}^i(k))$ is a smooth vector valued function, $\bar{\chi}^i(k)=(\chi^1(k),\ldots,\chi^i(k))^T, W^i(k)$, $i=1,\ldots,r$ is the respective on-line adapted weight matrix; $\bar{W}_i$ is a weight matrix with constant entries and $rank(\bar{W}_i)=n_i$. The neural network identifier (3) has the NBC form which is explained in section III-C. The parameters W_i, z_i and r are used and described as in [4]. In this paper the discrete-time RHONN (3) is trained with the Extended Kalman Filter (EKF) algorithm.

B. Training algorithm based on the extended Kalman filter

It is known that the Kalman filter estimates the state of a linear system with additive state and output noises [20],[23]. Due to the fact that the neural network mapping is nonlinear, an EKF-type is required [4]. The training goal is to find the optimal weight values which minimize the prediction error.

In this paper, we use the EKF described by

$$w_i^j(k+1) = w_i^j(k) + \eta_i^j K_i^j(k) e_i^j(k)$$

where

$$K_i^j(k) = P_i^j(k) H_i^j(k) M_i^j(k)$$

$$P_i^j(k+1) = P_i^j(k) - K_i^j(k) H_i^{jT} P_i^j(k) + Q_i^j(k)$$

for $i=1,\ldots,N$

$$e_i^j(k+1) = \chi_i^j(k) - x_i^j(k)$$

where $e_i^j(k)$ is the respective identification error, $P_i^j(k)$ is the prediction error covariance matrix at step k, $w_i^j(k)$ is the jth weight (state) vector in the ith subsystem, $\chi_i^j(k)$ is the jth plant state, $x_i^j(k)$ is the jth neural network state, $K_i^j(k)$ is the Kalman gain matrix, $Q_i^j(k)$ is the state noise covariance matrix, $R_i^j(k)$ is the associated measurement noise covariance matrix. $M_i^j(k)$ and $H_i^j(k)$ are computed as in [5]. For the time-varying learning algorithm proposed in this paper it is as used by [5], where matrices $Q_i^j(k)$ and $R_i^j(k)$ are calculated in a recursive way such that minimizes the identification error.

C. Block controller design

In order to introduce the proposed method, consider a class of discrete-time nonlinear perturbed system which can be presented in the form NBC consisting of r blocks [4].

$$\chi^1(k+1) = f^1(\chi^1(k),k) + b^1 \chi^2(k)$$

$$\chi^i(k+1) = f^i(\chi^i(k),k) + b^i \chi^{i+1}(k)$$

$$\chi^r(k+1) = f^r(\chi(k),k) + b^r \chi^2(k),u(k)$$

$$y(k) = h(\chi(k),k) = \chi^1(k)$$

where χ^i represents the ith state of the system, with $\chi=(\chi^1,\ldots,\chi^r)^T$, $\chi^1 \in \Re^{ni}$. The numbers n_i, $i=1,\ldots,r$ define the structure of the plant and satisfy $n_i \le n_{i+1}$ and $\Sigma_1^r n_i = n$. It is assumed that $rank\left(\frac{b^i(\chi^{i+1}(k))}{\partial \chi^{i+1}(k)}\right) = n_i$, $i=1,\ldots,r-1$, and $rank\left(\frac{b^r(\chi(k)u(k))}{\partial u(k)}\right) = n_r = m \ \forall \chi \in \chi$, that ensures the system (8) be controllable. The control law now will be designed based on the NN identifier (3) updated with the EKF-type algorithm (4)-(7). Applying the block control technique [1] and using (8), we introduce the following iterative transformation:

$$\varepsilon^1(k) = \chi^1(k) - \chi_d^1(k)$$

$$\varepsilon^i(k) = \chi^i(k) - \chi_d^i(k), \quad i = 2, ..., r$$

where χ_d^i is the desired value for χ^i and

$$\chi_d^2(k) = b_1^+ [K_1 \varepsilon^1(k) - \tilde{f}_1(\chi^1(k), k)]$$

$$\chi_d^{i+1}(k) = b_i^+ [K_i \varepsilon^i(k) - \tilde{f}_i(\chi^i(k),k)]$$

where $\tilde{f}_1(\chi^1(k), k) = f_1(\chi^1(k), k) + \chi_d^1(k+1)$, with $i=2,\ldots,r$ $\tilde{f}_i(\square) = f_i(\chi^1(k),\ldots,\chi^i(k)) + \chi_d^i(k+1)$, with K_i a Schur matrix. The transformation (9) and (10) reduces system (8) to the following form:

$$\varepsilon^1(k+1) = K_1 \varepsilon^1(k) + b_1 \varepsilon^2(k)$$

$$\varepsilon^i(k+1) = K_i \varepsilon^i(k) + b_i \varepsilon^{i+1}(k), \quad i=2,\ldots,r-1$$

$$\varepsilon^r(k+1) = b_r(k)(\chi(k)) + b_r u(k) - \chi_d^r(k+1)$$

From (11) $\varepsilon^r(k+1)=0$ and $u(k)$, is the control signal necessary to close the loop. The following conditions are assumed: Only the structure of (1) is known, while the

parameters and perturbations are unknown and the plant state vector χ is available for the measurement.

IV. Glucose-Insulin Model Identification, Control and Experiment Design

For this work, we propose a neural identifier (12) in the form which corresponds to system structure (1). Note that the NBC form is a particular case of the triangular form where each *i*th block is linear with respect to the vector χ^{i+1}. This applies to each subsystem of (12). The control scheme is based on the discrete-time block control. This procedure is applied to the decentralized neural identifier (12).

A. *Neural network identifier*

Using model (1), the following discrete-time RHONN is proposed with NBC structure (8):

$$x^1(k+1) = W_1(k)z_1(\chi^1(k)) + \bar{W}_1 x^2(k)$$

$$x^2(k+1)=W_2(k)z_2(\chi^2(k))+\bar{W}_2 x^3(k)$$

$$x_l^3(k+1)=W_3(k)z_3(\chi^3(k))+\bar{W}_3 x^4(k)$$

$$x^4(k+1)=W_4(k)z_4(\chi^6(k))+\bar{W}_4 x^5(k)$$

$$x^5(k+1)=W_5(k)z_5(\chi^7(k))+\bar{W}_5 x^6(k)$$

$$x^6(k+1) = W_6(k)z_6(\chi^6(k)) + \bar{W}_6 u_c(k)$$

where $x_l^m(k)$ is the estimate of $\chi^i(k)$, m=1,…,6; $i=1,...,8$ and $l=1,...,3$, $u_c(k)$is the subcutaneous insulin injected at patient with T1DM which corresponds to the control signal; $w_{i,j}(k)$ are the respective time-varying adapted weights computed with the EKF described on subsection III-B. The weights $\bar{w}_i$ are constant positive values, which are selected initially arbitrarily and modified in order to reduce the identification error. Finally S(·) is a sigmoid function defined as (13)

$$s(\chi^i(k))=\frac{1}{1+\exp(-\beta\chi^i(k))},\ \beta\rangle 0$$

We use a neural model (12) due to the fact that the parameters, external disturbances and some dynamics of the plant (1) to be controlled are unknown. Then, to approximate the plant complete model (1), we propose a neural identifier (12) which reproduces the behavior of the plant, without the identification of the plant parameters.

The advantage of the neural identifier (12) is that it allows the application of the block control described in subsection III-C. So, the control algorithm will be designed based on the proposed NN identifier (12).

B. *Block Controller Design*

Considering a full state measurements, the control objective is to develop the insulin dosification to bring the glucose concentration at normoglycemia level, using the discrete-time block control technique define

$$z^1(\chi^1(k))=\begin{bmatrix} S(\chi^1(k)) \\ S(\chi^1(k))S(\chi^3(k)) \\ S(\chi^5(k)) \end{bmatrix},\ z^4(\chi^6(k))=S(\chi^6(k))$$

$$z^2(\chi^2(k))=\begin{bmatrix} S(\chi^2(k)) \\ S(\chi^3(k))S(\chi^1(k)) \\ S(\chi^2(k))S(\chi^4(k)) \end{bmatrix},\ z^5(\chi^7(k))=S(\chi^7(k))$$

$$z^3(\chi^3(k))=\begin{bmatrix} S(\chi^3(k)) \\ S(\chi^4(k)) \\ S(\chi^5(k)) \end{bmatrix},\ z^6(\chi^8(k))=S(\chi^8(k))$$

with

$$W_1=\begin{bmatrix} w_{11}(k) & w_{12}(k) & w_{13}(k) \end{bmatrix},\ W_2=\begin{bmatrix} w_{21}(k) & w_{22}(k) & w_{23}(k) \end{bmatrix},$$

$$W_3=\begin{bmatrix} w_{31}(k) & 0 & 0 \\ 0 & w_{32}(k) & 0 \\ 0 & 0 & w_{33}(k) \end{bmatrix},\ W_4=\begin{bmatrix} w_{41} \end{bmatrix},\ W_5=\begin{bmatrix} w_{51} \end{bmatrix},\ W_6=\begin{bmatrix} w_{61} \end{bmatrix}$$ and

$$\bar{W}_1=\bar{w}_1,\ \bar{W}_2=\bar{w}_2,\ \bar{W}_3=\begin{bmatrix} \bar{w}_{31} & \bar{w}_{32} & \bar{w}_{33} \end{bmatrix},\ W_4=\bar{w}_4,\ \bar{W}_5=\bar{w}_5,\ \bar{W}_6=\bar{w}_6$$

The high order term is given by the product of activation functions S(·) (13) in (14).

At the first step, let us define $\chi_d^1(k)$ the glucose level concentration reference. To control the glucose level, we define the $\varepsilon^1(k)$ as

$$\varepsilon^1(k) = \chi^1(k) - \chi_d^1(k) = x^1(k) - \chi_d^1(k) + \Delta^1(k) \quad (1)$$

where $\chi_d^1(k)$ is the desired value for $\chi^1(k)$, $x^1(k)$ is the estimation for $\chi^1(k)$ and $\chi\Delta^1(k)$ is the identification error. Applying the block control technique for the first block on the neural network identifier (12), we have

$$\varepsilon^1(k+1) = \tilde{f}_1(\chi^1(k),k) + \bar{w}_1\chi^2(k) + \tilde{\Delta}^1(k) = k^1\varepsilon^1(k) + \tilde{\Delta}^1(k) \quad (2)$$

where $\tilde{f}_1(\chi^1(k),k)=W_1(k)z^1(\chi^1(k))-\chi_d^1(k+1)$, $|k^1|\langle 1,\ k^1\varepsilon^1(k)$ is the desired dynamics for $\varepsilon^1(k)$ and $\tilde{\Delta}^1(k)=\Delta^1(k+1)$. Then the desired value $\chi_d^2(k)$ for $\chi^2(k)$ is calculated from the first block on (12) as

$$\chi_d^2(k)=\left[\bar{w}_1\right]^{-1}\left[\tilde{f}_1(\chi^1(k),k)+k^1\varepsilon^1(k)\right] \quad (3)$$

At the second step, given $\chi_d^2(k)$ as the desired value for the glucose mass $\chi^2(k)$, a second error $\varepsilon^2(k)$ is defined as

$$\varepsilon^2(k) = \chi^2(k) - \chi_d^2(k) = x^2(k) - \chi_d^2(k) + \Delta^2(k)$$

and applying the block control technique for the second block on (12), we have

$$\varepsilon^2(k+1)=\tilde{f}_2(\chi^2(k),k)+\bar{w}_2\chi^3(k)+\tilde{\Delta}^2(k)=k^2\varepsilon^2(k)$$

where $\tilde{f}_2(\chi^2(k),k)=W_2(k)z^2(\chi^2(k))$, $|k^2|\langle 1,\ k^2e^2(k)$ is the desired dynamics for $\varepsilon^2(k)$ and $\tilde{\Delta}^2(k) = \Delta^2(k+1)$. Thus, applying the

block control procedure for each block of the system (12) the control value $u_{cl}(k)$ is calculated as follows

$$u_{cl}(k)=\left[\bar{w}_6\right]^{-1}\left[\tilde{f}_6(\chi^6(k),k)+k^6\varepsilon^6(k)\right]$$

where $\tilde{f}_2(\chi^2(k),k) = w_2(k)z^2(\chi^2(k))$, $\left|k^6\right|\langle 1,\ k^6e^6(k)$ is the desired dynamics for $\varepsilon^6(k)$ and $\tilde{\Delta}^6(k)=\Delta^6(k+1)$

The basal insulin is preprogrammed by the endocrine doctor and this insulin is released during the day. The preprandial boluses are calculated by each T1DM patient and administrated fifteen minutes before to each meal. The control algorithm uses this information to make a better adjust of glucose concentration. Then the basal insulin is added to insulin proposed by the control algorithm. The control signal in SCL of (2) is formed as follows

$$u_c(k) = u_{cl}(k) + K_b u_b(k) + K_p u_p(k).$$

Where K_b and K_p modulate basal insulin ($u_b(k)$) and preprandial insulin ($u_p(k)$) respectively.

C. *Safety system*

The following safety conditions are included to limit, approximate and include the necessary requirements that the controller should have in case of being applied to T1DM patients: The controller only supplies insulin, cannot remove it (control in one-way) and if the glucose concentration is below the action level of hypoglycemia the insulin pump is suspended; for every 30 minutes of suspension one microbolus of insulin is supplied to prevent catheter occlusion.

Considering the safety system conditions the control signal is transformed as follows

$$u_s(k)=f(u_c(k)+K_b u_b(k)+K_p u_p(k) \quad (4)$$

where f is the safety function; K_b and K_p modulate basal insulin (u_b) and preprandial insulin (u_p) respectively.

Finally, insulin delivery is quantified with a resolution of 50mU insulin according to the resolution of current commercial infusion pumps.

D. *Experiments design*

The simulation is based on a standard diet therapy for all the patients composed of the following amount of CHOs: 41gr. at breakfast, 60gr. at lunch and 57gr. at dinner. Basal insulin u_b and insulin to carbohydrates ratio (ICR) necessary to compute the dosage of preprandial insulin u_p are described for each T1DM patient on table I.

We simulated three days to ensure that the same initial conditions at second night; we compare OL therapy vs close-loop automatic control. In open- loop, T1DM patients have a insulin pump therapy that consists in calculating insulin doses according to their own DIR for basal insulin and ICR for preprandial insulin. The basal insulin is preprogrammed by the endocrinologist and this insulin is released by the insulin pump along the day. The preprandial boluses are calculated by each T1DM patient and administered generally in advance to the start of a meal intake (e.g.15 minutes before). The control algorithm uses this information to make a better adjustment of glucose concentration.

TABLE I.

Patient	*1*	*2*	*3*	*4*	*5*	*6*	*average*
ICR (UI/gr)	0.13	0.1	0.12	0.1	0.11	0.12	***0.1***
Basal (UI/h)	0.89	0.95	0.9	1.05	0.9	1.1	0.8

Constants the Insulin to Carbohydrates ratio (ICR) and Basal insulin ratio.

The following experiments are defined: Experiment one: The first test consists on administering 50% of preprandial boluses in open-loop; the same amount of preprandial insulin is given to CL configuration, using a SCL configuration. The reference signal is set to 90 mg/dl. Experiment two: The second test proposes four different signal references to the neural control algorithm which are: 80, 90, 100 and 110 mg/dl and keep the 50% preprandial boluses in order to show the accuracy of the control algorithm. Experiment three: The last test consists on showing the effect of feed-forward percentage of preprandial boluses; here we present the full CL (0% feedforward) compared with the values of 50 and 100% feedforward.

V. Simulation Results

In this section the simulation results are described corresponding to identification and control proposed in this work for glucose-insulin regulatory system with structure (1).

A. *Identification*

For the identification process, we consider the complete plant state and output measurement; we also add white noise to state and measurement processes to system with structure (1). The covariance matrices $Q_i^j(k)$ and $R_i^j(k)$ are initialized as diagonal matrices with random entries. These initial values are adjusted recursively in order to improve the neural identification process, as is explained in subsection III-B it is important to note that the proposed method presents good identification and the convergence time is very fast. To simulate the system we use a step time of 1 second. The convergence time is 20 sampling steps approximately and tracking performance is verified for all $\chi_i^j(k)$ variable states. We only show the output identification in figure 1 to demonstrate the accuracy of the proposed RHONN in subsection IV-A.

B. *Control*

The 6 virtual adult patients included in [13] were simulated. In experiment 1 Figure 2 the whole time window is considered, while in experiment 2 Figure 3 only the overnight period is considered (10 pm-7:45 am) and in experiments 3 Figure 4 only the postprandial period is considered (7:45 am-1:45 pm). In experiments 1 and 2 proposed in subsection IV-D1 and subsection IV-D2, respectively, initial glucose was the same in the OL and CL sessions, while in experiments 3 described in subsection IV-D3 the initial glucose has different

values due to previous CL basal control, we can see the three CL experiment starting in same glucose value.

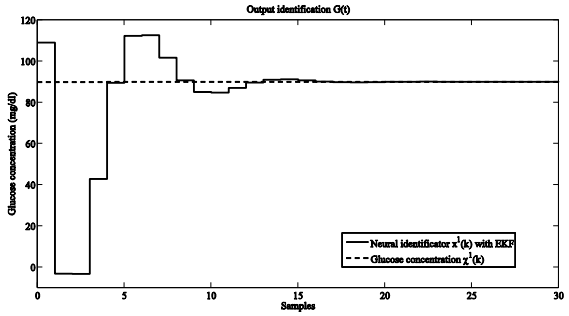

Figure 1. Output identification: glucose concentration $\chi^1(k)$ (dashed line); variable $x^1(k)$ identification with the EKF method (bold line).

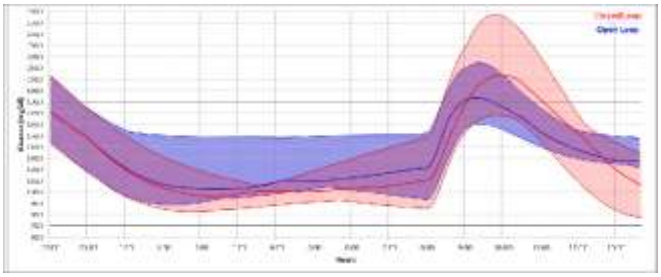

Figure 2. Experiment 1, Response NBC controller comparison OL (blue) vs CL (red) (target 90 mg/dl) for six patients. Overnight (10 pm second day-7:45 am third day) and postprandial (7:45am-1:45pm third day) periods.

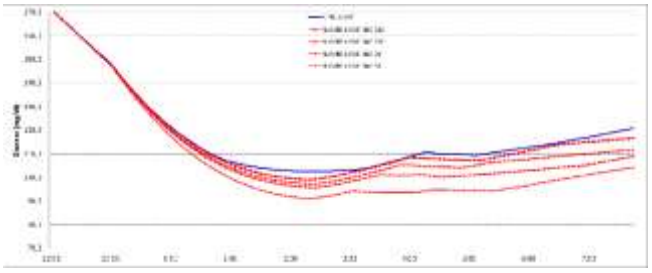

Figure 3. Experiment 2, Six patient median NBC controller comparison OL (blue) vs four target CL(red). Only overnight (10 pm second day-7:45am third day) period is showed.

Summarizing the experiment 1 as the average of six patients. At overnight, the mean glucose is reduced by 13.5 mg/dl and minimum glucose (percentile 2.5%) by 14.8mg/dl; Standard deviation (SD) is decreased in both cases. The timein tight glucose range 70-140 mg/dl is increase from 70.9±36.2 to 84.9±9.3 mg/dl. However in postprandial period no statistical differences were found. The insulin supplied in CL is greater than OL in both periods, for this reason the mean and percentile 2.5% is reduced.

The summarizes of experiment 2 as the average of six patients. At overnight period the mean or percentil 2.5% is driven to reference level, although this one is not achieved. The time in tight target evaluation shows not statistics differences between the four glucose target used. The insulin supplied is reduced when the glucose target is increased.

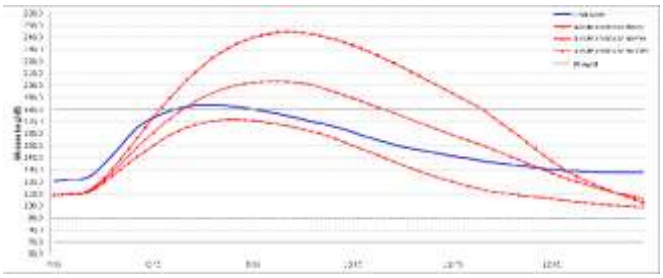

Figure 4. Experiment 3, Six patient median NBC controller comparison OL (blue) vs three different feedforwad (target 90 mg/dl) CL(red): 0% full CL and 100% basal control. Only postprandial (7:45 am- 10:45 pm third day) period is showed.

The experiment 3 can be summarized as the average of the six patients. At postprandial period the mean glucose is increased when the feed-forward is reduced. In full CL there are hypoglycemic events 0.5±1.1%.

VI. DISCUSION

Our methodology supposes that the model parameters and perturbations are unknown, this happens in the real life. But we have assumed too that the structure is known with Hovorka's model. Other models would give different structures and therefore different results, further works must focus in this matter. Also, we have suppose that the all states are measurable but to build the endocrine artificial pancreas only the subcutaneous glucose and insulin boluses are available. Deep studies have to focus in the design of a states observer.

We have chosen a target glucose of 90 mg/dl. Choosing a reference higher could induce hyperglycemia states. However if the target glucose was less than 90 mg/dl more hypoglycemia events would appear. In overnight period CL reduces hyperglycemic time (140±180 mg/dl) 26.5%±36.7 vs 12.7%±7.7 because in OL therapy the medician decides a basal ratio to keep the glucose far of 70 mg/dl. The 50% bolus priming feed-forward avoids the subjectivity in the prandial insulin through the ICR, the subjectivity may be due to stress situations, fats and proteins together with CHOs in the meals and the more important, the patients diabetologic education. The 50% of bolus priming that defines the feedforward in CL vs 100% in OL therapy causes that the postprandial CL glucose was slightly greater than in OL conditions (153.8±13.5 vs 158.5±23.8 mg/dl).

While the experiment 2 demonstrates that the NBC controller can drive the basal glucose, the exact target are not reached because we have suppose $K_b=1$ for every patients. Further work may be focused to fit K_b each patient in order to get every glucose target. The experiment 3 demonstrates that the full CL glucose average (without feedforward information) is the worse (182.5±28 mg/dl) and the control with basal control (with 100% feedforward) is the best (132.9±18.5 mg/dl), even it get better OL (153.8±13.5 mg/dl). The reason of this behavior is the amount of insulin supply in advance respect the meal. When the feedforward no exist, the controller have to calculate the insulin dose, but it do not realize until the glucose is increasing due a meal. This

situation generates a delay it causes instability in the controller.

VII. CONCLUSIONS

This paper provides an alternative for regulating a glucose-insuline system using artificial neural networks. This is possible to make by proposing a discrete-time recurrent neural identifier in order to reproduce the dynamical behavior of a discrete-time virtual patient model with T1DM. This neural identifier is trained with a time-varying learning algorithm called extended Kalman filter where a quickly convergence identification in silico is obtained by reducing the measurement and process noises covariance matrices. The block control technique is used to regulate the glucose-insulin level under different glucose inputs. Results obtained of the different experiments show that the controller designed is able to drive a glucose concentration to a desired level with various scenarios.

Acknowledgment

This work was supported by CONACYT (México) under scholarship number 284966 with support 350765.

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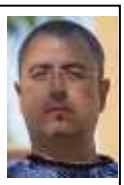

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