TREATMENT FOR T1DM PATIENTS USING NEURO-FUZZY INVERSE OPTIMAL CONTROL ALGORITHM: A RAPID PROTOTYPING IMPLEMENTATION

TRATAMIENTO DE PACIENTES T1DM UTILIZANDO UN ALGORITMO NEURO-DIFUSO DE CONTROL ÓPTIMO INVERSO: UN ENFOQUE DE PROTOTIPADO RÁPIDO

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Abstract: The condition of Type 1 Diabetes Mellitus (T1DM) occurs when the pancreas behaves abnormally, disabling insulin production. Therefore, glucose is not metabolized as a natural source of energy and remains in the bloodstream. This disease causes thousands of deaths around the world. Health sectors, as well as the scientific community, have strengthened efforts to provide effective treatments. In this work, an innovative neuro-fuzzy control approach for blood glucose regulation in T1DM virtual patients is discussed, defined the membership functions in order to determine the rate of insulin infusion for avoiding hyperglycemia and hypoglycemia events. Additionally, a rapid prototyping of the proposed control scheme is carried out by programming the proposed controller into the LAUNCHXL-F28069M development board from Texas Instruments Inc. Application of such prototype is done using the Uva-Padova simulator. The Control Variability Grid Analysis (CVGA), obtained from the Uva/Padova simulator clearly exhibits a satisfactory performance for the reduction of hyperglycemia and hypoglycemia events in a population of 10 virtual adults. This paper aims to expand diabetes research towards developing the Artificial Pancreas (AP) as a programmable device.

Keywords: Type 1 Diabetes Mellitus, Neuro-Fuzzy, Control, Development Board.

Resumen: La condición de Diabetes Mellitus Tipo 1 (DMT1) ocurre cuando el páncreas se comporta de manera anormal e impide la producción de insulina parcialmente o totalmente. Por lo tanto, la glucosa no es metabolizada para convertirse en una fuente natural de energía y permanece en el torrente sanguíneo. Esta enfermedad causa miles de muertes alrededor del mundo. Los sectores de salud, así como la comunidad científica, han fortalecido los esfuerzos para proporcionar tratamientos más efectivos. En este trabajo, se expone un novedoso enfoque de control neuro-difuso para la regulación de la glucosa en sangre en pacientes virtuales con DMT1. La estrategia es diseñada tal que las funciones de membresía están definidas para determinar la tasa de infusión de insulina para evitar...
1. INTRODUCTION

The most recent report of the International Diabetes Federation specifies that approximately 425 million people have diabetes, and in 2045 this number will grow to 629 million (George et al., 2015). This disease caused 4 million deaths and a health expenditure of at least US $727 billion dollars in 2017. Particularly, Type 1 Diabetes Mellitus (T1DM) is a severe metabolic condition where the pancreas is not able to produce enough insulin to keep control of glucose levels inside an att healthy range. This situation is caused by autoimmune destruction of β-cells, responsible of insulin pancreatic production. Moreover, T1DM increases the risk of cardiovascular diseases, retinopathy, nephropathy, neuropathies and the consequences with result from them as congestive heart failure and diabetic foot (Tuomilehto et al., 2015). These complications are associated with considerable morbidity, life ability reduction, physical disability and premature mortality (T. D. Control and C. T. R. Group, 1993). The discovery of insulin was revolutionary and innovative; until today the most common therapy is insulin injections to provide the body with such a hormone that is no longer produced. The insulin dose is calculated based on diet and a priori knowledge of the patient condition; thus, blood glucose monitoring is carried out manually by fingersticks which limit the tests number per day (Majithia et al., 2018). Hence, the scientific community is looking for all possible ways to bring an improving treatment; recently the concept of an Artificial Pancreas (AP) has arisen, which is, an automated closed-loop delivery system composed of three components: a glucose sensor, an infusion pump, and a computational procedure. It is intended that this procedure regulates glucose levels through automatic adjustments of insulin infusion and glucose measurements (Hovorka, 2005; U. D. of Health et al., 2011). Different efforts have been proposed for glycemic control. A model predictive control (MPC) approach for blood glucose regulation is proposed in (Magni et al., 2009); with promising results when tested in the UVa/Padova environment. In (Patek et al., 2012) a high-order sliding modes algorithm is used to regulate the blood glucose in T1DM; robust results are obtained with high precision in presence of physical disturbances such as ingestion of food and parametric uncertainty. A novel monitor is proposed in (Galadanci et al., 2012), which takes glucose readings, and through pattern recognition, the control law adapts to prevent hyperglycemic episodes in presence of disturbances as meal intake. Non-linear control strategies are developed in (Kovács, 2011) in order to track asymptotically the output of a mathematical model which describes glucose-insulin interaction for T1DM patients.

In this paper, an inverse optimal control (IOC) approach via a Lyapunov function is considered to compute insulin infusion for T1DM patients; a Recurrent High-Order Neural Networks (RHONN), trained by an Extended Kalman Filter (EKF), captures the complex glucose-insulin dynamics. Additionally, a rapid prototyping in the LAUNCHXL-F28069M development board from Texas Instruments Inc allows to program and debug the optimal control law. It can be clearly seen that included fuzzy inference improves insulin control action. The validation carried out using the Uva/Padova simulator illustrates that the proposed controlled scheme is able to keep blood glucose within safe ranges. It is expected that this neuro-fuzzy optimal control will expand diabetes research towards programmable devices in order to develop the Artificial Pancreas.

2. ON-LINE DISCRETE TIME NEURAL NETWORK

The study the discrete-time neural model is reviewed in different publications (Alanis et al., 2007; Rovithakis and Christodoulou, 2012; Leon et al., 2013; Romero-Aragon et al, 2014; Quintero-Manriquez et al., 2017; Rios et al., 2018); this paper uses theoretical fundamentals for Recurrent High Order Neural Networks (RHONN) as developed in (Rios et al., 2018).

Glucose-Insulin biological process is a positive system, i.e., its states, initial conditions, inputs,
and outputs are always nonnegative (Leon et al., 2013). According to this fact, an unknown discrete-time disturbed positive nonlinear system is considered as follows, 

\[ x_{k+1} = f(x_k) + g(u_k) + d(x_k), \quad (1) \]

where \( x \in \mathbb{R}^{13} \) is the system state at time \( k \in \mathbb{Z} \bigcup \{0\} \), \( u \in \mathbb{R} \) is a control input vector, \( f(\cdot) \) and \( g(\cdot) \) are unknown nonlinear maps and \( d(\cdot) \) characterizes unknown external disturbances and parameter variations; such is identified using an RHONN as follows,

\[
X_{1,k+1} = w_{1}x_{2},
\]

\[
X_{2,k+1} = w_{2}S(x_{1})S(x_{2}) + w_{3}S(x_{1}) + w_{4}x_{2} + w_{5}u,
\]

where \( w \) is an adjustable parameters vector and \( w \) is a fixed weights vector, which is used to ensure controllability of the neural model as proposed in (Rovithakis and Christodoulou, 2012). \( x_{1,k+1} = G_{1,k-1} \) and \( x_{2,k+1} = G_{1,k} \) are the estimated variables of glucose level, \( u \) is the insulin dose. In order to minimize the prediction error, an EKF in the RHONN training to find the optimal weights values is used, which is given by

\[
K_{i,k} = P_{i,k}H_{i,k}[R_{i,k} + H_{i,k}^{T}P_{i,k}H_{i,k}]^{-1},
\]

\[
w_{i,k+1} = w_{i,k} + \eta K_{i,k}e_{i,k}, \quad (3)
\]

\[
P_{i,k+1} = P_{i,k} - K_{i,k}H_{i,k}^{T}P_{i,k} + Q_{i,k},
\]

with

\[
H_{ij,k} = \frac{\partial x_{i,k}}{\partial w_{j,k}}|_{w_{j,k}=w_{j,i}}, \quad (4)
\]

\[
e_{i,k} = x_{i,k} - X_{i,k}, \quad (5)
\]

where \( K_{i} \in R^{L_{i,km}} \) is the Kalman gain matrix, \( P_{i} \in R^{L_{i,kl}} \) is the prediction error associated covariance matrix, \( H_{i} \in R^{L_{i,km}} \) is a derivatives matrix of neural network state \( x_{i} \) respecting the neural network weights vector \( w_{i,j} \), \( i = 1, \ldots, n \), \( j = 1, \ldots, l \). \( R_{i} \in R^{l,om} \) is the measurement noise associated covariance matrix, \( w_{i} \in R^{l} \) is the weight vector, \( \eta_{i} \) is a design parameter, \( e_{i} \in R \) is the respective identification error, \( Q_{i} \in R^{l,kl} \) is the states noise associated covariance matrix, and \( L_{i} \) is the number of neural network weights. \( P_{i}, Q_{i} \), and \( R_{i} \) are initialized as diagonal matrix. The learning convergence and robustness in (Alonis et al., 2007) are analyzed.

The used RHONN scheme is illustrated in Fig. 1; the Uva/Padova simulator constitutes the T1DM virtual patient, such simulator was in 2008 by the Food and Drug Administration (FDA) for the preclinical testing of control strategies to be used by the Artificial Pancreas, (Kovatchev et al., 2009; Man et al., 2014) and was developed by researchers at University of Virginia, USA and University of Padova, Italy. The academic version includes a thirty patients population (ten children, ten adolescents, and ten adults).

For T1DM treatment the main objective is hyperglycemic and hypoglycemic events preventing. According to this fact, a neural multi-step predictor (MSP) is proposed, which obtains a predicted glucose level within a prediction horizon of fifteen minutes.

### 3. NEURO-FUZZY INVERSE OPTIMAL CONTROL

Inverse Optimal Control (IOC) is applied in different fields (Sanchez and Ornelas-Tellez, 2016; Li et al., 2011; Freeman and Kokotovic, 2008; Ornelas et al., 2011a; Ornelas et al., 2011b). In (Ornelas et al., 2011a; Rios et al., 2018), this approach is analyzed, using a Control Lyapunov Function (CLF) to determine a control law which minimizes a cost function, i.e., the glucose level is controlled using the minimal amount of supplied insulin.

Let consider a positive nonlinear system

\[
x_{k+1} = f(x_{k}) + g(x_{k})u_{k}, \quad x_{0}=x(0), \quad (6)
\]

where \( x \in \mathbb{R}^{13} \) is the system state at time \( k \in \mathbb{Z} \bigcup \{0\} \), \( u \in \mathbb{R} \) is a control input vector, \( f(\cdot) \) and \( g(\cdot) \) are unknown nonlinear maps.

The optimal control law trajectory tracking is calculated as
\[ V := V(z_{k+1}) - V(z_k) + u_k^* R(\dot{z}_k) u_k^* \leq 0, \]

is satisfied.

Considering Definition 1, and in order to satisfy conditions (i) and (ii), the function \( V(z_k) \) is a quadratic candidate CLF taking the following form

\[ V(z_k) = \frac{1}{2} z_k^T P z_k \quad P = P^T > 0, \quad (10) \]

In order to ensure stability of the tracking error \( z_k \) in (¡Error! No se encuentra el origen de la referencia.), we substitute (¡Error! No se encuentra el origen de la referencia.) in the optimal control law (¡Error! No se encuentra el origen de la referencia.), to obtain

\[ u_k^* = - \frac{1}{4} R^{-1}(z_k) g^T(x_k) \frac{\partial V(z_{k+1})}{\partial \dot{z}_{k+1}}, \quad (11) \]

Considering (¡Error! No se encuentra el origen de la referencia.) as a positive system (¡Error! No se encuentra el origen de la referencia.), the optimal control law is rewritten as

\[ u_k^* = - \frac{1}{2} \left( R(z_k) + P_1(x_k) \right)^{-1} P_1(x_k, x_{\delta,k}), \quad (12) \]

with

\[ P_1(x_k, x_{\delta,k}) = \begin{cases} g^T(x_k) P \left( f(x_k) - x_{\delta,k+1} \right) & \text{for } f(x_k) \geq x_{\delta,k+1} \\ g^T(x_k) P \left( x_{\delta,k+1} - f(x_k) \right) & \text{for } f(x_k) \leq x_{\delta,k+1} \end{cases}, \quad (13) \]

\[ P_2(x_k) = \frac{1}{2} g^T(x_k) P g(x_k), \quad (14) \]

And

\[ R(z_k) = \frac{x_k^T r x_k}{\| x_{\delta,k+1} \|}, \quad (15) \]
In (Error! No se encuentra el origen de la referencia.), $V(\cdot)$ is a CLF; this control law is inverse optimal since it minimizes a cost functional.

Moreover, $P_1(\cdot)$, $P_2(x_k)$ are positive definite symmetric matrices and

$$(R(z_k) + P_2(x_k)) > 0,$$

which ensures the existence of the inverse in (12). The proposed scheme is illustrated in Fig. 2. Glucose level is regulated using a total insulin amount $u_k$, which by the optimal control law in (12) and the predicted glucose level $\hat{x}_{k+1}$ ($t = 15$ minutes) is estimated; $u_k$ is a fuzzy controller with the structure following

$$u_k = k_1u_1 + k_2u_2 + k_3u_3 + k_4u_4,$$

with

$$
\begin{align*}
    u_1 & = u_1^* + \text{Hbasal}, & \text{for} & \quad 300 \text{mg/dL} \geq x_{k+1} > 250 \text{mg/dL}. \\
    u_2 & = u_2^* + \text{basal}, & \text{for} & \quad 260 \text{mg/dL} \geq x_{k+1} > 170 \text{mg/dL}. \\
    u_3 & = u_3^*, & \text{for} & \quad 180 \text{mg/dL} \geq x_{k+1} > 70 \text{mg/dL}. \\
    u_4 & = 0, & \text{for} & \quad 110 \text{mg/dL} \leq x_{k+1}.
\end{align*}
$$

where $u_1^*$ is calculated by (12) and Hbasal, basal are defined in Table 1. This $gCH$ is according to a balanced diet for a diabetic adult patient; the basal infusion rate is defined to support the controller for hyperglycemia regulation using the predicted glucose level (see (16)).

4. PROTOTYPING AND EXPERIMENTAL RESULTS

Rapid prototyping is developed in two stages. The first one is the programming stage, i.e., the NF-IOC algorithm into a board is debugged and downloaded. This device is the LAUNCHXL-F28069M development board from Texas Instruments Inc. The second one is the communication stage. Uva/Padova Simulator with LAUNCHXL-F28069M are linked.

Once the NF-IOC is programmed into the board, the communication stage is developed. For this stage, a serial communication protocol with the same baud rate that the programming one is configured. This protocol sends and receives data in real-time of the glucose-insulin system between the Uva/Padova simulator and the LAUNCHXL-F28069M board. The whole closed-loop control is presented in Fig. 5.

In order to illustrate the connection between Uva-Padova Simulator and the Texas Instruments board, a picture of a virtual patient running on the desktop computer and the implemented controller into the LAUNCHXL-F28069M is displayed in Fig. 6.

The carbohydrates grams (gCH) per day intake, and the basal infusion rate are described in Table 1. This gCH is according to a balanced diet for a diabetic adult patient; the basal infusion rate is defined to support the controller for hyperglycemia regulation using the predicted glucose level (see (16)).

<table>
<thead>
<tr>
<th>Meal Protocol (gCH)</th>
<th>Basal Insulin Rate (mU/min)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Breakfast (6:00)</td>
<td>35</td>
</tr>
<tr>
<td>Snack (12:00)</td>
<td>20</td>
</tr>
<tr>
<td>Meal (15:00)</td>
<td>60</td>
</tr>
<tr>
<td>Dinner (19:00)</td>
<td>35</td>
</tr>
<tr>
<td>Snack (23:00)</td>
<td>20</td>
</tr>
<tr>
<td>basals</td>
<td>26.00</td>
</tr>
<tr>
<td>Hbasals</td>
<td>28.00</td>
</tr>
</tbody>
</table>

Tabla 1: Protocol for virtual patients
The proposed control strategy is tested with the ten adults population included in the mentioned simulator. For each virtual patient, an RHONN identifier is used to estimate the glucose behavior, as presented in Fig. 7. The closed-loop behavior is presented in Fig. 8, where reference is the desired trajectory, which is an ideal patient curve under insulin treatment and is compared with the blood glucose level in an adults average. In Fig. 9, the insulin infusion rate using the fifteen-minutes prediction is displayed; for instance, hypoglycemic and hyperglycemic case are avoided, before 12:00 hrs and after meal intake, at 15:00 hrs respectively.
5. CONCLUSIONS

In this paper, T1DM treatment using a novel neuro-fuzzy inverse optimal control is described. This treatment uses three interlinked strategies to regulate glucose level. The first one allows estimating the glucose-insulin dynamics. The second strategy, a multi-step neuronal predictor is used to predict the future glucose data, and the last strategy aims to keep the glucose level into the desired trajectory using an inverse optimal control approach with fuzzy switching. The controller implementation into rapid prototyping board is able to keep glucose within normal levels for 24 hours of treatment on ten adults’ patients. These results illustrate the proposed NF-IOC control scheme importance for new technologies in order to desing the Artificial Pancreas.

REFERENCES


Fig. 10. CVGA for ten adults population.


