# The artificial pancreas: the development of closed-loop algorithms in the present

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Abstract

*About 422 million people worldwide have diabetes. It has no cure so far. But when it comes to biomedical engineering, we can see a glimmer of hope. Now, you are not committed to taking continuous insulin doses because your artificial pancreas will do that for you. The artificial pancreas facilitates the patient's disease journey both psychologically and physically. It is equipped with a blood glucose monitor and an insulin pump, making it like a natural pancreas in its functionality. But behind every invention that is beneficial to humanity are complications and sometimes algorithms.*

## I. Introduction

According to WHO, diabetes affects around 422 million people globally. Diabetes is directly responsible for 1.6 million deaths per year. Over the last few decades, both the number of cases and the prevalence of diabetes have significantly increased. It causes severe problems such as blindness, kidney failure, heart attacks, stroke, and lower limb amputation [1]. Unfortunately, diabetes is an incurable disease, so the Person with Diabetes(PWD) must regulate the glucose in the blood, forgetting to enjoy his/her life without any suffering.

The biomedical engineers were racing the future for an artificial pancreas instead of a damaged one. In 1977, a revolution erupted in biomedical engineering when Professor Roman Hovorka at the University of Cambridge invented the first artificial pancreas(Closed-Loop System)[2].

The research paper will go in deep about artificial pancreases, especially the closed-loop System, how it works, and recommendations for future research inspired by the results.

## II. The Incurable Disease

### i. Brief about the Pancreas

The pancreas is a pear-shaped vital part of the digestive system and is known as a mixed gland due to having both exocrine and endocrine functions. The endocrine portion consists of a group of different types of cells (islets of Langerhans). The islets of Langerhans cells are three types, Alpha, Beta, and Delta. Each of these cells secretes a specific hormone. For instance, Alpha cells secrete glucagon that raises blood glucose levels raises blood glucose levels. Besides, Beta cells secrete insulin that regulates sugar metabolism and maintains normal sugar levels in the blood. [3] Unfortunately, low insulin

can lead to an accumulation of glucose in the blood, a situation known as hyperglycemia, and to the metabolic disorder diabetes mellitus [4].

ii. Type 1 Diabetes

When you eat carbohydrates, chemicals in your small intestine break them down into single sugar molecules called glucose. The small intestine absorbs glucose. Then, the glucose starts to transfer into the bloodstream. When the bloodstream reaches your pancreas, beta cells detect the rising glucose levels and release insulin into your bloodstream to decrease glucose levels and keep your blood glucose in a normal range.[5]

In type 1 diabetes, your white blood cells mistake your beta cells for foreign invaders. In an autoimmune response, the white blood cells release antibodies to destroy beta cells. Thus, the insulin in the blood decreases or disappears, which leads to many problems and complications.[6]
Glucose cannot enter your cells without insulin. As a result, they develop a strong need for the calories that glucose should provide. In addition, the glucose builds up in the bloodstream with a condition known as hyperglycemia.[7]

## III. The Glimmer of hope

i. Artificial Pancreas

So, if you are a type 1 diabetes case, your objective is to maintain a healthy blood glucose level by inserting the dosages of insulin required to lessen the blood glucose level. Thus, the artificial pancreas plays a role in this series of functions by making it continuously [8].

The artificial pancreas (AP) is an insulin pump connected to a continuous glucose monitor system (GCMS) that is controlled by a receiver (For example, handheld device) using sophisticated software algorithms to make the whole thing work. The purpose is to automate as much as possible blood glucose (BG) regulation, so the wearer doesn't have to take fingerstick blood sugar measurements and then calculate how much insulin to inject or decrease depending on those results. Some systems can even turn off insulin administration automatically if the CGMS detects low blood sugar levels. Some methods are also experimenting with carrying glucagon with insulin in the pump to raise blood sugar as needed.[9]

ii. Types of Artificial Pancreas

So, using an artificial pancreas (AP) is essential for people who experience diabetes, especially Type 1 Diabetes. However, many insulin delivery systems exist, each with its mechanisms, algorithms, and certain returns. When discussing kinds of artificial pancreases, there are mainly three types according to the official UK site for diabetes.

1- Bionic Pancreas:
It works like the CLS by pumps to deliver insulin and glucagon (which raises glucose in the blood). The pumps relate to an app to provide coordination between the pancreas devices.

2- Implanted artificial pancreas:
It is an insulin delivery device that features a gel that can detect changes in glucose levels by enabling a high insulin release rate when the glucose level increases and vice versa.

3- Closed-Loop System (CLS):
It consists of three components an insulin pump to store and deliver insulin, a Continuous Glucose Monitoring System (GCMS), and an algorithm-based control system. (As shown in figure 1) [10]
We will focus on the CLS because of its high potential benefits. It is the widely recognized version of the AP. Furthermore, many research papers and experiments done on it. Thus, the data available is accurate and detailed.

## IV. Closed-Loop Systems: A Close Look

i. Historical Appearance

The closed-Loop glucose system idea is not new. The concept was introduced in the 1960s [11]. However, many limitations existed then, including algorithm simplicity, the inadequate size of the CLS

components, the CGMS accuracy, and the need for intravenous access. These limitations led to a search for alternative systems for a long time.

Later in 1978, a study was performed to test the feasibility of using insulin pumps to deliver subcutaneously (under the skin) rapid-acting insulin [12]. An extensive advantage of using subcutaneous (SC) delivery systems is the decreased invasive nature. The problem with that strategy is that subcutaneous (SC) delivery systems can have considerable delays because they are inserted into the interstitial fluid of the cells under the skin while


Figure 1: CLS is considered as one of the most promising devices for patients with Type 1 Diabetes, it consists of an insulin pump (the small cuboid-like apparatus) which may have the control algorithm inserted in it, a CGMS (the pieces at the bottom-right), and a communication device to enable doctors and experts to watch the device and patient state [11].

insulin is automatically released in the bloodstream. So, the SC systems insulin needs time to move to the bloodstream before giving an effect. In addition, glucose often diffuses into a subcutaneous fluid, which contributes to the time lag.[14]

Consequently, manual intervention was needed. Although development was slow, the last 20 years' improvement efforts resulted in a substantial increase in the efficiency and utility of the pump technology used, improvements in the components' technology, the CGMS reliability, and algorithm refinements.

In 2009, the simplest form of the CLS became commercially available. It could suspend glucose up to 2 hours when hypoglycemia is detected. Fortunately, post-marketing studies showed a remarkable decrease in the duration and frequency of nocturnal hypoglycemia [15]. Many studies are conducted, hoping that the CLS can help patients infected with diabetes.

ii. The Algorithms in CLS: Natural introduction

The advancement of the algorithms and the complexity to improve the CLS performance in realistic situations was a central part of the CLS and AP technology. Moreover, designing the algorithms of AP, scientists' main goal was creating an artificial pancreas that mimics the performance of a natural one.

How does a natural pancreas work? This question was critical for improving algorithms in an artificial pancreas. Scientists have studied the human pancreas for many years and quantitatively simulated its function using various methodologies and complexity levels. The mathematical model created by Banzi, and coauthors is one of the most trustworthy models (shown in Figures 2 and 3).

$$
\begin{cases}
\dfrac{dG_H(t)}{dt} = \dfrac{1}{V_H^G}\left[Q_L^G G_L(t) + \gamma_T^G (G_T(t))^{\alpha} - Q_H^G G_H(t) - R_H^G\right] \\
\dfrac{dG_L(t)}{dt} = \dfrac{1}{V_L^G}\left[Q_A^G G_H(t) - Q_L^G G_L(t) + R_L^G\right], \\
\dfrac{dG_T(t)}{dt} = \dfrac{1}{V_T^G}\left[Q_P^G\left(G_H(t) - \gamma_T^G G_T(t)\right) - R_T^G\right], \\
\dfrac{dI_H(t)}{dt} = \dfrac{1}{V_H^I}\left[Q_L^I I_L(t) + \gamma_T^I (I_T(t))^{\beta} - Q_H^I I_H(t)\right], \\
\dfrac{dI_L(t)}{dt} = \dfrac{1}{V_L^I}\left[Q_A^I I_H(t) - Q_L^I I_L(t) + R_{PIR} - R_L^I\right], \\
\dfrac{dI_T(t)}{dt} = \dfrac{1}{V_T^I}\left[Q_P^I\left(I_H(t) - \gamma_T^I I_T(t)\right) - R_T^I\right],
\end{cases}
$$

Figure 2: Here is a mathematical model for some fluids in a healthy human body: insulin, glucagon, and glucose. There are 6 ODEs of 4 compartments [16].

We know that a model like that may look quite confusing or intimidating, but it is not. It represents the concentrations of the two hormones related to the level of glucose in the blood, insulin and glucagon, and the resulted concentration of glucose. The model consists mainly of a system of 6 Ordinary Differential Equations (ODEs) for four

compartments or parts of the body: heart and lungs, liver, other tissues, and pancreas.

An ODE is an equation in which you want to find a function of (usually) time for an object. Therefore, we want an equation. If we input a value of time, we get the desired object value. In this case, it is the concentrations of the hormones and glucose in the blood. In an ODE, we determine the equation for the function using the relation between it and its instantaneous rate of change (known in mathematics as "derivative" the d/dt).

Here is a brief list of the notation used:

Variable

V : Volume (dl) G : Glucose concentration (mg/dl) I : Insulin concentration (mU/l) Q : Vascular blood flow rate (dl/min) Subscripts:

H: Heart and lungs L: Liver T: Tissues A: Hepatic artery PIR: Peripheral insulin release s: Stored insulin b: Labile (variable) insulin G: Glucose I: Insulin Γ: Glucagon Parameters:

R - γ - p - α - δ - σ - β

In general, the balancing mass equation for glucose, insulin, and glucagon takes the ODE form:

$$V\frac{M}{\mathrm{d}t} = Q\left(M_{\text{in}} - M_{\text{out}}\right) + R_p - R_c$$

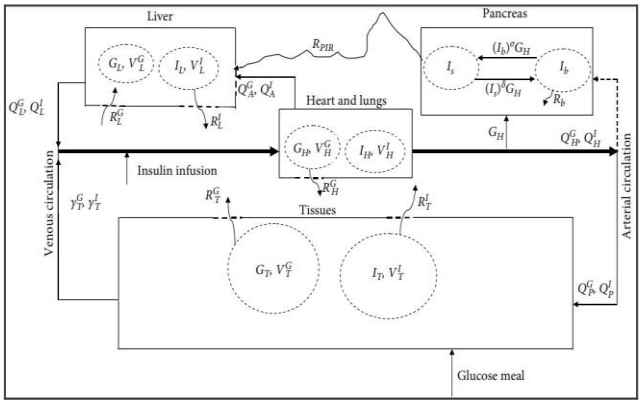
V: Compartment volume M: concentration

Q: blood flow rate

$R_p$, $R_c$: Metabolic production and consumption rates

While developing the artificial pancreas, scientists and engineers certainly were inspired by the systems of equations modeling the natural pancreas secretions behavior. However, it is impossible to use these systems because they model the "behavior" of the pancreas that they are not instructions that can be followed. Also, artificial pancreas systems cannot always measure the concentrations of the hormones and glucose accurately and instantly. Subsequently, prediction models and error-correcting algorithms are necessary to supply the human body with stable glucose rates, and that's where the importance of the control algorithms comes [14].

Figure 3: Here is a schematic representation of a diabetic




person according to Banzi and coauthors' model [16].

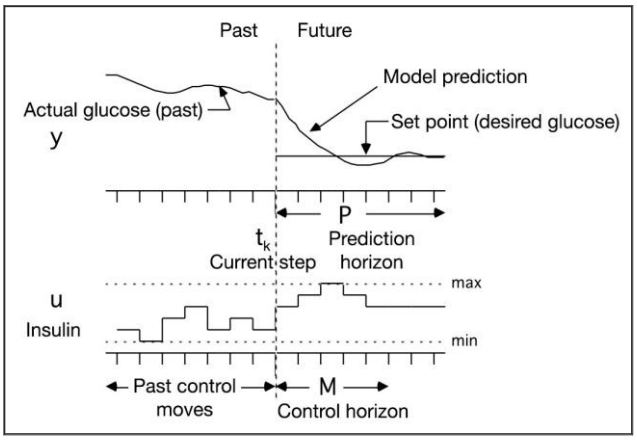
iii. The Main Algorithms in the CLS

Many algorithms are frequently used in the CLS control devices. In addition, algorithms can be implemented in different ways. They are just principles. There are three main types of algorithms, Model Predictive Control, Proportional–Integral- Derivative, and Fuzzy Logic Control: Here, we will present these main strategies and algorithms involved in technology.

1- Model Predictive Control (MPC):

The MPC depends on a model used to predict the effect of controlled moves (decisions) in discrete-time periods (steps) on future glucose level output. Then, optimization is performed to select the best movements that make the glucose level in the desired range while maintaining a set point (target).

The mathematical models used in MPC can have many forms, but the normal formulation includes



continuous Ordinary Differential Equations. These equations can be linear (represented as a combination of straight lines or nonlinear) At each step, integration (finding anti-derivatives) or solving the equations based on the current-state values is necessary Linear ODEs can be solved analytically and have closed-form exact solutions, while nonlinear ODEs solutions are approximated, but they often perform better optimizations**.** (as shown in figure 4).

Figure 4: Here is a basic demonstration of the MPC concept, a set point is determined, and the algorithm uses past moves and the prediction horizon information in addition to the CGMS to optimize the insulin infusion rates to keep glucose levels in the desired range[17].

The parameters used in the system of ODEs can be fixed or adaptive, while adaptive values may sound promising. They must be applied with care because they may result in unstable systems.

Correcting the model according to the measurements differs from predictions. It treats the difference between the measured output and the model prediction at the current step as a constant. The correction happened only after the prediction. However, better approaches that make smart but more complex corrections like the Kalman filter.[18]

A study was performed on six adults in 2014 to test the efficiency of the MPC and its ability to reduce postprandial (after lunch and dinner) glucose excursions. During the study, the patients wore a DiAs platform. It is a portable system that communicates wirelessly with the sensor and insulin pump and has a control algorithm. DiAs streamed the patient data, and the team involved in the protocol remotely monitored the status of the patients and the devices. The study lasted for 42 hours. The results were satisfactory compared to the conventional Open-Loop System (OLS) involves taking insulin boluses for meals:

Time in the desired range: 94.83% vs. 68.2%.

Time in hypoglycemia: 1.25% vs. 11.9%.

Overnight Time in the desired range: 89.4% vs. 85.0%

Time-in-hypo: 0.00% vs. 8.19%, where the first percentage is for the CLS and the second one for the OLS [19].

2- Proportional-Integral-Derivative (PID):

PID is an algorithm that operates by tracking the error between the measured output (Process Variable-PV) and the setpoint (SP) in each step (as shown in figure 5). Then, it computes correction values. It measures mainly three values and adds them to have a sense for error correction and decision-making:

The error percentage value (proportional) – The error area between the curve of the PV values over time and SP (Integral) – The rate of deviation of PV from SP. PID has a general form of:

$$u(t) = u_{bias} + K_c\, e(t) + \frac{K_c}{\tau_I}\int_0^t e(t)dt - K_c\tau_D\frac{d(PV)}{dt}$$

*u*(t) is a function of time that represents the algorithm control variable. Kc is the controller gain constant. It determines the percentage of the strength gained by the error signal. A Higher Kc value will lead to more aggressive correction behavior.
*u*bias is a constant set to the control variable value when the control is switched from manual to automatic mode to provide a smoother transition, especially when the error value is low.
e(t) = SP − PV, τI, and τD are the integral and derivative terms. Respectively, High values of τI will cause the integral part action to have a weaker effect on the algorithm. In contrast, high values of τD strengthen the effect of the derivative side.
Since the CLS can't have continuous feedback, discrete-time steps must be used in calculations [20], and the average is taken from each step, which can

$$u(t) = u_{bias} + K_c\, e(t) + \frac{K_c}{\tau_I}\sum_{i=1}^{n_t} e_i(t)\Delta t - K_c\tau_D\frac{PV_{n_t} - PV_{n_t-1}}{\Delta t}$$

be modeled as:
Despite PID being a widespread and very useful algorithm, it fails to moderate the large glucose excursions after meals (early hyperglycemia and late hypoglycemia) because of the dependence in PID on only real-time changes in the glucose sensor.[21]

One of the recent solutions to this problem is Insulin Feedback (IFB) modification. It is based on experiments that illustrated that plasma insulin

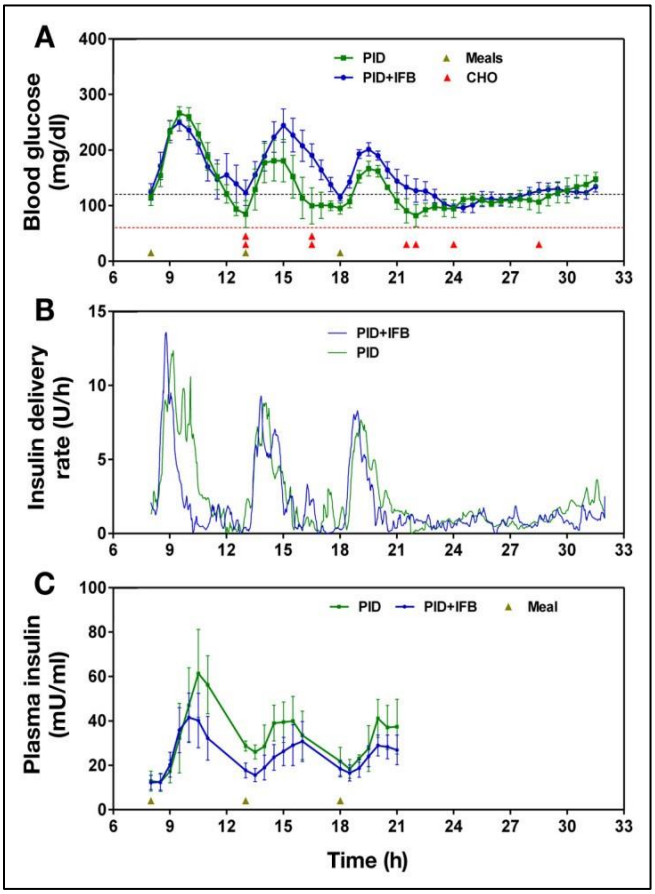



Figure 5: A Comparison between an AP with PID only and that with PID + IFB. Black dashed line indicates BG target (120 mg/dl); red dashed line indicates hypoglycemic threshold (60 mg/dl); target range: (70 180) mg/dl. Brown triangles represent meals, and each red triangle indicates a single hypoglycemic event [23].

suppresses its secretion [22]. IFB accounts for the insulin delivery history and reduces the next insulin delivery based on model predictions for the subcutaneous, plasma, and interstitial insulin levels, instead of depending solely on real-time sensors data which has a time lag because of using SC systems. IFB's equations system has the form **(as in figure 6).**

ISC, Ip, and IEFF are estimates of real-time glucose levels. ID is the insulin delivery value, and (n-1) denotes an estimate 1 min previously. α, β and γ are parameter values determined, and the subscripts denote the parameter insulin type or the order.

In 2012, a study was done on four subjects aged 1528 years to determine the effects of the IFB modification. The performance of PID combined with IFB was compared with that of PID alone. The Medtronic Closed System and its PID algorithm were used in the study. In addition, the algorithm calculations were calculated by a laptop computer that received data each minute from the GCMS and sent corresponding commands to the insulin pump. The study data has taken 24 hours in which no snacks were allowed, and the patients had their meals with no announcements given to the system controller.

No episodes of hypoglycemia took place during the PID + IFB control time as opposed to 8 under PID only time. Six of them happened in 3-5 hours after a meal. PID control tended to a higher frequency of blood glucose levels under the target range (< 70 mg/dl) contrasting the tendency of PID + IFB control to achieve glucose levels above the range ( > 180 mg/dl). The problem may be solved by using "more aggressive" tuning parameters that can reduce the duration of high glucose levels. It is worth mentioning that this study used the same controller gain constant while other studies increased it by a factor of 2 to negate the steady-state effect that IFB cause. The results graph was obtained, and it appears in figure 6 [23].

It supports that the IFB modification in decreasing the excursions of glucose levels (except during dinner) and was able to decrease the hypoglycemia risk. Besides, achieving more stable rates, avoiding both hypoglycemia and hyperglycemia.

$$I_{SC}(n) = \alpha_{11} * I_{SC}(n-1) + \beta_1 + * I_D(n-1)$$

$$I_P(n) = \alpha_{21} * I_{SC}(n-1) + \alpha_{22} * I_P(n-1) + \beta_2 * I_D(n-1)$$

$$I_{EFF}(n) = \alpha_{31} * I_{SC}(n-1) + \alpha_{32} * I_P(n-1) + \alpha_{33} * I_{EFF}(n-1) + \beta_3 * I_D(n-1)$$

$$IFB(n) = \gamma_1 * I_{SC}(n) + \gamma_2 * I_P(n) + \gamma_3 * I_{EFF}(n)$$

Figure 6: The system of equations used for the IFB modification [23].

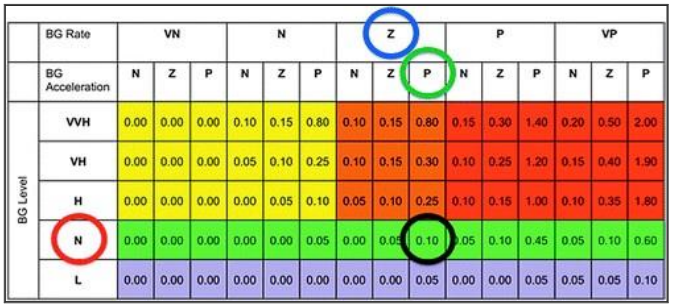
3- Fuzzy Logic Controller (FLC):

Fuzzy Logic (FL) is an algorithm that is fundamentally distinct from other algorithms. Other algorithms use precisely formulated mathematical models for calculations to make decisions. FL depends on linguistic rules and human experience to determine the solution to a problem. The difference between traditional model-based algorithms and FL is that FL assigns values (probabilities) between 0 and 1 for inputs. Giving an output according to probability instead of using only false "0" and true "1" in what is known as "Boolean Logic"

For instance, if the range of normal glucose levels was set to be (70 – 180) mg/dl, a Boolean Logic algorithm would treat 182 mg/dl as being strictly high and would take decisions like that for a glucose level of 270 mg/dl. FL is a more "natural" algorithm since it usually operates like our thinking, although one drawback is that it requires a lot of data and pre-defined rules to work [24].

In FL, a value may belong partially to more than one set and can be useful in the AP case since it is important to stay in a safe range rather than looking for a strict solution. FLC in AP has three terms or sets: glucose level, glucose rate, and glucose acceleration (rate of glucose rate). These sets simulate the reasoning of expert diabetes clinicians. A design for an FLC algorithm is (as shown in figure 7).

You may think that an algorithm like FL would be less reliable or efficient because of its tolerance with rules and ranges, but it is a very robust algorithm and challenges both MPC and PID in performance, and FLC has a great capability of incorporating physiological parameters like illnesses, anxiety, and exercise. Unlike other algorithms, it is highly customizable and designed to emulate human thinking and experience.



| | BG Rate | VN | | | N | | | Z | | | P | | | VP | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | BG Acceleration | N | Z | P | N | Z | P | N | Z | P | N | Z | P | N | Z | P |
| BG Level | VVH | 0.00 | 0.00 | 0.00 | 0.10 | 0.15 | 0.80 | 0.10 | 0.15 | 0.80 | 0.15 | 0.30 | 1.40 | 0.20 | 0.50 | 2.00 |
| | VH | 0.00 | 0.00 | 0.00 | 0.05 | 0.10 | 0.25 | 0.10 | 0.15 | 0.30 | 0.10 | 0.25 | 1.20 | 0.15 | 0.40 | 1.90 |
| | H | 0.00 | 0.00 | 0.00 | 0.00 | 0.05 | 0.10 | 0.05 | 0.10 | 0.25 | 0.10 | 0.15 | 1.00 | 0.10 | 0.35 | 1.80 |
| | N | 0.00 | 0.00 | 0.00 | 0.00 | 0.00 | 0.05 | 0.00 | 0.05 | 0.10 | 0.05 | 0.10 | 0.45 | 0.05 | 0.10 | 0.60 |
| | L | 0.00 | 0.00 | 0.00 | 0.00 | 0.00 | 0.00 | 0.00 | 0.00 | 0.05 | 0.00 | 0.00 | 0.05 | 0.05 | 0.05 | 0.10 |

Figure 7: FLC uses a set of rules tolerant of small deviations of values. Here N, Z, and Prefer to negative, zero, and positive. L, N, and H mean low, normal, and high, respectively with V denoting "Very". The FLC will evaluate the value (state) of each term and output the number bounded by these states (black circle) [25].

Seven subjects were recruited and enrolled in a 24-hour research study in 2013 to test FLC for use in AP, and the results were very pleasing. The glucose levels stayed in the target range (70 – 180) mg/dl 65.0% of the time, and 76.3% of the time if we extended the range to 200 mg/dl FLC was able to completely avoid any hypoglycemia glucose levels with a time percentage of 0.1% under 70 mg/dl and 0.0% under 60 mg/dl (hypoglycemia level) and showed a great ability to avoid hyperglycemic events with the glucose levels being only 0.1% in the hyperglycemia events range with them lying mostly in the period from 8-pm to 2-am [25]. (As shown in figure 8)

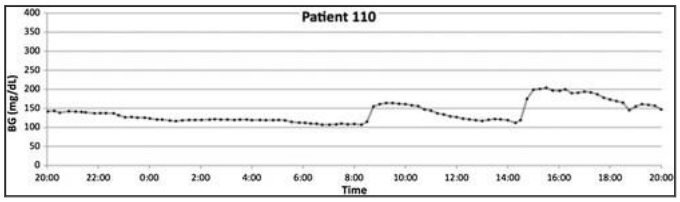



Figure 8: A graph showing the blood glucose levels throughout the 24 hours in one of the study subjects. High stability in the glucose levels is noticed and no hypoglycemia or hyperglycemia is recorded [25].

## V. Comparison, Which Approach is Better?

The research on AP algorithms in the last decades has shown great diversity in the methods used to achieve glucose stability from conventional meal boluses to automatically operated and advanced

insulin delivery systems. Also, many algorithms with MPC, PID, and FL as examples have been introduced in that field. Thus, what is the best method or algorithm?

Scientists and researchers have always considered this as a tough question, as there are a lot of factors that cause problems for any answer presented. First, all the discussed algorithms can be applied in different ways with different results.

A graph like that shown in Boquete's paper, which discussed the approaches used (figure 9)**,** can help to get primary data about the efficiency and capability of the approaches, using them for comparison purposes can be misleading because each algorithm has no unified tuning or parameterization.

MPC ODEs can be very complicated or relatively simple. The gain constant in PID can have different values. Modifications like IFB and FMPD (fading memory proportional derivative) can be executed to modify the behavior of PID.

On the other hand, FL depends mainly on the experience of the person defining the operation rules. Boquete, a strong MPC proponent noticed that and mentioned it explicitly at the end of his discussion: *"I also agree that it is very difficult, even in simulation studies, to have a valid comparison of different algorithms. One way or another, an algorithm must be tuned based on some performance criterion, so if particular MPC and PID algorithms are tuned with different criteria, then there is no good way to compare them."* [17, p. 11].

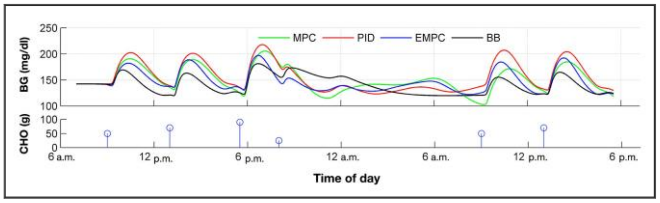



Figure 9: A representation for the average performance of the popular algorithms' controllers over 9 simulated subjects. MPC is a standard Model Predictive Control implementation, PID is for an ordinary Proportional-Integral-Derivative control, EMPC is a multiple model probabilistic MPC, and BB represents optimal Basal-Bolus [17].

A case for the difference in results obtained due to inconsistent conditions is presented by Garry M. Steil, Bequette's colleague, and a PID proponent, and shown in figures 10 and 11.

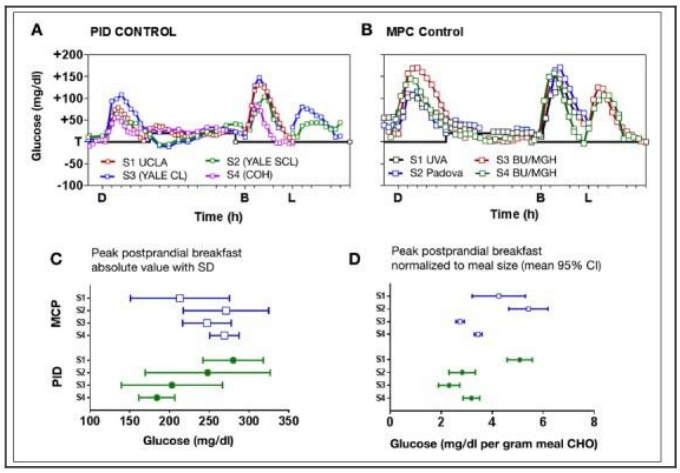



Figure 10: 4 Studies [26 − 29] that show more stable glucose rates in PID control compared to the rates in MPC control, S(x): study no. (x). UCLA: University of California, UVA: University of Virginia, BU/MGH: Boston University/Massachusetts General Hospital, COH: City of Hope. CL: closed-loop, SCL: semi-closed loop, SD: standard deviation; CI: confidence interval: CHO, carbohydrate.

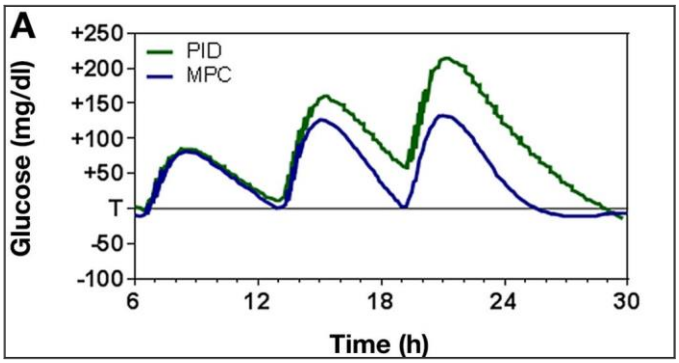



Figure 11: A model simulation in which an MPC control is compared to a PID one. In contrary to the previous studies, the MPC glucose rates appear to be more stable than that of PID [30].

However, the algorithms' fundamental properties can determine the merits and demerits of each algorithm, give engineers and clinicians a good image of it. For instance, MPC is a general framework that has additional inputs or variables incorporated in a standard MPC model. Besides, the objective can include the desired insulin-on-board range, which continues to have

pharmacodynamic effects for several hours in the prediction horizon.

Nevertheless, the main problem concerning MPC is that some of the model parameters, particularly those responsible for decreasing basal requirement need to be identified from the control data and must be used in the control algorithm. So, increased amounts of data points (at least equal to the number of model parameters) are necessary to identify the parameters and keep the sensitivity of the estimates adjusted [31].

The disadvantage in MPC is that forms with a great number of equations (high order) result in longer computational times and more battery energy consumption. While discussing PID controllers, it is agreed that they are popular, known to be robust due to their integral action. They often have parameters that can be tuned other than the three standard ones, such as absolute and rate limits, anti-reset windup features, and derivative filters [17]. Also, PID can be modified with many algorithms that improve its performance and like IFB and FMBD.

FL is a simple but reliable algorithm, and applying it affects glucose rates that are almost always in the desired range. Also, FL is highly customizable and emulates human deductive thinking quite well, but FL is dependent on experience. It can be subjected to mistakes and non-optimal performance as the human experience is not perfect by nature. Also, FL requires large amounts of data so that the rules contain and can define every possible glucose and insulin state (inputs) and its respective control action (outputs) [24]

Subsequently, what is the answer to the question with which we started this section? Well, a definitive answer for this question in the meantime might not be currently available due to the parametric and structure uncertainty problems found in any recent comparison study. Although using standards that clinicians can agree on may reduce the severity of this problem. But I think that the question that we can answer and may represent the present and potentially the future of research objectives is: how can the algorithms we use and the AP, in general, be improved? The answers to this question are in the next section.

## VI. Results

According to a 6-month trial by the National Institute of Diabetes and Digestive and Kidney Diseases. It was testing the CLS on the Diabetes type 1 patients for targeting glycemic range.

During the trial, patients who utilized the closed-loop device had lower glycated hemoglobin levels. The closed-loop system had beneficial glycemic effects during the day and at night, with the latter being more noticeable in the second half of the night. The glycemic advantages of closed-loop management were observed in the first month of the study and lasted for six months. The study population included both insulin pump users and injectable insulin users spanning a wide age range (14 to 71 years) and baseline range of glycated hemoglobin levels (5.4 to 10.6 percent), with similar results across these and other baseline features of the cohort.

Patients had to be at least 14 years old and have a clinical diagnosis of type 1 diabetes; they also had to have been treated with insulin for at least a year using a pump or several daily injections, with no restriction on the glycated hemoglobin level. The experiment included a 2-to-8-week run-in phase (the length of which depended on whether the case had before used a pump or constant glucose monitor) to gather baseline data and teach patients how to use the devices.

The use of a closed-loop system was linked to a higher percentage of time spent in a target glycemic range than the use of a sensor-augmented insulin pump in this 6-month experiment, including type 1 diabetes patients.[25]

## VII. Future Research

It is important to declare that a few problems and gaps in the development of the CLS were not in

the previous studies and research. We will address these problems here and introduce probable solutions for them:

Inconsistent or ambiguous algorithm standards: a great portion of the studies not mentioned in detail. The implementation of the algorithm's methods in their research design and methods section or even adhere to them in some cases as the control algorithm may differ from the simulation algorithm in a simulation study. Examples of standards that should be well acquainted with are the applied parameters tuning, the algorithm version used, the number of steps, and their duration in the control and prediction horizons in MPC. This consistency problem causes inaccurate information and sometimes underestimating an algorithm due to unfair methodology. Clear information about algorithms and precise methodology documentation should be a necessity in any study that includes experiments whether they are on real subjects or simulations.

Not enough / inadequate data: A major problem with regards to the research done on AP till now is the eminent lack of experiments on real subjects. Most of the studies of AP made so far have included 7 – 10 persons at maximum. In addition, the scarcity of experiments. It might be surprising that the first outpatient study made based on MPC was reported in 2014. Absence of diversity in the studies made because they are usually made in North America on adult North American patients. Diversity in characteristics of subjects plays an important role as a factor to ensure that a medical procedure is suitable and beneficial for a wide range of people and conditions. Unfortunately, a device like AP may not work well and provide desired stable glucose levels for Asian children.

Diverting attention to AP studies, increasing their number as well as widening the health conditions, and geographical range of them will lead to the accuracy of the information available.

Possible improvements for the algorithms:
Although the algorithms used in the AP CLS have greatly improved and got better since the CLS's first introduction in 1964, they are still not close to being perfect, and there is still definitely a place for improvement.

Taking PID as an example, a deviation measure with its specific experimentally obtained parameter can be introduced to the algorithm along with IFB to favor staying in the target range overachieving smooth glucose changes to avoid nocturnal hypoglycemia and hyperglycemia. The added existence of the IFB modification is essential to provide data about the insulin delivery history and make predictions for the insulin and glucose levels to allow the deviation measure to function efficiently. Research on introducing a deviation measure may provide valuable insight into the potential of this modification.

A possible suggestion concerning FLC is developing a mobile application that connects the FLC database in the AP with the clinician computer and provides regular data about the insulin and glucose levels history. This app can allow the clinician to communicate with the patient and keep an eye on his condition wirelessly. The interesting part is that FLC is highly customizable and operates like ours using linguistic rules. The app could achieve a special benefit as it allows the clinician to monitor the patient status and modify the operation rules of the FLC through his computer according to the patient individual statistics and update them to be adjusted to the patient's needs. Such a mobile app can increase the efficiency of the algorithm and facilitate the communications between the clinician and the patient and between the clinician and the FLC. The app may attain pleasing and useful results.

## VIII. Conclusion

For years, scientists have studied the natural pancreas and have been able to mathematically simulate its function using various methodologies and complexity levels. The mathematical model

created by Banzi and coauthors is one of the dependable and not overly complicated models. Scientists' primary objective in developing the algorithms of the closed-loop system was to create an artificial pancreas that performs similarly to a natural one. Because of the high potential benefits of the closed-loop system, we decided to review it. Moreover, it has been the subject of several studies and tests. It consists of an insulin pump (the small cuboid-like apparatus) that may have the control algorithm inserted, a GCMS (the pieces at the bottom-right), and a communication device that allows doctors and experts to monitor the device and patient's condition. However, the development of algorithms and the addition of complexity to increase CLS performance in actual settings was and continues to be a key component of CLS and AP technologies. According to the volunteers that used the CLS, they completely forgot that they have diabetes, and the results were unexpected on the other hand, CLS has few problems and gaps, so we reconsidered these problems and find solutions to increase the efficiency of the project. AP aims to change the life of the patients mentally, psychologically, socially to make about half a million people get their work done without any suffering.

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