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 eventos de hiperglucemia e hipoglucemia. Adicionalmente, se lleva a cabo un prototipado rápido programando la ley de control óptimo inverso en la tarjeta de desarrollo LAUNCHXL-F28069M de Texas Instruments Inc. El análisis de la variabilidad de control (Siglas en inglés CVGA) obtenido a través del simulador Uva/Padova muestra claramente un desempeño satisfactorio para la reducción de hiperglucemia e hipoglucemia en una población de 10 adultos virtuales. De esta manera, el trabajo tiene como objetivo expandir la investigación de la diabetes hacia el Páncreas Artificial (PA) como un dispositivo programable.

Palabras clave: Diabetes Mellitus tipo 1, Neuro-Difuso, Control, Tarjeta de Desarrollo.

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,

$$x_{k+1} = f(x_k) + g(u_k) + d(x_k), \tag{1}$$

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

$$\begin{aligned} \chi_{1,k+1} = &\quad w_1^{'} x_2, \\ \chi_{2,k+1} = &\quad w_1 S(x_1) S(x_2) + w_2 S(x_1) \\ &+ w_3 S(x_2) + w_2^{'} x_2 + w_3^{'} u, \end{aligned} \tag{2}$$

where w is an adjustable parameters vector and $w^{'}$ is a fixed weight vector, which is used to ensure controllability of the neural model as proposed in (Rovithakis and Christodoulou, 2012). $x_{1,k+1} = G_{k-1}$ and $x_{2,k+1} = G_k$ are the estimated variables of glucose level, u_k 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

$$\begin{aligned} K_{i,k} = &\quad P_{i,k} H_{i,k} [R_{i,k} + H_{i,k}^T P_{i,k} H_{i,k}]^{-1}, \\ w_{i,k+1} = &\quad w_{i,k} + \eta K_{i,k} e_{i,k}, \\ P_{i,k+1} = &\quad P_{i,k} - K_{i,k} H_{i,k}^T P_{i,k} + Q_{i,k}, \end{aligned} \tag{3}$$

with,

$$H_{ij,k} = \left[\frac{\partial x_{i,k}}{\partial w_{ij,k}} \right]^T_{w_{i,k} = w_{i,k+1}}, \tag{4}$$

$$e_{i,k} = x_{i,k} - \chi_{i,k}, \tag{5}$$

with $K_i \in R^{L_i \times m}$ is the Kalman gain matrix, $P_i \in R^{L_i \times L_i}$ is the prediction error associated covariance matrix, $H_i \in R^{L_i \times m}$ is a derivatives matrix of neural network state x_i respecting the neural network weights vector $w_{i,j}$, $i = 1, ..., n$, $j = 1, ..., l$, $R_i \in R^{m \times m}$ is the measurement noise associated covariance matrix, $w_i \in R^{L_i}$ is the weight vector, η_i is a design parameter, $e_i \in R$ is the respective identification error, $Q_i \in R^{L_i \times L_i}$ 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 (Alanis *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 withing 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 determinate 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

$$x_{k+1} = f(x_k) + g(x_k) u_k \quad x_0 = x(0), \tag{6}$$

where $x \in \Re^{13}$ is the system state at time $k \in \mathbb{N} \bigcup \{0\}$, $u \in \Re$ is a control input vector, $f(\bullet)$ and $g(\bullet)$ are unknown nonlinear maps. The optimal control law trajectory tracking is calculated as

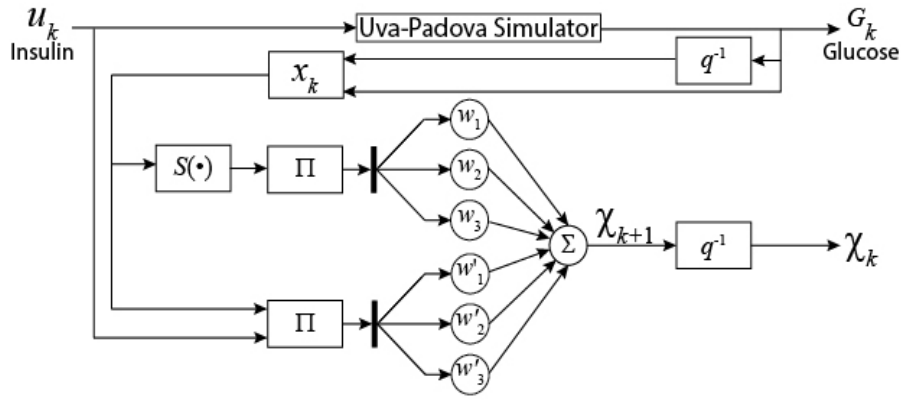


Figure 1: RHONN scheme for glucose identification.

$$u_k^* = -\frac{1}{2}R^{-1}(z_k)g^T(x_k)\frac{\partial V(z_{k+1})}{\partial z_{k+1}}, \quad (7)$$
$$V(0) = 0.$$

with

$$z_k = x_k - x_{\delta,k}, \quad (8)$$

$$z_{k+1} = f(x_k) + g(x_k)u_k - x_{\delta,k+1}, \quad (9)$$

where $R(z_k) = R^T(z_k) > 0$ is a matrix-valued function for all x_k, $x_{\delta,k}$ is the desired trajectory, $z_k \in R^n$ is the tracking error. In (6) using (7) for reaching the trajectory, a definition is proposed as follows (Ornelas et al, 2011a):

Definition 1: Consider the tracking error as (8). The control law defined in (7) will be inverse optimal stabilizing along the desired trajectory $x_{\delta,k}$ if:

i. for system (6) achieves (global) asymptotic stability of $x_k = 0$, along reference $x_{\delta,k}$;

ii. $V(z_k)$ is (radially unbounded) positive definite function such that the inequality $\overline{V} := V(z_{k+1}) - V(z_k) + u_k^{*T} R(z_k) u_k^* \leq 0,$ 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

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

In order to ensure stability of the tracking error z_k in (8), we substitute (10) in the optimal control law (7), to obtain

$$u_k^* = -\frac{1}{4}R^{-1}(z_k)g^T(x_k)\frac{\partial z_{k+1}^T P z_{k+1}}{\partial z_{k+1}}, \quad (11)$$

Considering (6) as a positive system [16], the optimal control law is rewritten as

$$u_k^* = \left| -\frac{1}{2}\left(R(z_k) + P_2(x_k)\right)^{-1} P_1(x_k, x_{\delta,k}) \right|, \quad (12)$$

with

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

$$P_2(x_k) = \frac{1}{2}g^T(x_k)Pg(x_k), \quad (14)$$

and

$$R(z_k) = \frac{x_k^T r x_k}{\| x_{\delta,k+1} \|}, \quad (15)$$

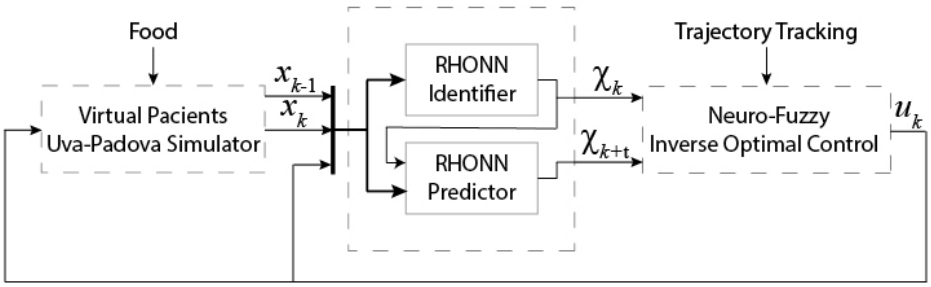


Fig. 2. Block diagram of closed-loop control system with prediction.

In (10), V(•) is a CLF; this control law is inverse optimal since it minimizes a cost functional. Moreover r, $P_1(\bullet)$, $P_2(x_k)$ 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 χ_{k+t} ($t=15$ *minutes*) is estimated; u_k is a fuzzy controller with the structure following

$$u_k = k_1u_1 + k_2u_2 + k_3u_3 + k_4u_4, \qquad (16)$$

with

$u_4 = u_k^* + \text{Hbasal}$, for $300\text{mg/dL} \geq \chi_{k+t} > 250\text{mg/dL}$
$u_3 = u_k^* + \text{basal}$, for $260\text{mg/dL} \geq \chi_{k+t} > 170\text{mg/dL}$
$u_2 = u_k^*$, for $180\text{mg/dL} \geq \chi_{k+t} > 70\text{mg/dL}$
$u_1 = 0$, for $110\text{mg/dL} \leq \chi_{k+t}$

where u_k^* is calculated by (12) and Hbasal, basal are defined in Table I. These fuzzy sets are llustrated in fig. 3.

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. Uva/Padova simulator runs on a desktop computer, which includes the virtual patients, a glucose sensor, and an insulin pump. In this application, ten adults are analyzed.

The proposed scheme for the programming stage is illustrated in Fig. 4. In this scheme, the controller is implemented via Matlab & Simulink of Mathworks® using a Serial Communication Interface (SCI) with a baud rate $921600\ bits/s$.

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)).

Tabla 1: Protocol for virtual patients

Meal Protocol (*gCH*)					**Basal Insulin Rate (*mU/min*)**	
Breakfast (6:00)	Snack (12:00)	Meal (15:00)	Dinner (19:00)	Snack (23:00)	basal	Hbasal
35	20	60	35	20	26.00	28.00

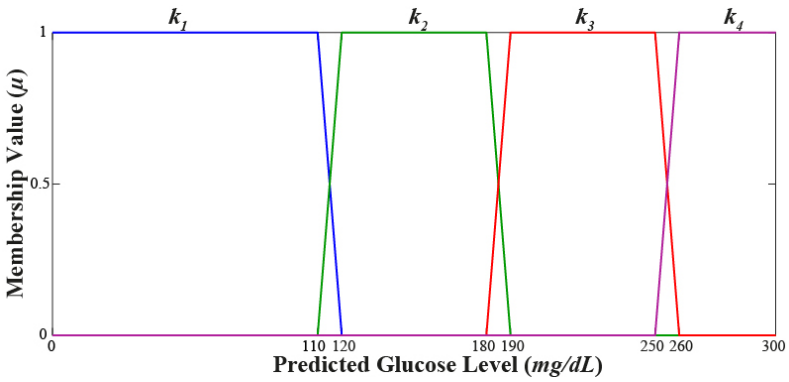


Fig. 3. Fuzzy set for the control gains.

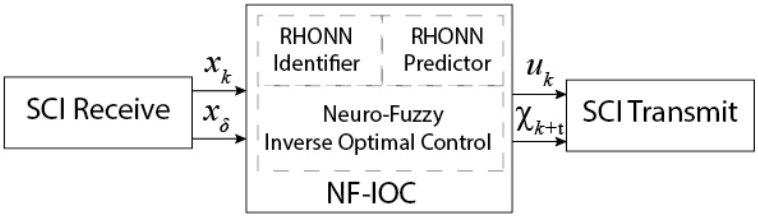


Fig. 4. Matlab & Simulink SCI to LAUNCHXL-F28069M.

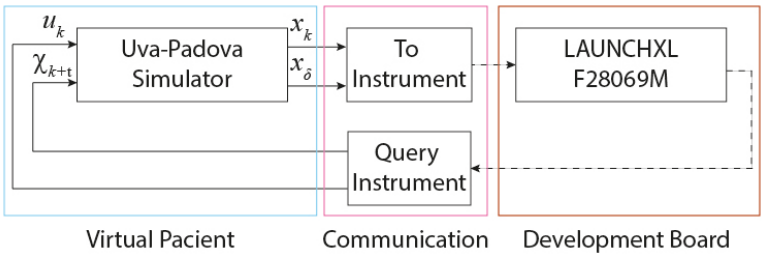


Fig. 5. Closed-loop diagram.

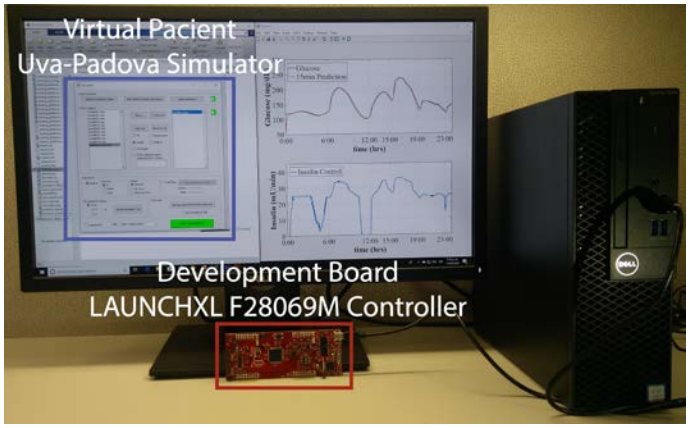


Fig. 6. Closed-loop real connection.

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.

The Control Variability Grid Analysis (CVGA) is a visualization method of the glucose level included in the Uva-Padova simulator. Also CVGA, the patients are plotted according to X-Y coordinates for the minimum and the maximum of the glucose reading in the test time lapse. The Fig. 10 illustrates the test results to the ten adults population using the proposed controller, the glycemic effectiveness of 100% is achieved.

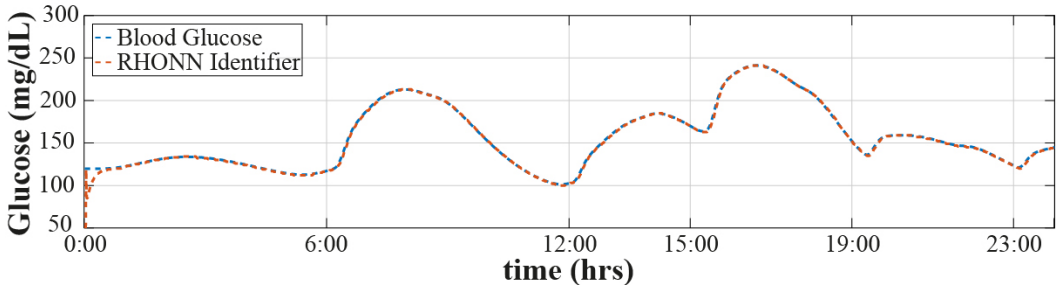


Fig. 7. Blood glucose and RHONN identifier comparison for the adults average.

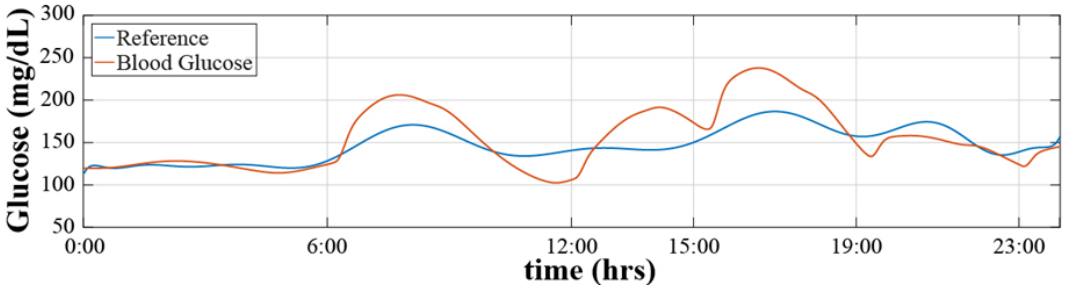


Fig. 8. Trajectory tracking for adults average with NF-IOC.

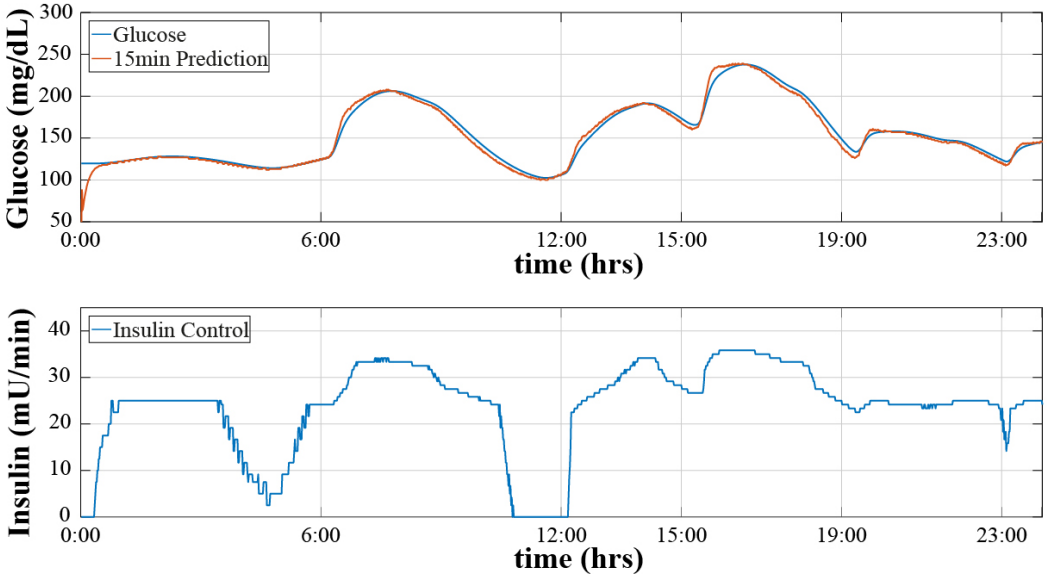


Fig. 9. Closed-loop glucose control for adults average with NF-IOC.

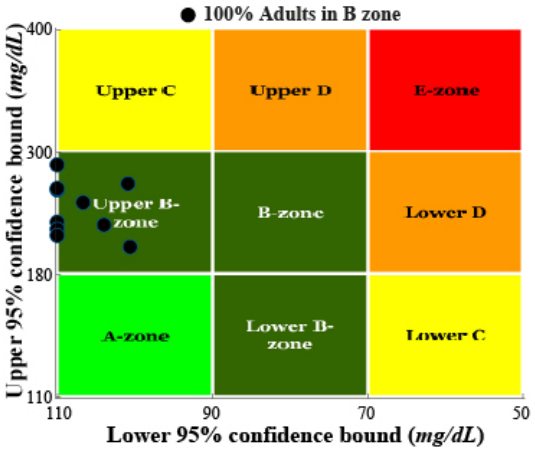


Fig. 10. CVGA for ten adults population.

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 aimes 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

Alanis A. Y., Sanchez E. N., and Loukianov A. G. (2007). *Discrete-time adaptive backstepping nonlinear control via high-order neural networks*. IEEE Transactions on Neural Networks, **vol. 18**, no. 4, pp. 1185–1195.

Freeman R. and Kokotovic P. V. (2008). *Robust nonlinear control design: state-space and Lyapunov techniques*. Springer Science & Business Media.

Galadanci J., Shafik R., Mathew J., Acharyya A., and Pradhan D. (2012). *A closed-loop control strategy for glucose control in artificial pancrea. Systems*. Electronic System Design (ISED). International Symposium on, pp. 295–299.

George K., Alberti M. M., DeFronzo R., Ferrannini E., and Zimmet P. (2015). *Chapter 2: The Classification and Diagnosis of Diabetes Mellitus*. International Textbook of Diabetes Mellitus, **vol. 2**. Wiley-Blackwell, 4 ed.

Hovorka R. (2005). *Continuous glucose monitoring and closed loop systems*. Diabetic Medicine, **vol. 23**, no. 1, pp. 1–12.

Kovács L., Szalay P., Beny B., and Chase G. (2011). *Asymptotic output tracking in blood glucose control. a case study*. 50th IEEE Conference on Decision and Control and European Control Conference. pp. 59–64.

Kovatchev B. P., Breton M., Dalla Man C., and Cobelli C. (2009). *In silico preclinical trials: a proof of concept in closed-loop control of type 1 diabetes.*

Leon B. S., Alanis A. Y., Sanchez E. N., Ornelas-Tellez F., and Ruiz-Velazquez E. (2013). *Neural inverse optimal control applied to type 1 diabetes mellitus patients*. Analog Integrated Circuits and Signal Processing, **vol. 76**, no. 3, pp. 343–352.

Li W., Todorov E., and Liu D. (2011). *Inverse optimality design for biological movement systems*. IFAC Proceedings Volumes**,** **vol. 44**, no. 1, pp. 9662–9667.

Majithia A., Wiltschko A., Zheng H., Walford G., and Nathan D. M. (2018). *Rate of change of premeal glucose measured by continuous glucose monitoring predicts postmeal glycemic excursions in patients with type 1 diabetes: Implications for therapy*. Journal of Diabetes Science and Technology, **vol. 12**, no. 1, pp. 76–82, 2018. PMID: 28868899.

Magni L., Forgione M., Toffanin C., Man C. D., Kovatchev B., Nicolao G. D., and Cobelli C. (2009*). Run-to-run tuning of model predictive control for type 1 diabetes subjects: In silico trial*. Journal of Diabetes Science and Technology, **vol. 3**, no. 5, pp. 1091–1098, 2009. PMID: 20144422.

Man C. D., Micheletto F., Lv D., Breton M., Kovatchev B., and Cobelli C. (2014). *The uva/padova type 1 diabetes simulator: new features*. Journal of diabetes science and technology, **vol. 8**, no. 1, pp. 26–34.

Ornelas F., Sanchez E. N., and Loukianov A. G. (2011). *Discrete-time nonlinear systems inverse optimal control: A control lyapunov function approach*. Control Applications (CCA), IEEE International Conference on, pp. 1431–1436, IEEE.

Ornelas-Tellez F., Sanchez E. N., Loukianov A. G., and Navarro-López E. M. (2011). *Speed-gradient inverse optimal control for discrete-time nonlinear systems*. Decision and Control and European Control Conference (CDC-ECC), 50th IEEE Conference on, pp. 290–295, IEEE.

Patek S., Magni L., Dassau E., Karvetski C., Toffanin C., Nicolao G. D., Favero S. D., Breton M., Dalla-Man C., Renard E., Zisser H., F. D. III, Cobelli C., and Kovatchev B. (2012). *Modular closed-loop control of diabetes.* IEEE Transactions on Biomedical Engineering, **vol. 59**, pp. 2986–2999.

Quintero-Manriquez E. , Sanchez E. N., Harley R. G., Li S. , and Felix R. A. (2017). *Neural sliding mode control for induction motors using rapid control prototyping.* IFAC-PapersOnLine, **vol. 50**, no. 1, pp. 9625–9630.

Rios Y. Y., García-Rodríguez J. , Sanchez O. , Sanchez E. N., Alanis A. Y., Ruiz-Velázquez E. , and Arana N. (2018). *Inverse optimal control using a neural multi-step predictor for T1DM treatment*. vol. The International Joint Conference on Neural Networks (IJCNN), pp. 1–6.

Romero-Aragon J. C., Sanchez E. N., and Alanis A. Y. (2014). *Fpga neural identifier for insulin-glucose dynamics.* World Automation Congress (WAC). pp. 675–680, IEEE.

Rovithakis G. A., and Christodoulou M. A. (2012). *Adaptive control with recurrent high-order neural networks: theory and industrial applications.* Springer Science & Business Media.

Sanchez E. N. and Ornelas-Tellez F. (2016). *Discrete-time inverse optimal control for nonlinear systems.* CRC Press.

Stene L., Harjutsalo V., Moltchanova E., Tuomilehto J., DeFronzo R., Ferrannini E., and P. Zimmet. (2015). *Chapter 3: The Classification and Diagnosis of Diabetes Mellitus.* International Textbook of Diabetes Mellitus, **vol. 2.** Wiley-Blackwell, 4 ed.

T. D. Control and C. T. R. Group. (1993). *The effect of intensive treatment of diabetes on the development and progression of long-term complications in insulin-dependent diabetes mellitus*. New England Journal of Medicine, **vol. 329**, no. 14, pp. 977–986, 1993. PMID: 8366922.

U. D. of Health, H. S. Food, and D. Administration. (2011) *The Content of Investigational Device Exemption (IDE) and Premarket Approval (PMA) Applications for Artificial Pancreas Device Systems*. Center for Devices and Radiological Health, 1 ed. Guidance for Industry and Food and Drug Administration Staff.