DOI: https://doi.org/10.33103/uot.ijccce.21.3.2

Review on Positive Control for Glycemia Regulation in Type One Diabetes

Amer B. Rakan[1], Taghreed MohammadRidha[2]
[1]*Petroleum Process Eng. College, University of Tikrit, Salahddin, Iraq.*
[2]*Control and Systems Eng. Dept., University of Technology, Baghdad, Iraq.*
[1]*amerbasheer@tu.edu.iq*, [2]*Taghreed.m.ridha@uotechnology.edu.iq*

Abstract— *This paper aims to present the literature related to the regulation of Type 1 Diabetes Mellitus (T1DM) via positive control and constrained control. This idea of positive control was derived because the control input (insulin) can only be infused/injected (one direction control). The main operation of insulin is to reduce glycemia back to euglycemia. If glycemia goes into hypoglycemia; the only possible way is to stop insulin injection temporarily, and the patient must take some carbohydrates to raise glycemia. Also, hyperglycemia can be treated by estimating the amount of meals taken by the patient using an estimator. Since meals are a positive factor, the controller gives an adequate positive action to eliminate the effect of meals. This paper reviews the research work related to regulating glycemia that considered the positivity of insulin as a control input. The impact of considering the positive control in the design is the fact that any negative decision will be cut off to zero. In such case, the system is left open-loop and will be out of control.*

Index Terms— *Artificial Pancreas, Constrained Contro , T1DM, Positive Control.*

I. INTRODUCTION

Diabetes is one of the most critical diseases in the world [1]. It is a chronic illness mainly caused by incomplete insulin production or less insulin sensitivity (T1DM) [2]. Also, T1DM requires glucose monitoring and intensive insulin therapy [3]. In the bloodstream, glucose concentration (The difference between the stream of glucose into the blood and its uptake by the cells [4]) is naturally regulated by two hormones: insulin generated by (βeta –cells) and glucagon generated by (αlfa-cells). These hormones are together secreted by the islets of Langerhans in the pancreas [5,6]. These hormones have a reciprocal effect. Type One Diabetes Miletus (T1DM) is caused by the destruction or loss of (β –cells), thus, insulin production stops [7,8]. When the Blood Glucose (BG) concentration increases by more than 180 mg/dl (hyperglycemia) the risk of cerebral stroke, cardiac arrests, renal failure, and loss of vision increases [9]. In this case, insulin may be injected/infused exogenously to return glucose to its normal concentration (80 mg/dl – 120 mg/dl). Injection/Infusion of insulin is done in two ways: manually or automatically. Manual injection/infusion of insulin may lead to overdose and this causes hypoglycemia (glucose concentration less than 70 mg/dl). Hypoglycemia has a more sudden effect and can quickly escalate to become life-threatening, so the risk of infection of diabetic coma may occur [9,10,11].

Received 16/4/2021; Accepted 25l7l2021

 ISSN (Print) 1811-9212 *ISSN (Online) 2617-3352*

DOI: https://doi.org/10.33103/uot.ijccce.21.3.2

Therefore, an Artificial Pancreas (AP) platform has been envisioned for more than 50 years. AP is a device designed to automatically regulate the needed blood glucose concentration [12] because it provides sufficient insulin automatically throughout the day [13]. An (AP) has intended perfection for patients with T1DM in their lifestyle since it does not only permit automatic control of the levels of glycemia, but it also keeps patients comfortable. Where the patient avoids manual insulin injection throughout the day [12]. AP consists of a glucose sensor for computing glucose concentration, an insulin pump that helps infusion insulin, and a control algorithm [14,15]. The control algorithm must depend on feedback to compute the correct dose [16,17]. Concerning it must take into account that insulin is a non-negative input i.e. insulin can not be taken out from the bloodstream and insulin can reduce glycemia only. Therefore, the control algorithm must be designed to be positive (operate in one direction (injection only)) and robust to prevent hypoglycemia episodes [18,19]. Thus in the case of hypoglycemia, insulin (infusion/injection) must be stopped immediately. Hence the importance of the positive control design arises. *Fig*.1 shows the AP components:

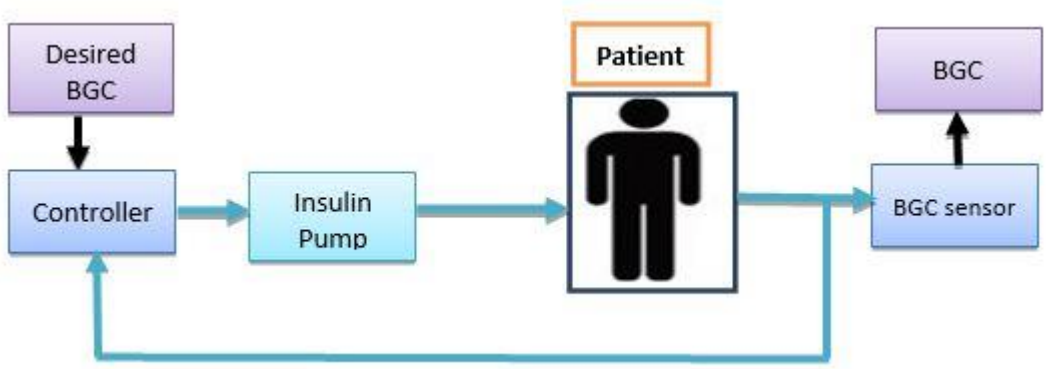

FIG. 1. BLOCK DIAGRAM OF AP COMPONENTS

For this reason, a research on this topic will be presented here. For any research, the main challenge is to design an adaptable AP that protects the trade-off between postprandial hyperglycemia and delayed hypoglycemia [20,21]. Long-period hyperglycemia can be prevented by giving a suitable positive control action. This control action (amount of insulin) is dependent on the amount of glucose that enters the body.

In the next section, T1DM treatments are presented after that a general idea about the concept of positivity control will be presented. Then, a literature review related to positivity and positive control is illustrated. Finally, a brief conclusion and perspective of future work are given.

II. T1DM TREATMENTS

T1DM is also known as juvenile diabetes because it most often affects children and adolescents. It happens as a result of the autoimmune destruction of beta cells, which leads to the loss of insulin production. Because of a long time between the onset of autoimmunity and the onset of diabetes, more than 80-90 percent of the beta cells have been destroyed [22].

After the discovery of insulin in 1921 [20], exogenous insulin is the only treatment for T1DM. At the beginning of treatment, insulin is injected manually without testing the BGC

Received 16/4/2021; Accepted 25l7l2021

DOI: https://doi.org/10.33103/uot.ijccce.21.3.2

in the bloodstream. Because the methods used to calculate BGC and previous medical treatment methods for maintaining and controlling BGC were ineffective. In fact, it is difficult to give a diabetic patient the correct amount and type of insulin [5].

Then, in the middle of the last century, a sensor (Continuous Glucose Monitoring (CGM)), was discovered to measure the concentration of blood glucose as shown in *Fig*. 2. Therefore, in order to overcome these shortcomings of modern medical treatments, several studies have been conducted in recent years to address the limitations of current medical treatments. Studies have found that diabetics need regular and appropriate therapeutic doses to treat high blood glucose levels. Also, doses should not be excessive so as not to lead to low blood glucose levels. So this could be with multiple regular insulin injections or "continuous subcutaneous insulin injections" (CSII) delivered through an automated pump as shown in Fig. 2 [20].

FIG. 2. INSULIN DELIVERY SYSTEM MINIMED640G SYSTEM, INSULIN PUMP IN BLACK; AND A CGM IN WHITE

III. INPUT CONSTRAINT: POSITIVITY OF THE CONTROL

The majority of biological processes have positive input. Glucose-insulin dynamics is one of these biological processes that do have not the physiological ability to deal with non-positive actions.

To clarify the idea of a positive system mathematically, the model (Magdelaine model [23]) can be given as follows:

$$\dot{x(t)} = \begin{bmatrix} 0 & -kci & 0 \\ 0 & 0 & 1 \\ 0 & -\frac{1}{Te^2} & -\frac{2}{Te^2} \end{bmatrix} x(t) + \begin{bmatrix} 0 \\ 0 \\ \frac{Km}{Vm\,Te^2} \end{bmatrix} u(t) + \begin{bmatrix} ki - ko \\ 0 \\ 0 \end{bmatrix} \quad (1)$$

where $x_1(t)[\mathrm{mg/dL}]$ blood glucose, $x_2(\mathrm{t})\,[\mathrm{U/dL}]$ plasma insulin, and $x_3(\mathrm{t})\,[\mathrm{U/(dL.\,min)}]$ rate of change, K_{ci} insulin sensitivity [mg/(U min)]. K_i liver production of glucose [mg/dL/min]. $K_o = 128/\mathrm{M}\,[\mathrm{mg/dL/min}]$ consumption of brain, km[min]a static gain, $V_m[\mathrm{dL}] = 2{,}5\mathrm{M}$ is the insulin distribution volume, and $u(t)[\mathrm{U/min}]$ is the external injection of insulin (it is the control action). Glycemia is physically a positive variable [21].

Received 16/4/2021; Accepted 25l7l2021

DOI: https://doi.org/10.33103/uot.ijccce.21.3.2

Therefore, the system must be subject to positive constraint with a lower bound $u \geq 0$ [19,24].

The system is under positive constraints namely i) avoided hypoglycemia ii) the control action is non-negative: (injection/infusion) of insulin can't be taken out of the body [25].

This review is presented for the following reasons:

1. Any negative control action means, there is over-dose, therefore hypoglycemia happens.
2. If the controller is not designed to be positive, this means the saturation must be used to cut the control action when $u<0$ and this means the system behaves like an open-loop system.

In the next section, previous studies are concerned with designing a positive control or constraint control such (model predictive control) to regulate glycemia at a target range will present.

IV. LITERATURE REVIEW

In this section, the literature related to design a positive control for glycemia regulation will be presented. One of the most and famous studied control strategies is Model Predictive Control, (MPC); which has viewed suitable performances in clinical and *in silico* environments [26-28]. MPC was chosen because of its demonstrated ability to estimate the best control action and deal with feedback, state constraints, and disturbances [29,30]. In MPC, the aim is to compute the better value for the manipulated variable u(t) [22]. MPC is well-known in this area because it takes care of the design's device constraints. This model-based controller often needs model linearization (if nonlinear models are used) and parameter recognition to cope with changes in device parameters, which is the main disadvantage of MPC. This makes individual parameter tuning more difficult. Below some studies in this field are presented.

A. Model Predictive Control (MPC)

Insulin injection doses are not continuous or discrete input. Because insulin doses are injected into the patient as small pulses [31]. Therefore, in [32], Impulsive Zone Model Predictive Control (IZMPC) was applied to T1DM. It was satisfying for a good performance in long-term-model. The main disadvantage, this controller was examined on one patient with known and regular meals. Both the control input (insulin injection) and state (BG) are constraints to be positive. Therefore, hypoglycemia and hyperglycemia are prevented. Also, from the result, the first case assumed in hyperglycemia condition, the controller was steer glycemia to normal zone in only 3.5 hours. This controller may be examining in more than one patient (many patients) with unknown and irregular meals to show if it satisfying the AP condition.

In [33], impulsive Zone Model Predictive Control, (iZMPC) was studied. Constraints were considered for both state and input (insulin injection/infusion). In a region that is assumed to be polyhedron. The (control/prediction) horizon should be large enough to computation for the entire insulin effect (because of its positive-ness, the overdoses are hard to compensate). But in this work, only the worst case of the prediction disturbance was considered for the MPC. Then, it was assumed to be zero. That's mean no information regarding the meals was passed to the MPC. This study was tested on 5 patients that are considered as in, (Magdelaine et al. (2015)). At the end, the problem of glycemic regulation

Received 16/4/2021; Accepted 25l7l2021

DOI: https://doi.org/10.33103/uot.ijccce.21.3.2

in T1DM patients in a target window was satisfied. The insulin injection (controller) remained positive in contrast if a disturbance (meal) enters the system. But the controlled process is slightly slower because the controller takes more time to compensate for disturbances.

In [34], it was dealt with a new estimation and control approach (MPC and Moving Horizon Estimation (MHE)) for glycemia managing in T1DM. A constraint was added to both input (control input) and output (blood glucose) to remain on the safe side (positive quantities). This combination of MPC/MHE was tested *in silico* trials of ten virtual patients using the commercially available UVA/Padova. The results show several notes of this simulation, containing less (hypoglycemia) status, without raising the number of (hyperglycemia) status. This means after meal intake blood glucose had hypoglycemic events with the same number of hyperglycemic events. This is not acceptable for a patient with T1DM as mentioned above. The advantage of this controller had faster insulin delivery to meal consumption, and shorter insulin pump suspension, resulting in smoother blood glucose trajectories.

In [35], an MPC with integral action, (called Integral MPC (IMPC)) was proposed. Glycemia was regulated to target the existence of disturbance and model uncertainties. The main advantages over designing an IMPC are a control scheme, an augmented system. Which takes into consideration the (integral action), a cost function, and a model-based optimization issue. Although, the system has significant constraints, on the control input (insulin injection) and output (blood glucose limitation) together. This study was examined on the one hundred pragmatic patients of the UVA/Padova simulator for 14 days. IMPC has steered the glycemia to the normal range, by reducing hyperglycemic events without any hypoglycemic events. This means this controller not fully managing hyperglycemic events and the blood glucose remains unsmooth in the target zone.

In [36], a pulsatile zone model predictive control (pZMPC) was presented to glycemic regulation in (T1DM). The main advantage of this algorithm in disparity with the others, glycemia is regulated in the patient by infusing a short duration insulin bolus, both hypoglycemia and hyperglycemia are predicted and estimated. An observer was employed to compute plant model uncertainties also it was ensured the stability of the closed-loop, and it can be applied under small modifications. Constraints were included in both input (insulin infusion) and state (glycemia). Tow state observer was considered in this work, for calculation of plant-model uncertainties, where the (meals) considering as the most considerable disturbance. This controller was tested on 10 virtual adult patients. For the mutual closed-loop planner the controller administration insulin in elegant-bolus style, since a full carbohydrate meal take-in rate was considered. When meals are declared with a 30% error, the performance was not significantly degraded. In contrast, for the full closed-loop planner, the input disturbance observer allowed an improvement of glycemic control concerning missed announced cases. While in [37], pZMPC was published under a real observer. Thus, the sensitivity of insulin was observed throughout the day. pZMPC in this case was taken into account along with the nominal information of the sensitivity of insulin in the postprandial phase. The results showed the best information in time-invariant environments. Also, the results showed the blood glucose rises to hyperglycemic after meal intake, this indicates low response and low sensitivity to a meal.

The standard ZMPC is one of the types of MPC, that controlled the predicted output (glycemia) at a target range rather than in a specific set-point. This operation is done by obtaining the optimal insulin injection (optimal future inputs) [38,39]. But the study in [40] showed that the iZMPC had the best qualification than ZMPC. The iZMPC was present less

Received 16/4/2021; Accepted 25l7l2021

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time out the euglycemia range. The comparison of the performance of these controllers showed that the standard ZMPC was present 70% of the time inside the normal zone, and on the other side, the iZMPC was spent 92.5%.

Studies above depending on constrained both the input and output to remain in the safety zone. This sometimes leads to saturating the system. The solution is to design a positive control for glycemia regulation without any constrained and any saturates. This controller depending on the computing of the positively invariant set of the system under the closed-loop. This is due to the fact that blood glucose management is a non-negative control problem. In the following, there is another controller designed to be positive in the design.

B. Positive Sliding Mode Controller

A positive Sliding Mode Control (SMC) was designed in [2], to deal with physical constraints of biological systems for glycemia regulation on the fasting phase. The constraints of positivity were applied to this controller and PIS computed her for the first time for two states only. This non-negative control was examined *in silico* on the (T1DM) patients model. This model was derived from real-life clinical data. The simulation results were performed on three virtual patients only. The results show that glycemia was taken more time to regulated in the target zone (response relatively slow) and the hypoglycemic events were fully prevented, this is one of the main challenges of any controller. The positive SMC is a proof of concept and the design can be extended to include hypoglycemia constraint. This controller must be examined on more patients and must take the case of after meal. Also, the robustness of this controller was not examined.

The MPC and SMC were both applied in [41]. A nominal plant model identified was assumed for each controller. Also, the common dynamic parameters were computed under 60% variation, insensitivity of insulin, time action of insulin, and absorption time of carbohydrate (CHO). The results showed that the MPC had the best efficiency in preventing hypo and hyperglycemic episodes. Although, it was not eligible for protection in its performance under parametric divergence in the model. In contrast case, the SMC and the nominal case had the ability to maintain results. From these results, this study aims to take the advantage of MPC and SMC (hybrid control) should be taken to improve the model performance, for disturbance and parametric variation. But in this case, the hybrid controller does not fully guarantee the prevention of hypoglycemia events.

C. Positive State Feedback Controller

In [42,20], a non-negative (positive) state feedback control was designed for the long-term T1DM model. The Positive state feedback, in which all system states are positive, is less challenging to design than SMC. Positivity constraints were inserted in the design. This leads to calculating the largest Positive Invariant Set (PIS). Therefore, the control action (insulin injection) remains positive for all times. Although (PIS) is a specific region and limits the movement of system trajectories, it was guaranteed that the glycemia error remains positive under this controller. This controller was examined through the fasting phase on 5 T1DM virtual patients. This controller was failed to regulate glycemia in the postprandial phase. After meal injection, the glucose concentration remains a long period in hyperglycemia. However, in the fasting phase, it is preventing hypoglycemic events and it is faster than SMC.

A positive state feedback control (which so-called hypo-free strategy (HFS)) was designed in [43]. It is different from the study in [42]. In this study, the desired

Received 16/4/2021; Accepted 25l7l2021

DOI: https://doi.org/10.33103/uot.ijccce.21.3.2

hyperglycemia rectification bolus was found in actual time to significantly derive glycemia to the normal range. The positivity of input/state trajectories was proven using the notion of PIS. This control strategy was examined for all the UVA/Padova virtual patients. This was happened during the fasting phase and in a hybrid closed-loop phase. For state estimation, a standard (Luenberger Observer) was used. From the results, hypoglycemia was avoided in both the fasting and meal phases. In meals, where carbohydrate (CHO) was intake, it was wrongly estimated by the patient. Therefore, in the case of under-estimates of the CHO, the percentage of time in an objective level increased in comparison HFS with Open-Loop (OL). While the percentage of time above the target level decrease with the same comparison. This leads to the hyperglycemia was minimized. In the case of overestimates of CHO. The ratio of time in the objective level was the same in (HFS) and OL. But the ratio of time above objective was a little increased in (HFS). Therefore, hypoglycemia was avoided. The control law may be too conservative for some patients, which is a disadvantage of this tuning procedure. Also, in the postprandial phase, the system remains long period in the hyperglycemic region, and this danger for patients.

D. PID Controller

The PID controller was built to reach minimum steady-state error for the output [44]. The architecture of a PID controller does not necessitate a detailed mathematical model for tuning. Proportional – Integral - Derivative controller parameters Kp, Ki, and Kd were tuned to the find best values, of the control action [45]. However, optimal tuning cannot be easy, particularly when there are external disruptions such as meals. It was discovered that a fully automatic PID is insufficient to achieve the hyperglycemia reduction and hypoglycemia prevention trade-off. PID does not cope with the constraint of positivity alone. For example, in [46], an anti-reset windup strategy was implemented to prevent undershooting dangerous toward hypoglycemia.

Therefore, in [47] two strategies of the controller were applied. These are the proportional, integral, and derivative (PID) control in the state space form. It was applied during the fasting phase. This control was composed of a combination of both state feedback and positive PID control. Constraints were developed to state and input. The state feedback control is responsible for steering the glycemia to a target range. PID is responsible for refusing any disturbances when glycemia is in the normal zone.

Another controller was applied and tested in this study. It is an MPC with an impulsive input with satisfying input and state constraints. It could be used at any time of the day (during fasting or the postprandial phase).

The controller of the strategy was tested with a one-day virtual protocol on 50 virtual patients. From the simulation result of this study. See that the PID was spent less time than iZMC in the range (140 – 180 mg/dl). PID was spent 76.09 min. while iZMPC spent 83.91 min. Also, in the range greater than 180 mg/dl. The PID controller was spent 4.99 min, while iZMPC spent less time (1.87 min.). Thus these strategies are needed more accurately for disturbance estimation and more robustness to prevent glycemia from raising hyperglycemia. Also, the results show that both strategies have a good performance with low to moderate plant-model mismatch.

In [48], the author suggested a multiple model strategy by alternative closed-loop method for subcutaneous insulin delivery in T1DM. The proposed system was modeled around five different operating points. Then, five PID controllers are tuned to achieve the objectives of control performance such as required settling time and bounded of overshot and undershoot are obtained for each transfer function related to the operating point. The

Received 16/4/2021; Accepted 25l7l2021

DOI: https://doi.org/10.33103/uot.ijccce.21.3.2

main *in silico* results of this work is no severe hypoglycemia with limited hyperglycemia events. In this work, the hyperglycemia risk does not completely treat.

New modern technology for hypoglycemia avoidance was suggested in [49]. The insulin algorithm employs a proportional–derivative controller with insulin feedback, whereas the CHO algorithm employs a predictive, quantified proportional–derivative controller. The proposed closed-loop algorithm prevented hypoglycemia episodes by issuing alarms to encourage patients to consume carbohydrates. The study indicates that blood glucose levels may be anticipated and that most hypoglycemia occurrences caused by external disturbances can be avoided. Extra fast-acting CHO is consumed to avoid hypoglycemia. However, in a closed-loop system, the CHO action is insufficient. The system must be notified of the ingested CHO; otherwise, the insulin controller will over-act to any BG rise, perhaps causing hypoglycemia again.

TABLE 1. OVERVIEW OF THE SELECT STUDIES ON AP CONTROLLER DESIGN AUTHOR

Author	Study Design	Comment
P. S. Rivadeneira, A. Ferramosca, and A. H. Gonz 2016	IZMPC	examined on one patient with known and regular meals. Both the control input (insulin injection) and state (BG) are constraints to be positive.
A. H. González, P. S. Rivadeneira, A. Ferramosca, N. Magdelaine, and C. H. Moog, 2017.	iZMPC	Constraints were considered for both state and input. This study was tested on 5 patients with disturbance meal
D. A. Copp, R. Gondhalekar, and J. P. Hespanha 2018.	MPC/MHE	tested *in silico* trials of ten virtual patients. The results show several notes of this simulation, containing less (hypoglycemia) status, without raising the number of (hyperglycemia) status.
P. Abuin, P. S. Rivadeneira, A. Ferramosca, and A. H. González, 2020.	pZMPC	pZMPC was published under a real observer and tested on 10 virtual adult patients. The controller mange the BGC to normal range, but BGC raises to hyperglycemia after meal intake.
E.S. Juan, H. Alejandro, and P. S. Rivadeneira, 2017.	ZMPC	The comparison of the performance of these controllers showed that the standard ZMPC was present 70% of the time inside the normal zone, and on the other side, the iZMPC was spent 92.5%.
K. Menani, T. Mohammadridha, N. Magdelaine, M. Abdelaziz, and C. H. Moog, 2017.	positive Sliding Mode Control (SMC)	Firstly the PIS was found in this study. This controller was examined on 3 patients and take more time to regulate glycemia to normal range in the fasting phase.
T. MohammadRidha, P. S. Rivadeneira, N. Magdelaine, M. Cardelli, and C. H. Moog, 2019.	Positive State Feedback Controller	The PIS was found under this controller for all system states, and BGC was regulated without hypoglycemia in fasting phase.
L. M. Huyett, E. Dassau, H. C. Zisser, and F. J. Doyle, 2015.	PID controller	Robust controller against disturbances but not cope with positivity constrained
E. Sereno, M. A. Caicedo, and P. S. Rivadeneira, 2018.	PID in state-space form	Hybrid controllers consist of a combination of a PID controller for disturbance rejection and a state feedback controller for positivity constrained. The BGC was regulated to the normal range.

Received 16/4/2021; Accepted 25l7l2021

DOI: https://doi.org/10.33103/uot.ijccce.21.3.2

From the above studies related to design a positive controller, one can see all the preventing hypoglycemic events in both scenarios (with or without meal). However, hypoglycemic events were fully prevented at all times but there was no guaranty for such prevention. This represents an important challenge for any controller in designing any AP. The block diagram in *Fig*. 3, shows the formulation of this controller. See that there is no estimator, thus the controller can not cancel the effect of the disturbances (meals). Therefore the hypoglycemic events can not be eliminated.

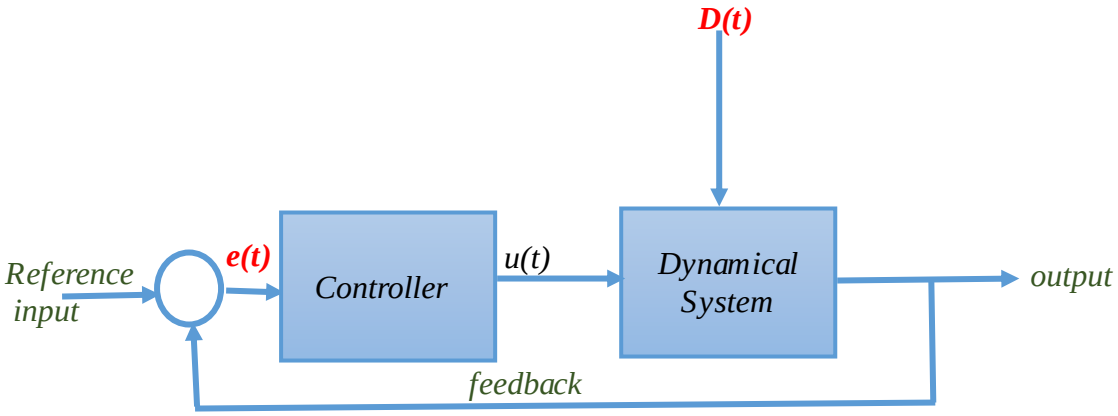

FIG. 3. BLOCK DIAGRAM OF THE APPLIED CONTROLLER

V. CONCLUSIONS

In any study, managing glycemia in the normal zone is the main challenge. Therefore, the main problem is to design AP that matches the functioning of the real pancreas.

In this paper, a simplified explanation is provided about T1DM, its causes, and how it is treated. Then, a brief idea of positive control is presented. This paper also includes previous studies in which a positive control was designed along with the reasons that lead to applicate positive control on T1DM models.

Therefore, the following can be concluded from the studies related to design a positive control that:

Hypoglycemia is completely avoided due to the preventing of any overdoses of insulin. This is the main benefit of positive control. However, the hypoglycemia was prevented before the meal intake, whereas the hyperglycemia was not completely prevented after meal intake. Since meal intake is a positive factor, the control action remains positive, but will not maintain hyperglycemia.

The perspective is to design a positive control able to maintain glycemia in a normal zone after meal intake. This depends mainly on the estimation of the meal intake. Thus, this operation is required to design a suitable robust observer. The block diagram in *Fig*. 4, shows a brief idea of the operation.

Received 16/4/2021; Accepted 25l7l2021

 ISSN (Print) 1811-9212 ISSN (Online) 2617-3352

DOI: https://doi.org/10.33103/uot.ijccce.21.3.2

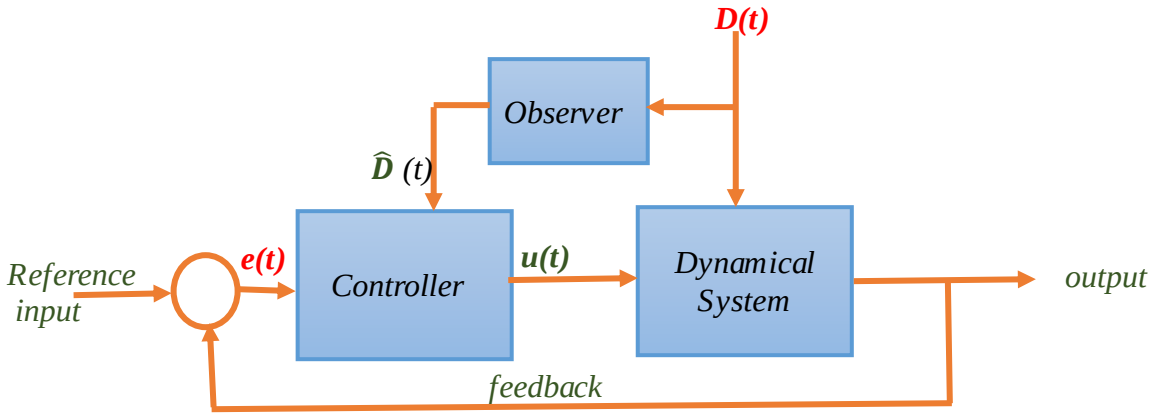

FIG. 4. BLOCK DIAGRAM OF THE PROPOSED CONTROLLER

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